

Ultrasound-mediated radical cascade reactions: Fast synthesis of functionalized indolines from 2-(((N-aryl)amino)methyl)acrylates

Milene M. Hornink, Vinicius R. Nascimento, Julia L. Couto, Caroline S. Santos, Leandro H. Andrade*

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CEP 05508-000 São Paulo, SP, Brazil

ARTICLE INFO

Keywords:

Indolines
Sono-Fenton
Ultrasound
Pulsed ultrasound
Functionalized indolines
Organic synthesis

ABSTRACT

Novel functionalized indolines were synthesized from 2-(((N-aryl)amino)methyl)acrylates and formamides under ultrasonic irradiation for the first time. Aiming to develop a straightforward and easy-to-implement methodology for the synthesis of indolines, an instrumentation setup was designed, including ultrasound (US) equipment (Ultrasonic Horn; tip diameter of 12.7 mm, 20 kHz, maximum power of 400 W), an open reaction flask, and an inexpensive and green catalyst (1 mol%; $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$; CAS: 7782-63-0) without the need for anhydrous conditions. The use of the sono-Fenton process in the presence of formamides and 2-(((N-aryl)amino)methyl)acrylates afforded a broad range of functionalized indolines within 60 s in high yields. Several experimental parameters of the ultrasound-assisted reaction were evaluated, such as amplitude (40–80%), sonication time (15–60 s), and pulsed ultrasonic irradiation. A 60 s silent reaction did not produce the desired indoline. The optimized conditions for US-mediated reactions allowed the production of functionalized indolines in high isolated yields (up to 99%, 60 s reaction, pulse ration 1 s:1 s, US amplitude 60 %).

1. Introduction

The chemical effects of the irradiation of liquids with ultrasonic waves has been known for nearly a century [1]. However, in recent years the applications of ultrasonic waves have increased in the synthesis of organic [2,3] and inorganic [4] materials, especially for a green synthetic approach. Among the advantages of the ultrasound in synthesis is the possibility of achieving reaction selectivity that is not possible with conventional heating, enhancing selectivity [5,6] and improving reaction rates and yields [7–9]. Due to these advantages, there has been development in ultrasound-mediated organic synthesis that enables new applications in industry [10].

The chemical and mechanical effects that are enabled by cavitation extend the application of this methodology to a broad scope of organic reactions. Synthetic applications involve homogeneous and heterogeneous reactions [11] (i.e., solid–liquid phase reactions [12] and liquid–liquid heterogeneous reactions [13]), reactions performed in alternative solvents (i.e., ionic liquids [14] and water [15]) and also, reaction pathways with ionic or radical intermediates [16] (i.e., Grignard reaction, [17] Suzuki-Miyaura reaction, [18] Sabatier reaction, [19] radical reaction [20], and oxidation reactions [21]).

The ability of ultrasound to generate radicals is a known process that depends on certain ultrasonic parameters, such as frequency and acoustic power [22]. Ultrasound-generated radicals are mainly used as radical chain initiators in polymer chemistry [23,24]. The application of ultrasound to promote radical reactions and capture the radicals for synthetically producing heterocycles is a scarce research topic. The synthesis of bioactive compounds has also been improved by the advantages of ultrasound, and ultrasound has become an attractive tool for the improvement and discovery of protocols to produce heterocycles [25,26], including molecules of pharmaceutical interest [27].

In this context, we note the relevance of the development of synthetic methodologies for functionalized indolines. The indoline nucleus is a nitrogen-containing ring found in indole terpenoid alkaloids that have been isolated from plants and exhibit interesting biological activities [28]. For example, bis-indoline alkaloids such as compound **B**, isolated from *Tabernaemontana contorta*, show chemopreventive activity [29]. Jerantinine A (**A**) showed in vitro cytotoxicity against oral carcinoma cells [30]. The indoline scaffold is also found in drug candidates (**C**) that exhibit anti-inflammatory and antioxidant activities [31] (Fig. 1).

There are few examples of synthetic strategies for indolines based on radical cyclization reactions (Fig. 2A). For example, Brucelle *et al.*

* Corresponding author.

E-mail address: leandroh@iq.usp.br (L.H. Andrade).

<https://doi.org/10.1016/j.ultsonch.2021.105778>

Received 1 July 2021; Received in revised form 15 September 2021; Accepted 1 October 2021

Available online 7 October 2021

1350-4177/© 2021 The Author(s).

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

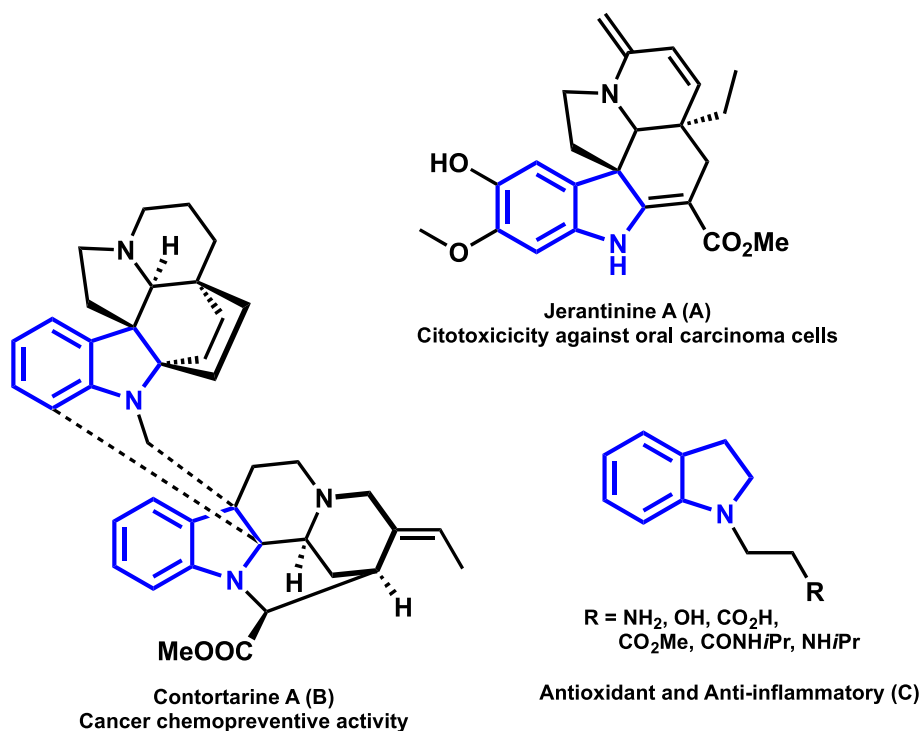


Fig. 1. Indoline alkaloids and reported biological activities.

employed 2-Allyl-1-azidobenzenes, iodine-based reagent and triethylborane. After 3–7 h, indolines were obtained in good yields [32]. Other strategy was based on the intramolecular radical cyclization of 3,3-difluoroallyl compounds, which were prepared from pre-functionalized 2-bromo-anilines. The cyclization step was carried out in the presence of AIBN as radical initiator and stoichiometric amount of Bu₃SnH (4–6 h reaction) [33].

We envisioned a synthetic strategy for functionalized indolines based on the use of 2-(((N-aryl)amino)methyl)acrylates and formamides as building blocks (Fig. 2B). sono-Fenton process was chosen to generate hydroxyl radicals [34–38] and consequently, carbamoyl radicals, which in the presence of the proper radical acceptor can yield the functionalized indolines. Notably, the main application of the sono-Fenton reactions is in the wastewater cleaning process via the removal of organic compounds [34–38]. The Fenton reaction involves the generation of hydroxyl radicals from Fe²⁺ and H₂O₂ in acid media (Fig. 2B). It is common to blend the Fenton reaction and ultrasonic irradiation, which is currently named sono-Fenton, to enhance hydroxyl radical generation, thus improving the degradation of organic pollutants.

Herein, we present the application of the sono-Fenton process in formamides to promote a radical cascade reaction for the synthesis of novel functionalized indolines (a 60 s process, Fig. 2B). The reaction was carried out with an inexpensive and green catalyst (1 mol%; FeS₂O₄·7H₂O; CAS: 7782–63-0). Formamides were used as reagents and solvents, which overcome the utilization of unattractive solvents, such as benzene and hexane.

2. Experimental

2.1. General information

The reagents were purchased from Sigma-Aldrich. Reactions were monitored using a GCM-QP2010SE instrument (Shimadzu) with low-resolution electron impact (EI; 70 eV) equipped with an RTX-5MS capillary column. GC/MS conditions: injector 260 °C; detector: 110 °C; pressure: 100 kPa; column temperature: method 1 (19 min) = 3 min at 80 °C, increase by 15 °C/min to 280 °C, maintain for 3 min at

280 °C; method 2 (24 min) = 3 min at 80 °C, increase by 15 °C/min to 280 °C, maintain for 8 min at 280 °C. Thin-layer chromatography (TLC) was conducted with Merck silica gel 60 F254 precoated plates and visualized with UV light. Flash column chromatography was performed on silica gel (200–300 mesh). ¹H NMR and spectra were recorded on a Varian Inova-300 (300 MHz) or a Bruker AIII 500 MHz (500 MHz) spectrometer. The chemical shifts (δ) are reported in ppm using TMS as an internal standard (CDCl₃ at δ 7.26 ppm). Proton-decoupled ¹³C NMR spectra were recorded on a Varian-300 (75 MHz) or a Bruker AIII 500 MHz (125 MHz) spectrometers. The chemical shifts (δ) are reported in ppm relative to the residual solvent peak (CDCl₃ at δ 77.0). High-resolution mass spectra were recorded using a MicroToF Bruker Daltonics instrument and ESI-TOF techniques. Melting points were determined in a Büchi B-545 melting point instrument.

Ultrasound-assisted reactions were carried out in a Branson Digital Sonifier-450 instrument (EDP N° 100–132-890R; 20 kHz, 400 W, horn diameter of 12.7 mm). For comparison purpose, “silent reactions” were carried out in a magnetic stirrer instrument (IKA ® C- MAG- HS 4; 1500 rpm).

2.2. Experimental setup for the US-assisted reactions

The experimental setup for the US-assisted reactions considered reaction volume and starting material concentration (Table 1), which are frequently described in synthetic methodologies. Also, Table 1 presents the acoustic power of the sono-Fenton reactions in formamide and *N*-Methylformamide (For more details, see Supporting Information).

2.3. General procedure for preparation of methyl-2-((phenylamino)methyl)acrylates S3a-k

Na₂CO₃ (1.17 g, 11 mmol) was added to a solution of the appropriate aniline (10 mmol) in DMF (20 mL). The mixture was cooled to 0 °C and methyl 2-(bromomethyl)acrylate (1.97 g, 11 mmol) was added dropwise. The mixture was stirred for 3 h at room temperature. Then, distilled water (100 mL) was added, and the aqueous layer was extracted with ethyl acetate (4 × 50 mL). The organic layers were combined,

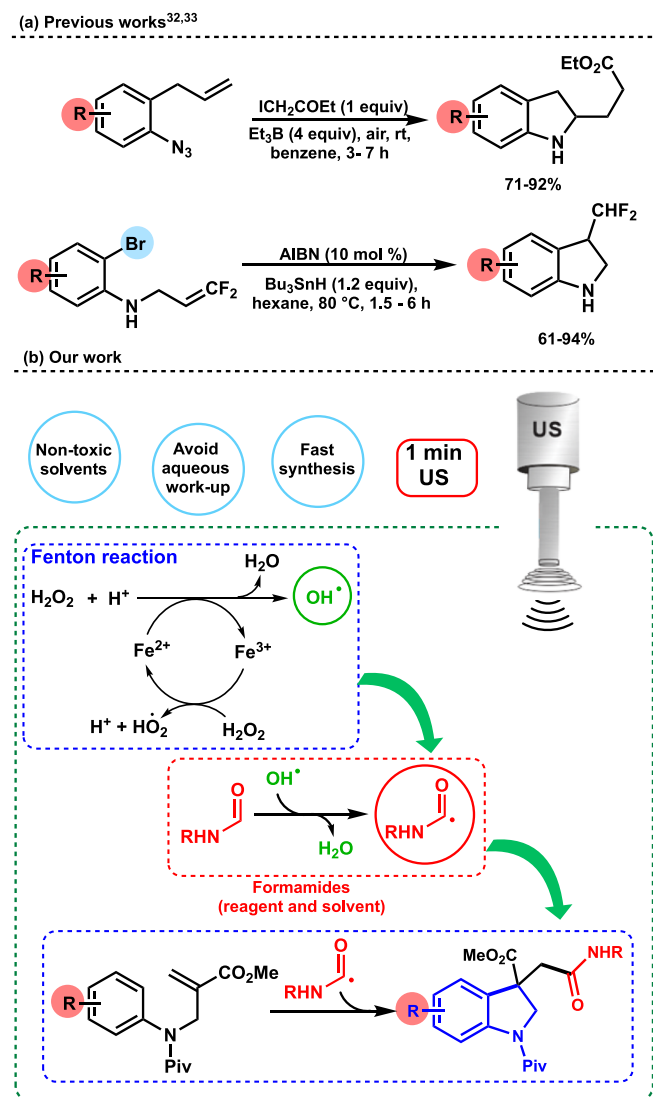


Fig. 2. (a) Previous works involving radical cascade reactions for synthesis of indolines (b) Our work: a fast approach enabled by ultrasonic irradiation to construct novel functionalized indolines.

Table 1

Experimental conditions of the US-assisted reaction.

Reagent	Concentration
2-((N aryl)amino)methylacrylate 1a	50 mM
Volume of solution	3 mL
US frequency	20 kHz
Nominal electric power	400 W
Acoustic power	Formamide: 14.0 W N-Methylformamide: 10.7 W

washed with brine (100 mL), dried over MgSO_4 , and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent.

2.4. General procedure for preparation of methyl-2-((N-phenylpivalamido)methyl)acrylates 1a-1 k

Triethylamine (0.68 mL, 5.5 mmol) was added to a solution of methyl-2-((phenylamino)methyl)acrylate (0.96 g, 5 mmol) in DCM (20 mL). Then, the mixture was cooled to 0 °C and trimethylacetyl chloride

(0.68 mL, 5.5 mmol) was added dropwise. The reaction mixture was stirred for 16 h at room temperature. Then, DCM (30 mL) was added. The organic layer was washed with distilled water (30 mL) and brine (30 mL), dried over MgSO_4 , and filtered, and the solvent was removed under reduced pressure. The crude material was purified by flash column chromatography on silica gel using hexane/ethyl acetate as the eluent.

methyl 2-((N-phenylpivalamido)methyl)acrylate (1a): White solid, M.p.: 54–56 °C, yield 1.276 g, (54 %); TLC (85:15; Hexane/AcOEt); Rf = 0.25; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.04 (s, 9H), 3.68 (s, 3H), 4.50 (s, 2H), 5.75 (s, 1H), 6.32 (s, 1H), 7.15–7.23 (m, 2H), 7.28–7.41 (m, 3H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 29.5, 41.1, 51.8, 53.3, 126.3, 128.1, 129.0, 129.5, 135.8, 143.9, 166.6, 177.8 ppm; **MS** (EI^+) m/z (relative intensity) 275 (M^+ , 2), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3$ [$\text{M} + \text{Na}$] $^+$: 298.1419 Found ($\text{M} + 23$): 298.1424.

methyl 2-((N-(p-tolyl)pivalamido)methyl)acrylate (1b): White solid, M.p.: 94–96 °C, yield 0.360 g, (48 %); TLC (85:15; Hexane/AcOEt); Rf = 0.17; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.04 (s, 9H), 2.36 (s, 3H), 3.68 (s, 3H), 4.47–4.48 (m, 2H), 5.72–5.73 (m, 1H), 6.30–6.11 (m, 1H), 6.98–7.10 (m, 2H), 7.11–7.19 (m, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 21.1, 29.5, 41.0, 51.8, 53.3, 126.1, 129.2, 129.6, 135.8, 138.0, 141.2, 166.7, 177.9 ppm; **MS** (EI^+) m/z (relative intensity) 289 (M^+ , 5), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$: 290.1756 Found ($\text{M} + 1$): 290.1754.

methyl 2-((N-(m-tolyl)pivalamido)methyl)acrylate (1c): White solid, M.p.: 54–56 °C, yield 0.734 g (36 %); TLC (85:15; Hexane/AcOEt); Rf = 0.31; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.05 (s, 9H), 2.35 (s, 3H), 3.68 (s, 3H), 4.47–4.49 (m, 2H), 5.74–5.75 (m, 1H), 6.31–6.32 (m, 1H), 6.96–7.01 (m, 2H), 7.10–7.14 (m, 1H), 7.20–7.25 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 21.3, 29.5, 41.1, 51.8, 53.3, 125.9, 126.4, 128.8 (2C), 129.9, 135.7, 139.0, 143.8, 166.7, 177.8 ppm; **MS** (EI^+) m/z (relative intensity) 289 (M^+ , 4), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$: 290.1756 Found ($\text{M} + 1$): 290.1746.

methyl 2-((N-(4-methoxyphenyl)pivalamido)methyl)acrylate (1d): White solid, M.p.: 79–81 °C, yield 0.763 g (50 %); TLC (9:1; Hexane/AcOEt); Rf = 0.14; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.05 (s, 9H), 3.69 (s, 3H), 3.82 (s, 3H), 4.47–4.48 (m, 2H), 5.71–5.72 (m, 1H), 6.30–6.31 (m, 1H), 6.84–6.87 (m, 2H), 7.08–7.11 (m, 2H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 29.5, 40.9, 51.8, 53.4, 55.4, 114.0, 126.2, 130.6, 135.8, 136.5, 159.0, 166.7, 178.0. ppm; **MS** (EI^+) m/z (relative intensity) 305 (M^+ , 6), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$: 306.1705 Found ($\text{M} + 1$): 306.1695.

methyl 2-((N-(4-fluorophenyl)pivalamido)methyl)acrylate (1e): White solid, M.p.: 89–91 °C, yield 1.503 g (27 %); TLC (85:15; Hexane/AcOEt); Rf = 0.23; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.05 (s, 9H), 3.69 (s, 3H), 4.47–4.48 (m, 2H), 5.72–5.74 (m, 1H), 6.31–6.33 (m, 1H), 7.02–7.08 (m, 2H), 7.15–7.19 (m, 2H). ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 29.5, 41.0, 51.9, 53.2, 115.9 (d, $J_{\text{C,F}}$ = 22.6 Hz), 126.7, 131.2 (d, $J_{\text{C,F}}$ = 8.5 Hz), 135.7, 139.8 (d, $J_{\text{C,F}}$ = 3.2 Hz), 161.9 (d, $J_{\text{C,F}}$ = 248.6 Hz), 166.6, 177.9 ppm; **MS** (EI^+) m/z (relative intensity) 293 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{20}\text{FNO}_3$ [$\text{M} + \text{H}$] $^+$: 294.1506 Found ($\text{M} + 1$): 294.1507.

methyl 2-((N-(3-fluorophenyl)pivalamido)methyl)acrylate (1f): White solid, M.p.: 61–63 °C, yield 0.760 g (38%); TLC (85:15; Hexane/AcOEt); Rf = 0.54; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.06 (s, 9H), 3.69 (s, 3H), 4.48–4.49 (m, 2H), 5.73–5.74 (m, 1H), 6.32–6.33 (m, 1H), 6.93–6.97 (m, 1H), 6.99–7.07 (m, 2H), 7.31–7.36 (m, 1H) ppm; $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 29.5, 41.2, 51.9, 53.1, 115.3 (d, $J_{\text{C,F}}$ = 21.0 Hz), 116.8 (d, $J_{\text{C,F}}$ = 21.4 Hz), 125.3 (d, $J_{\text{C,F}}$ = 3.7 Hz), 126.6, 130.1 (d, $J_{\text{C,F}}$ = 9.1 Hz), 135.6, 145.4 (d, $J_{\text{C,F}}$ = 9.1 Hz), 162.6 (d, $J_{\text{C,F}}$ = 248.9 Hz), 166.5, 177.8 ppm; **MS** (EI^+) m/z (relative intensity) 293 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{20}\text{FNO}_3$ [$\text{M} + \text{H}$] $^+$: 294.1506 Found ($\text{M} + 1$): 294.1501.

methyl 2-((N-(4-chlorophenyl)pivalamido)methyl)acrylate (1g): White solid, M.p.: 121–124 °C, yield 0.937 g (60 %); TLC (9:1; Hexane/AcOEt); Rf = 0.14; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 1.05 (s, 9H),

3.69 (s, 3H), 4.47–4.48 (m, 2H), 5.72–5.73 (m, 1H), 6.31–6.328 (m, 1H), 7.12–7.15 (m, 2H), 7.32–7.35 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.5, 41.1, 51.9, 53.2, 126.8, 129.3, 130.8, 133.9, 135.6, 142.3, 166.5, 177.8 ppm; **MS** (EI^+) m/z (relative intensit) 309 (M^+ , 2), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{20}\text{ClNO}_3$ [$\text{M} + \text{H}$] $^+$: 310.1210 Found ($\text{M} + 1$): 310.1205.

methyl 2-((N-(4-bromophenyl)pivalamido)methyl)acrylate (1h): White solid, M.p.: 128–130 °C, yield 0.812 g (43 %); TLC (Hexanes-AcOEt: 90–10); Rf = 0.17; ^1H NMR (CDCl_3 , 500 MHz) δ 1.05 (s, 9H), 3.69 (s, 3H), 4.47–4.48 (m, 2H), 5.72–5.73 (m, 1H), 6.31–6.32 (m, 1H), 7.06–7.09 (m, 2H), 7.47–7.51 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.5, 41.1, 51.9, 53.1, 121.9, 126.8, 131.2, 132.3, 135.6, 142.9, 166.5, 177.7 ppm; **MS** (EI^+) m/z (relative intensity) 353 (M^+ , 3), 355 (3), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{20}\text{BrNO}_3$ [$\text{M} + \text{H}$] $^+$: 354.0705 Found ($\text{M} + 1$): 354.0687.

methyl 2-((N-(4-(trifluoromethyl)phenyl)pivalamido)methyl)acrylate (1i): White solid, M.p.: 90–92 °C, yield 0.532 g (31 %); TLC (9:1; Hexane/AcOEt); Rf = 0.17; ^1H NMR (CDCl_3 , 500 MHz) δ 1.06 (s, 9H), 3.69 (s, 3H), 4.50–4.51 (m, 2H), 5.76–5.77 (m, 1H), 6.33–6.35 (m, 1H), 7.33–7.35 (m, 2H), 7.63–7.65 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.5, 41.3, 51.9, 53.1, 123.7 (q, $J_{\text{C,F}}$ = 247.4 Hz), 126.3 (q, $J_{\text{C,F}}$ = 3.6 Hz), 127.0, 129.8, 130.2 (q, $J_{\text{C,F}}$ = 32.9 Hz), 135.5, 147.1, 166.5, 177.8 ppm; **MS** (EI^+) m/z (relative intensity) 343 (M^+ , 2), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{20}\text{F}_3\text{NO}_3$ [$\text{M} + \text{H}$] $^+$: 344.1474 Found ($\text{M} + 1$): 344.1476.

methyl 4-(N-(2-(methoxycarbonyl)allyl)pivalamido)benzoate (1j): White solid, M.p.: 95–97 °C, yield 0.885 g (53 %); TLC (9:1; Hexane/AcOEt); Rf = 0.21; ^1H NMR (CDCl_3 , 500 MHz) δ 1.05 (s, 9H), 3.67 (s, 3H), 3.93 (s, 3H), 4.51–4.52 (m, 2H), 5.75–5.76 (m, 1H), 6.33–6.34 (m, 1H), 7.26–7.29 (m, 2H), 8.03–8.06 (m, 2H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.5, 41.3, 51.9, 52.4, 53.0, 126.9, 129.3, 129.7, 130.5, 135.6, 148.1, 166.2, 166.5, 177.8 ppm; **MS** (EI^+) m/z (relative intensity) 333 (M^+ , 3), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$: 334.1655 Found ($\text{M} + 1$): 334.1633.

methyl 2-((N-([1,1'-biphenyl]-2-yl)pivalamido)methyl)acrylate (1k): White solid, M.p.: 93–95 °C, yield 0.475 g (31%); TLC (85:15; Hexane/AcOEt); Rf = 0.26; ^1H NMR (CDCl_3 , 500 MHz) δ 1.08 (s, 9H), 3.53 (d, J = 16.0 Hz, 1H), 3.63 (s, 3H), 4.79 (d, J = 16.0 Hz, 1H), 5.63 (s, 1H), 6.21 (s, 1H), 7.17 (d, J = 7.9 Hz, 1H), 7.30 (td, J = 7.5, 1.9 Hz, 1H), 7.35–7.45 (m, 7H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 29.50, 41.25, 51.93, 53.09, 122.57, 124.74, 126.25, 126.27, 126.30, 126.33, 126.99, 129.81, 130.06, 130.32, 135.51, 147.14, 166.44, 177.82 ppm; **MS** (EI^+) m/z (relative intensity) 351 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{22}\text{H}_{25}\text{NO}_3$ [$\text{M} + \text{H}$] $^+$: 352.1913 Found ($\text{M} + 1$): 352.1901.

2.5. General procedure for the ultrasound-assisted reactions with formamides

A glass flask ($\varnothing$ = 2.5 cm; 15 mL) was charged with formamide (3 mL), 2-((N-aryl)amino)methyl acrylates (**1a-k**) (0.15 mmol) and sulfuric acid 98% (7.9 μL , 0.15 mmol). To this mixture were added a freshly prepared aqueous solution of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (15 μL , 100 mM) and aqueous hydrogen peroxide 30 % (30.6 μL , 0.3 mmol). The reaction mixture was irradiated for 60 s by an ultrasonic horn (Branson, 20 kHz, amplitude 60%, $\varnothing$ = 12.7 mm) with the probe inserted in the center of the solution 0.2 mm from the bottom of the glass flask. The mixture was sonicated continuously or in pulsed mode (probe ON/OFF 1 s).

For GCMS analysis, a sample of the crude reaction mixture (500 μL) was removed and quenched with 500 μL of saturated aqueous solution of NaHCO_3 and extracted with CHCl_3 (2 $\times$ 0.5 mL). The organic layer was removed and dried over MgSO_4 , filtered in a glass Pasteur pipet containing cotton at the bottom and analyzed by TLC and GC/MS.

To the remaining reaction mixture (2.5 mL), 1 eq of NaHCO_3 (10.5 mg, 0.125 mmol) was added. A 2.0 mL sample was transferred to a round flask, and the formamide was removed by distillation under vacuum. The crude reaction material was purified by flash column

chromatography on silica gel using chloroform/methanol as the eluent.

Note: For ultrasound-assisted reactions with compounds **1i**, **jk**, and **1m**, 30% of *t*-BuOH was added as a cosolvent.

methyl 3-(2-amino-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (2a): pale yellow solid, M.p.: 174–177 °C, yield 30.8 mg (97 %); TLC (95:5; $\text{CHCl}_3/\text{MeOH}$); Rf = 0.28; ^1H NMR (CDCl_3 , 500 MHz) δ 1.40 (s, 9H), 2.57 (d, J = 16.1 Hz, 1H), 3.34 (d, J = 16.1 Hz, 1H), 3.72 (s, 3H), 4.26 (d, J = 11.3 Hz, 1H), 5.09 (d, J = 11.3 Hz, 1H), 5.51 (br s, 1H), 5.63 (br s, 1H), 7.04 (dt, J = 7.4 Hz, 1.3 Hz, 1H), 7.22–7.29 (m, 2H), 8.23 (d, J = 8.3 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.5, 40.3, 43.0, 52.9, 52.9, 57.6, 119.0, 123.0, 124.0, 129.5, 131.1, 144.2, 171.9, 172.6, 176.8 ppm; **MS** (EI^+) m/z (relative intensity) 318 (M^+ , 5), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{22}\text{N}_2\text{O}_4$ [$\text{M} + \text{Na}$] $^+$: 341.1477 Found ($\text{M} + 23$): 341.1477.

methyl 3-(2-amino-2-oxoethyl)-5-methyl-1-pivaloylindoline-3-carboxylate (2b): white solid, M.p.: 199–202 °C, yield 33.1 mg (99 %); TLC (95:5; $\text{CHCl}_3/\text{MeOH}$); Rf = 0.30; ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.30 (s, 3H), 2.55 (d, J = 16.1 Hz, 1H), 3.34 (d, J = 16.1 Hz, 1H), 3.72 (s, 3H), 4.24 (d, J = 11.3 Hz, 1H), 5.06 (d, J = 11.3 Hz, 1H), 5.46 (br s, 1H), 5.59 (br s, 1H), 7.02 (s, 1H), 7.07 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.3 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.0, 27.5, 40.2, 43.0, 52.9, 52.9, 57.7, 118.7, 123.3, 130.0, 131.1, 133.7, 141.9, 171.9, 172.7, 176.5 ppm; **MS** (EI^+) m/z (relative intensity) 332 (M^+ , 3), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4$ [$\text{M} + \text{Na}$] $^+$: 355.1634 Found ($\text{M} + 23$): 355.1628.

methyl 3-(2-amino-2-oxoethyl)-6-methyl-1-pivaloylindoline-3-carboxylate (2c): white solid, M.p.: 159–161 °C, yield 28.5 mg (86%); TLC (95:5; $\text{CHCl}_3/\text{MeOH}$); Rf = 0.48; Major isomer: ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.33 (s, 3H), 2.44 (d, J = 15.8 Hz, 1H), 2.54 (d, J = 16.0 Hz, 1H), 3.70 (s, 3H), 4.23 (d, J = 11.3 Hz, 1H), 5.08 (d, J = 11.3 Hz, 1H), 5.65 (br s, 1H), 5.72 (br s, 1H), 6.86 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 8.11 (s, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 18.4, 27.5, 40.3, 43.1, 52.6, 52.9, 57.9, 119.6, 122.5, 126.8, 128.3, 139.7, 144.2, 172.0, 172.7, 176.6; **MS** (EI^+) m/z (relative intensity) 332 (M^+ , 3), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 333.1814 Found ($\text{M} + 1$): 333.1798.

Minor isomer: ^1H NMR (CDCl_3 , 500 MHz) δ 1.38 (s, 9H), 2.27 (s, 3H), 3.28–3.31 (m, 2H), 3.73 (s, 3H), 4.71–4.76 (m, 2H), 5.49–5.52 (m, 2H), 6.81 (d, J = 7.6 Hz, 1H), 7.16 (t, J = 7.9 Hz, 1H), 8.12 (s, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 21.7, 27.6, 39.3, 40.3, 52.8, 53.7, 57.8, 116.8, 124.7, 129.1, 129.7, 133.8, 144.7, 172.3, 173.4, 176.8; **MS** (EI^+) m/z (relative intensity) 332 (M^+ , 3), 57 (100).

methyl 3-(2-amino-2-oxoethyl)-5-methoxy-1-pivaloylindoline-3-carboxylate (2d): white solid, M.p.: 205–208 °C, yield 34.0 mg (97 %); TLC (95:5; $\text{CHCl}_3/\text{MeOH}$); Rf = 0.36; ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.56 (d, J = 16.1 Hz, 1H), 3.31 (d, J = 16.1 Hz, 1H), 3.73 (s, 3H), 3.78 (s, 3H), 4.26 (d, J = 11.3 Hz, 1H), 5.06 (d, J = 11.3 Hz, 1H), 5.42 (br s, 1H), 5.58 (br s, 1H), 6.707–6.87 (m, 2H), 8.17 (dd, J = 8.5, 0.8 Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.6, 40.0, 42.9, 52.9, 53.0, 55.7, 57.7, 109.2, 113.8, 119.7, 132.5, 137.8, 156.4, 171.7, 172.4, 176.2; **MS** (EI^+) m/z (relative intensity) 348 (M^+ , 5), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{24}\text{N}_2\text{O}_5$ [$\text{M} + \text{Na}$] $^+$: 371.1583 Found ($\text{M} + 23$): 371.1586.

methyl 3-(2-amino-2-oxoethyl)-5-fluoro-1-pivaloylindoline-3-carboxylate (2e): white solid, M.p.: 180–183 °C, yield 33.4 mg (99%); TLC (95:5; $\text{CHCl}_3/\text{MeOH}$); Rf = 0.29; ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.59 (d, J = 16.2 Hz, 1H), 3.30 (d, J = 16.1 Hz, 1H), 3.74 (s, 3H), 4.27 (d, J = 11.3 Hz, 1H), 5.09 (d, J = 11.3 Hz, 1H), 5.52 (br s, 1H), 5.64 (br s, 1H), 6.86–7.05 (m, 2H), 8.17–8.24 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 27.5, 40.1, 42.8, 52.8, 53.1, 57.8, 110.3 (d, $J_{\text{C,F}}$ = 24.6 Hz), 115.9 (d, $J_{\text{C,F}}$ = 22.5 Hz), 120.0 (d, $J_{\text{C,F}}$ = 7.8 Hz), 132.8 (d, $J_{\text{C,F}}$ = 7.8 Hz), 140.3 (d, $J_{\text{C,F}}$ = 2.3 Hz), 159.3 (d, $J_{\text{C,F}}$ = 243.7 Hz), 171.5, 172.1, 176.6; **MS** (EI^+) m/z (relative intensity) 336 (M^+ , 3), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{21}\text{FN}_2\text{O}_4$ [$\text{M} + \text{Na}$] $^+$: 359.1383 Found ($\text{M} + 23$): 359.1380.

methyl 3-(2-amino-2-oxoethyl)-6-fluoro-1-pivaloylindoline-3-carboxylate (2f): white solid, M.p.: 152–154 °C, yield 39.1 mg (93%);

TLC (95:5; CHCl₃/MeOH); Rf = 0.51; Major isomer: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H)*, 2.57 (d, *J* = 16.2 Hz, 1H), 3.34 (d, *J* = 16.2 Hz, 1H), 3.72 (s, 3H), 4.26 (d, *J* = 11.3 Hz, 1H), 5.13 (d, *J* = 11.3 Hz, 1H), 5.65 (br s, 1H), 5.73 (br s, 1H), 6.70–6.75 (m, 1H)*, 7.13–7.17 (m, 1H), 7.99–8.03 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.4, 40.1, 40.3, 52.3, 53.0*, 58.3, 107.1 (d, *J*_{C,F} = 29.4 Hz), 111.1 (d, *J*_{C,F} = 20.0 Hz), 114.9 (d, *J*_{C,F} = 3.1 Hz), 126.5 (d, *J*_{C,F} = 2.5 Hz), 145.6 (d, *J*_{C,F} = 12.7 Hz), 159.0 (d, *J*_{C,F} = 245.5 Hz), 171.8, 172.5, 177.0; MS (EI⁺) *m/z* (relative intensity) 336 (M⁺, 1), 57 (100); HRMS (ESI-TOF) calcd for C₁₇H₂₁FN₂O₄ [M + Na]⁺: 359.1383 Found (M + 23): 359.1383.

Minor isomer: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H)*, 2.62 (d, *J* = 16.0 Hz, 1H), 3.61 (d, *J* = 16.1 Hz, 1H), 3.72 (s, 3H), 4.40 (d, *J* = 11.2 Hz, 1H), 5.07 (d, *J* = 11.2 Hz, 1H), 5.55–5.57 (m, 2H), 6.71–6.75 (m, 1H)*, 7.21–7.53 (m, 1H), 8.04–8.06 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.5, 40.4, 43.1, 52.2 (d, *J* = 2.6 Hz), 53.0*, 58.6, 110.6 (d, *J*_{C,F} = 23.3 Hz), 117.4 (d, *J*_{C,F} = 17.6 Hz), 123.5 (d, *J*_{C,F} = 10.4 Hz), 131.2 (d, *J*_{C,F} = 8.5 Hz), 146.7 (d, *J*_{C,F} = 6.6 Hz), 163.5 (d, *J*_{C,F} = 242.7 Hz), 172.1, 176.4, 176.8; MS (EI⁺) *m/z* (relative intensity) 336 (M⁺, 1), 57 (100).

* Superimposed in the respective spectrum

methyl 3-(2-amino-2-oxoethyl)-5-chloro-1-pivaloylindoline-3-carboxylate (2 g): white solid, M.p.: 186–189 °C yield 35.2 mg (99%); TLC (95:5; CHCl₃/MeOH); Rf = 0.30; ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.58 (d, *J* = 16.2 Hz, 1H), 3.32 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 4.26 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 11.4 Hz, 1H), 5.47 (br s, 1H), 5.58 (br s, 1H), 7.17–7.26 (m, 2H), 8.18 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.5, 40.3, 42.9, 52.7, 53.2, 57.8, 119.9, 123.2, 128.8, 129.5, 132.8, 142.9, 171.4, 172.0, 176.8; MS (EI⁺) *m/z* (relative intensity) 352 (M⁺, 1), 57 (100); HRMS (ESI-TOF) calcd for C₁₇H₂₁ClN₂O₄ [M + Na]⁺: 375.1088 Found (M + 23): 375.1088.

methyl 3-(2-amino-2-oxoethyl)-5-bromo-1-pivaloylindoline-3-carboxylate (2 h): white solid, M.p.: 203–206 °C, yield 41.6 mg (69%); TLC (98:2; CHCl₃/MeOH); Rf = 0.34; ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.58 (d, *J* = 16.1 Hz, 1H), 3.32 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 4.25 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 11.3 Hz, 1H), 5.47 (br s, 1H), 5.58 (br s, 1H), 7.30–7.43 (m, 2H), 8.13 (d, *J* = 8.7 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.5, 40.3, 43.0, 52.7, 53.2, 57.8, 116.1, 120.3, 126.1, 132.4, 133.1, 143.4, 171.4, 172.0, 176.8; MS (EI⁺) *m/z* (relative intensity) 396 (M⁺, 1), 398 (1), 57 (100); HRMS (ESI-TOF) calcd for C₁₇H₂₁BrN₂O₄ [M + Na]⁺: 419.0582 Found (M + 23): 419.0584.

methyl 3-(2-amino-2-oxoethyl)-1-pivaloyl-5-(trifluoromethyl)indoline-3-carboxylate (2i): pale yellow solid, M.p.: 156–159 °C, yield 41.6 mg (72 %); TLC (95:5; CHCl₃/MeOH); Rf = 0.56; ¹H NMR (CDCl₃, 500 MHz) δ 1.41 (s, 9H), 2.62 (d, *J* = 16.2 Hz, 1H), 3.39 (d, *J* = 16.2 Hz, 1H), 3.75 (s, 3H), 4.30 (d, *J* = 11.4 Hz, 1H), 5.18 (d, *J* = 11.3 Hz, 1H), 5.45 (br s, 1H), 5.55 (br s, 1H), 7.47 (s, 1H), 7.51–7.60 (m, 1H), 8.34 (d, *J* = 8.6 Hz, 1H). ¹³C NMR (CDCl₃, 125 MHz) δ 27.4, 40.4, 43.1, 52.6, 53.2, 58.0, 118.8, 120.1 (q, *J*_{C,F} = 3.9 Hz), 124.0 (q, *J*_{C,F} = 270 Hz), 125.8 (q, *J*_{C,F} = 32.6 Hz), 127.1 (q, *J*_{C,F} = 3.5 Hz), 131.6, 147.1, 171.3, 172.0, 177.2 ppm; MS (EI⁺) *m/z* (relative intensity) 386 (M⁺, 2), 57 (100); HRMS (ESI-TOF) calcd for C₁₇H₂₁F₃N₂O₄ [M + Na]⁺: 409.1351 Found (M + 23): 409.1351.

dimethyl 3-(2-amino-2-oxoethyl)-1-pivaloylindoline-3,5-dicarboxylate (2j): white solid, M.p.: 104–106 °C, yield 21.8 mg (75 %); TLC (95:5; CHCl₃/MeOH); Rf = 0.46; ¹H NMR (CDCl₃, 500 MHz) δ 1.41 (s, 9H), 2.60 (d, *J* = 16.2 Hz, 1H), 3.44 (d, *J* = 16.3 Hz, 1H), 3.73 (s, 3H), 3.89 (s, 3H), 4.28 (d, *J* = 11.3 Hz, 1H), 5.19 (d, *J* = 11.3 Hz, 1H), 5.54 (br s, 1H), 5.67 (br s, 1H), 7.91 (d, *J* = 1.8 Hz, 1H), 7.97–8.00 (m, 1H), 8.28 (d, *J* = 8.6 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.4, 40.5, 43.0, 52.1, 52.5, 53.2, 58.3, 118.2, 124.5, 125.5, 131.3, 131.8, 148.2, 166.5, 171.6, 172.2, 177.3; MS (EI⁺) *m/z* (relative intensity) 376 (M⁺, 2), 57 (100); HRMS (ESI-TOF) calcd for C₁₉H₂₄N₂O₆ [M + Na]⁺: 399.1532 Found (M + 23): 399.1530.

methyl 3-(2-amino-2-oxoethyl)-7-phenyl-1-pivaloylindoline-3-carboxylate (2 k): white solid, M.p.: 227–230 °C, yield 21.3 mg (36 %); TLC (95:5; CHCl₃/MeOH); Rf = 0.43; ¹H NMR (CDCl₃, 500 MHz) δ 1.13 (s, 9H), 2.39 (d, *J* = 16.4 Hz, 1H), 3.16 (d, *J* = 16.4 Hz, 1H), 3.73 (s, 3H),

4.25 (d, *J* = 11.3 Hz, 1H), 4.91 (d, *J* = 11.3 Hz, 1H), 5.34 (br s, 1H), 5.88 (br s, 1H), 7.15–7.25 (m, 3H), 7.28–7.31 (m, 1H), 7.32–7.38 (m, 2H), 7.37–7.43 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 27.9, 39.9, 41.6, 52.8, 54.1, 58.1, 121.8, 125.6, 126.6, 127.0, 128.4, 130.3, 133.7, 135.5, 140.5, 141.7, 172.0, 172.6, 178.4; MS (EI⁺) *m/z* (relative intensity) 394 (M⁺, 1), 57 (100); HRMS (ESI-TOF) calcd for C₂₃H₂₆N₂O₄ [M + Na]⁺: 417.1790 Found (M + 23): 417.1791.

methyl 3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3a): pale yellow solid, M.p.: 138–140 °C, yield 22.5 mg (68 %); TLC (99:1; CHCl₃/MeOH); Rf = 0.16; ¹H NMR (CDCl₃, 500 MHz) δ 1.40 (s, 9H), 2.51 (d, *J* = 15.6 Hz, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 3.27 (d, *J* = 15.7 Hz, 1H), 3.71 (s, 3H), 4.28 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 11.3 Hz, 1H), 5.54–5.55 (br m, 1H), 7.02–7.05 (m, 1H), 7.22–7.29 (m, 2H), 8.23–8.25 (m, 1H). ¹³C NMR (CDCl₃, 125 MHz) δ 26.4, 27.5, 40.3, 43.6, 52.9, 53.1, 57.7, 119.0, 122.9, 123.9, 129.4, 131.3, 144.2, 170.3, 172.7, 176.8; MS (EI⁺) *m/z* (relative intensity) 332 (M⁺, 1), 57 (100); HRMS (ESI-TOF) calcd for C₁₈H₂₄N₂O₄ [M + Na]⁺: 355.1634 Found (M + 23): 355.1631.

methyl 5-methoxy-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3b): pale yellow solid, M.p.: 92–95 °C, yield 20.5 mg (57 %); TLC (99:1; CHCl₃/MeOH); Rf = 0.10; ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.50 (d, *J* = 15.7 Hz, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 3.24 (d, *J* = 15.7 Hz, 1H), 3.71 (s, 3H), 3.77 (s, 3H), 4.27 (d, *J* = 11.3 Hz, 1H), 5.07 (d, *J* = 11.3 Hz, 1H), 5.59–5.60 (br m, 1H), 6.78–6.80 (m, 2H), 8.11–8.17 (m, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 26.4, 27.6, 40.0, 43.5, 52.9, 53.1, 55.7, 57.7, 109.2, 113.7, 119.6, 132.7, 137.8, 156.4, 170.2, 172.5, 176.2; MS (EI⁺) *m/z* (relative intensity) 362 (M⁺, 4), 57 (100); HRMS (ESI-TOF) calcd for C₁₉H₂₆N₂O₅ [M + Na]⁺: 385.1739 Found (M + 23): 385.1743.

methyl 5-methyl-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3c): white solid, M.p.: 119–122 °C, yield 22.5 mg (65 %); TLC (99:1; CHCl₃/MeOH); Rf = 0.16; ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.29 (s, 3H), 2.48 (d, *J* = 15.6 Hz, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 3.27 (d, *J* = 15.6 Hz, 1H), 3.71 (s, 3H), 4.25 (d, *J* = 11.3 Hz, 1H), 5.08 (d, *J* = 11.3 Hz, 1H), 5.64–5.65 (br m, 1H), 7.02 (s, 1H), 7.06 (d, *J* = 8.3 Hz, 1H), 8.10 (d, *J* = 8.3 Hz, 1H); ¹³C NMR (CDCl₃, 125 MHz) δ 21.0, 27.5, 40.2, 43.0, 52.9, 52.9, 57.7, 77.3, 118.7, 123.3, 130.0, 131.1, 133.7, 141.9, 171.9, 172.7, 176.5; MS (EI⁺) *m/z* (relative intensity) 346 (M⁺, 2), 57 (100); HRMS (ESI-TOF) calcd for C₁₉H₂₆N₂O₄ [M + Na]⁺: 369.1790 Found (M + 23): 369.1783.

methyl 6-methyl-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3d): white solid, M.p.: 69–71 °C, yield 23.9 mg (69 %); TLC (99:1; CHCl₃/MeOH); Rf = 0.28; ¹H NMR (CDCl₃, 500 MHz) δ 1.40 (s, 9H), 2.33 (s, 3H), 2.48 (d, *J* = 15.6 Hz, 1H), 2.81–2.83, (m, 3H), 3.26 (d, *J* = 15.7 Hz, 1H), 3.72 (s, 3H), 4.25 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 11.4 Hz, 1H), 5.60–5.61 (br m, 1H), 6.81 (d, *J* = 7.5 Hz, 1H), 7.10 (d, *J* = 7.7 Hz, 1H), 8.11–8.14 (m, 1H)* ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 18.4, 26.4, 27.5, 40.3, 43.7, 52.8, 54.0, 58.0, 116.8, 124.7, 126.7, 129.9, 133.8, 144.3, 170.6, 173.5, 176.8 ppm; MS (EI⁺) *m/z* (relative intensity) 346 (M⁺, 1), 57 (100); HRMS (ESI-TOF) calcd for C₁₉H₂₆N₂O₄ [M + Na]⁺: 369.1790 Found (M + 23): 369.1784.

methyl 4-methyl-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate: ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.26 (s, 3H), 2.40 (d, *J* = 15.3 Hz, 1H), 2.81–2.81, (m, 3H), 3.22 (d, *J* = 15.3 Hz, 1H), 3.69 (s, 3H), 4.73–4.78 (m, 2H), 5.66–5.67 (br m, 1H), 6.85 (d, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.9 Hz, 1H) 8.12–8.13 (m, 1H)* ppm; ¹³C NMR (CDCl₃, 125 MHz) δ 21.7, 26.4, 27.6, 40.0, 40.3, 52.8, 57.8, 58.1, 119.6, 122.5, 128.5, 129.0, 139.7, 144.7, 170.3, 172.8, 176.7 ppm; MS (EI⁺) *m/z* (relative intensity) 346 (M⁺, 1), 57 (100).

*superimposed in the corresponding spectrum

methyl 5-fluoro-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3e): white solid, M.p.: 145–147 °C, yield 24.6 mg (70 %); TLC (99:1; CHCl₃/MeOH); Rf = 0.11; ¹H NMR (CDCl₃, 500 MHz) δ 1.39 (s, 9H), 2.52 (d, *J* = 15.7 Hz, 1H), 2.82 (d, *J* = 4.8 Hz, 3H), 3.22 (d, *J* = 15.7 Hz, 1H), 3.73 (s, 3H), 4.28 (d, *J* = 11.3 Hz, 1H), 5.10 (d, *J* = 11.4 Hz, 1H), 5.74–5.75 (br m, 1H), 6.90–6.99 (m, 2H), 8.15–8.25

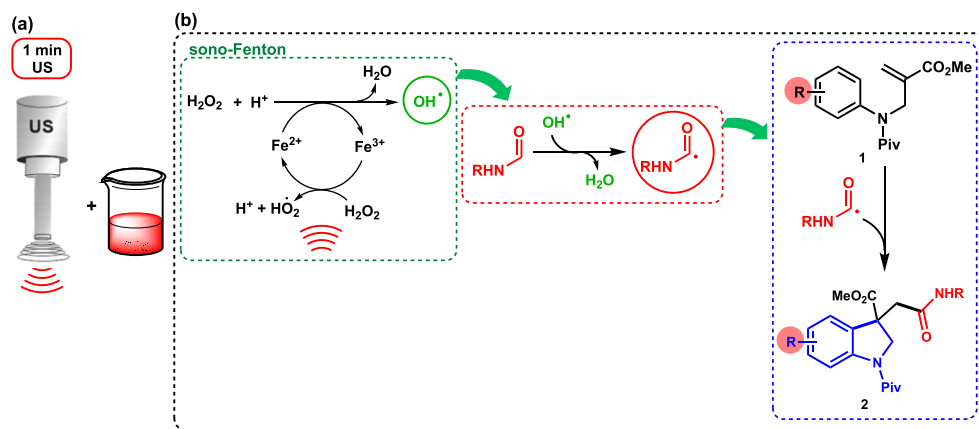


Fig. 3. Combining ultrasound and the Fenton reaction in formamide for fast indoline construction. (a) Experimental setup; (b) Sequence of radical reactions: hydroxyl radical generation, carbamoyl radical generation and indoline formation.

(m, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.4, 27.5, 40.1, 43.4, 53.0, 53.0, 57.9, 110.3 (d, $J_{\text{C,F}}$ = 24.7 Hz), 115.8 (d, $J_{\text{C,F}}$ = 22.5 Hz), 119.9 (d, $J_{\text{C,F}}$ = 7.9 Hz), 133.0 (d, $J_{\text{C,F}}$ = 8.0 Hz), 140.2 (d, $J_{\text{C,F}}$ = 2.1 Hz), 159.2 (d, $J_{\text{C,F}}$ = 243.4 Hz), 169.9, 172.2, 176.6 ppm; **MS** (EI^+) m/z (relative intensity) 350 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_2\text{O}_4$ [$\text{M} + \text{Na}$] $^+$: 373.1540 Found ($\text{M} + 23$): 373.1539.

methyl 6-fluoro-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3f): white solid, M.p.: 62–64 °C, yield 24.8 mg (71 %); TLC (99:1; $\text{CHCl}_3/\text{MeOH}$); R_f = 0.43; ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.51 (d, J = 15.7 Hz, 1H), 2.81* (d, J = 4.8 Hz, 3H), 3.26 (d, J = 15.7 Hz, 1H), 3.71 (s, 3H), 4.27 (d, J = 11.3 Hz, 1H), 5.15 (d, J = 11.3 Hz, 1H), 5.77 (br s, 1H), 6.69–6.73 (m, 1H)*, 7.13–7.15 (m, 1H), 7.99–8.01 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.3*, 27.4, 40.3, 40.7 (d, J = 2.5 Hz), 52.4, 52.9*, 58.4, 107.0 (d, $J_{\text{C,F}}$ = 29.5 Hz), 111.0 (d, $J_{\text{C,F}}$ = 20.0 Hz), 114.9 (d, $J_{\text{C,F}}$ = 3.1 Hz), 126.7 (d, $J_{\text{C,F}}$ = 2.4 Hz), 145.5 (d, $J_{\text{C,F}}$ = 12.8 Hz), 163.4 (d, $J_{\text{C,F}}$ = 242.8 Hz), 170.1, 172.5, 175.0; **MS** (EI^+) m/z (relative intensity) 350 (M^+ , 2), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{FN}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 351.1720 Found ($\text{M} + 1$): 351.1701.

Minor isomer: ^1H NMR (CDCl_3 , 500 MHz) δ 1.40 (s, 9H), 2.57 (d, J = 15.6 Hz, 1H), 2.81* (d, J = 4.8 Hz, 3H), 3.54 (d, J = 15.6 Hz, 1H), 3.70 (s, 3H), 4.44 (d, J = 11.2 Hz, 1H), 5.09 (d, J = 11.2 Hz, 1H), 5.82 (br s, 1H), 6.69–6.73 (m, 1H)*, 7.20–7.24 (m, 1H), 8.03–8.05 (m, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.3*, 27.4, 40.4, 43.7, 52.4 (d, $J_{\text{C,F}}$ = 2.2 Hz), 52.9*, 58.7, 110.5 (d, $J_{\text{C,F}}$ = 23.3 Hz), 117.6 (d, $J_{\text{C,F}}$ = 17.4 Hz), 123.6 (d, $J_{\text{C,F}}$ = 10.3 Hz), 131.0 (d, $J_{\text{C,F}}$ = 8.4 Hz), 146.8 (d, $J_{\text{C,F}}$ = 6.6 Hz), 159.1 (d, $J_{\text{C,F}}$ = 245.6 Hz), 170.4, 172.1, 176.8; **MS** (EI^+) m/z (relative intensity) 350 (M^+ , 2), 57 (100).

*superimposed in the corresponding spectrum

methyl 5-chloro-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3 g): white solid, M.p.: 138–140 °C, yield 23.9 mg (65 %); TLC (99:1; $\text{CHCl}_3/\text{MeOH}$); R_f = 0.13; ^1H NMR (CDCl_3 , 500 MHz) 1.39 (s, 9H), 2.52 (d, J = 15.6 Hz, 1H), 2.82 (d, J = 4.8 Hz, 3H), 3.24 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 4.28 (d, J = 11.4 Hz, 1H), 5.12 (d, J = 11.4 Hz, 1H), 5.58–5.59 (br m, 1H), 7.18–7.25 (m, 2H), 8.18 (d, J = 8.7 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.4, 27.4, 40.3, 43.5, 52.9, 53.1, 57.9, 119.9, 123.2, 128.7, 129.4, 133.0, 142.9, 169.9, 172.1, 176.8 ppm; **MS** (EI^+) m/z (relative intensity) 366 (M^+ , 2), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{ClN}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 367.1425 Found ($\text{M} + 1$): 367.1420.

methyl 5-bromo-3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylate (3 h): white solid, M.p.: 133–135 °C, yield 22.0 mg (53 %); TLC (99:1; $\text{CHCl}_3/\text{MeOH}$); R_f = 0.12; ^1H NMR (CDCl_3 , 500 MHz) δ 1.39 (s, 9H), 2.51 (d, J = 15.7 Hz, 1H), 2.82 (d, J = 4.9 Hz, 3H), 3.24 (d, J = 15.6 Hz, 1H), 3.73 (s, 3H), 4.27 (d, J = 11.4 Hz, 1H), 5.11 (d, J = 11.4 Hz, 1H), 5.60–5.61 (br m, 1H), 7.34–7.38 (m, 2H), 8.13 (d, J = 8.7 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) δ 26.4, 27.4, 40.3, 43.5,

52.9, 53.1, 57.8, 116.1, 120.3, 126.1, 132.3, 133.3, 143.4, 169.9, 172.1, 176.8 ppm; **MS** (EI^+) m/z (relative intensity) 378 (M^+ , 1), 380 (1), 57 (100). **HRMS** (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{23}\text{BrN}_2\text{O}_4$ [$\text{M} + \text{Na}$] $^+$: 433.0739 Found ($\text{M} + 23$): 433.0740.

methyl 3-(2-(methylamino)-2-oxoethyl)-1-pivaloyl-5-(trifluoromethyl)indoline-3-carboxylate (3i): white solid, M.p.: 173–176 °C, yield 24.1 mg (60 %); TLC (99:1; $\text{CHCl}_3/\text{MeOH}$); R_f = 0.11; ^1H NMR (CDCl_3 , 500 MHz) δ 1.41 (s, 9H), 2.55 (d, J = 15.7 Hz, 1H), 2.83–2.84 (m, 3H), 3.31 (d, J = 15.7 Hz, 1H), 3.74 (s, 3H), 4.32 (d, J = 11.3 Hz, 1H), 5.19 (d, J = 11.3 Hz, 1H), 5.64–5.65 (br m, 1H), 7.46 (s, 1H), 7.53 (d, J = 8.6 Hz, 1H), 8.33 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR (CDCl_3 , 125 MHz) 26.4, 27.4, 40.5, 43.6, 52.8, 53.2, 58.1, 118.7, 120.2 (q, $J_{\text{C,F}}$ = 3.73 Hz), 124.0 (q, $J_{\text{C,F}}$ = 270 Hz), 125.8 (q, $J_{\text{C,F}}$ = 32.5 Hz), 127.1 (q, $J_{\text{C,F}}$ = 3.87 Hz), 131.8, 147.1, 169.8, 172.1, 177.1 ppm; **MS** (EI^+) m/z (relative intensity) 400 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{23}\text{F}_3\text{N}_2\text{O}_4$ [$\text{M} + \text{H}$] $^+$: 401.1688 Found ($\text{M} + 1$): 401.1688.

dimethyl 3-(2-(methylamino)-2-oxoethyl)-1-pivaloylindoline-3,5-dicarboxylate (3j): white solid, M.p.: 72–75 °C, yield 24.0 mg (61 %); TLC (99:1; $\text{CHCl}_3/\text{MeOH}$); R_f = 0.22; ^1H NMR (CDCl_3 , 500 MHz) δ 1.41 (s, 9H), 2.54 (d, J = 15.7 Hz, 1H), 2.83 (d, J = 4.8 Hz, 3H), 3.35 (d, J = 15.7 Hz, 1H), 3.72 (s, 3H), 3.89 (s, 3H), 4.31 (d, J = 11.3 Hz, 1H), 5.20 (d, J = 11.3 Hz, 1H), 5.60–5.61 (br m, 1H), 7.90 (d, J = 1.8 Hz, 1H), 7.98 (dd, J = 8.6, 1.8 Hz, 1H), 8.29 (d, J = 8.6 Hz, 1H); ^{13}C NMR (CDCl_3 , 125 MHz) 26.4, 27.4, 40.5, 43.6, 52.1, 52.7, 53.1, 58.3, 118.2, 124.6, 125.5, 131.5, 131.8, 148.3, 166.5, 170.0, 172.3, 177.3; **MS** (EI^+) m/z (relative intensity) 390 (M^+ , 1), 57 (100); **HRMS** (ESI-TOF) calcd for $\text{C}_{20}\text{H}_{26}\text{F}_3\text{N}_2\text{O}_6$ [$\text{M} + \text{Na}$] $^+$: 413.1689 Found ($\text{M} + 23$): 401.1687.

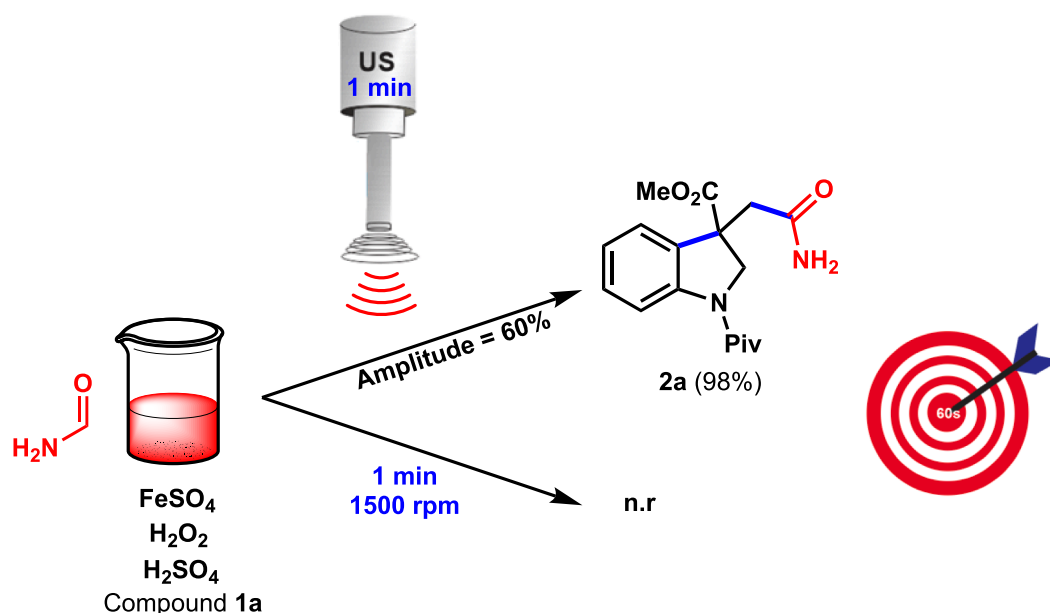
2.6. General procedure for the reactions with formamide under magnetic stirring

A glass flask (7 mL) was charged with formamide (3 mL), 2-(((N-aryl)amino)methyl)acrylate (**1a**) (0.15 mmol, 41.3 mg) and sulfuric acid 98% (7.9 μL , 0.15 mmol). To this mixture were added a freshly prepared aqueous solution of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (15 μL , 100 mM) and aqueous hydrogen peroxide 30% (30.6 μL , 0.3 mmol). The reaction mixture was stirred (1500 rpm) for 1 min at room temperature (IKA @ C-MAG- HS 4). The procedure for extraction and analysis was the same as described in section 2.5.

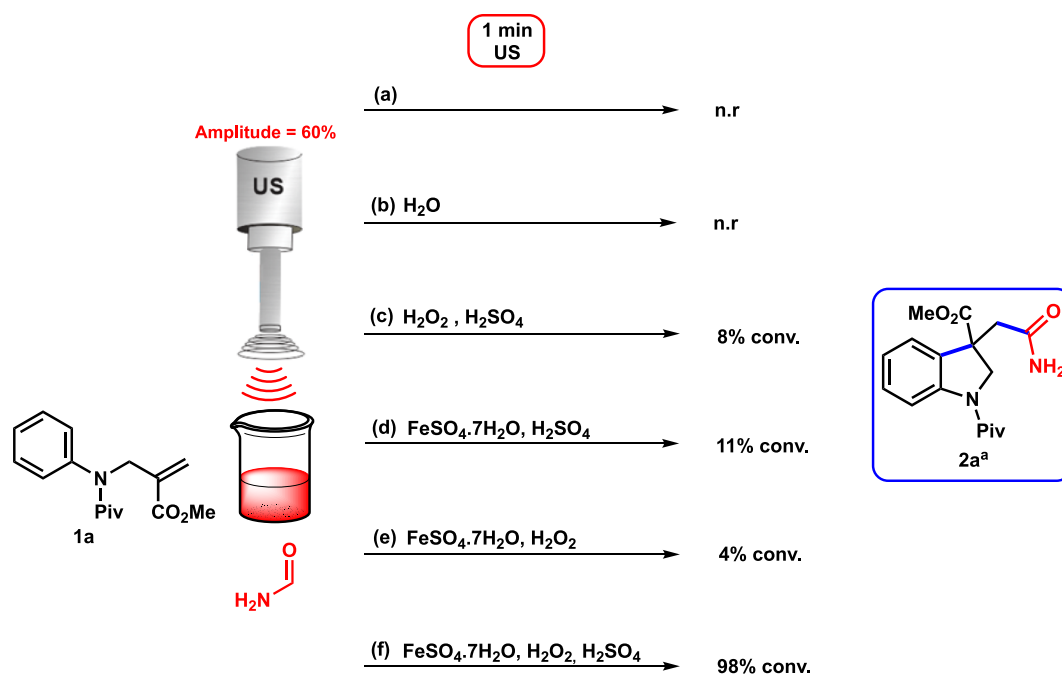
3. Results and discussion

3.1. Exploitation of ultrasonic irradiation on the generation of hydroxyl and carbamoyl radicals for the synthesis of indolines

The design of the experimental setup for the application of ultrasonic irradiation in organic synthesis is an essential step. Usually, the US-



Scheme 1. Evaluation of the Fenton and sono-Fenton reaction in formamide for synthesis of indoline 2a.



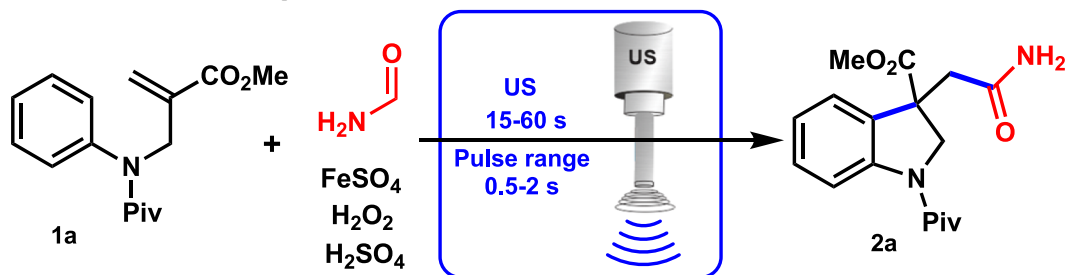
Scheme 2. Exploitation of ultrasonic irradiation and the Fenton reaction in formamide for indoline construction. ^aConversions were determined by GC–MS analysis.

assisted reactions are performed in an open flask with a large solvent volume, while several organic reactions employ volatile solvents (i.e. ethyl ether, acetone, CH₂Cl₂) and anhydrous conditions (i.e. reactions with Grignard reagents, organolithium reagents). In addition, the development of synthetic methodologies is usually performed on a small scale. Therefore, choosing the type of equipment, frequency and specific horn can be relevant for a specific chemical reaction or application.

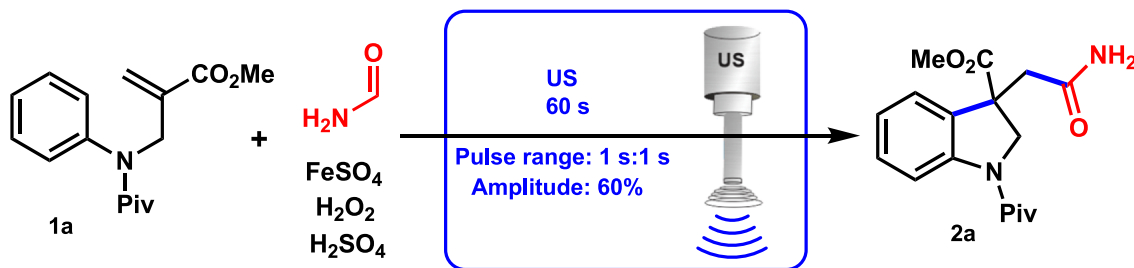
For our purpose, we decided to use equipment that can be easily found in most of the chemistry or biochemistry labs (Branson Digital Sonifier, 20 kHz, 400 W; Fig. 3a). Additionally, some reaction parameters aimed at high productivity and the development of a robust and fast methodology were considered (i.e., 60 s reaction, open flask, avoidance of an aqueous work-up). Our synthetic approach for indoline formation

relies on a sequence of radical reactions, including hydroxyl radical and carbamoyl radical generation, and their tandem addition/cyclization to 2-(((N-aryl)amino)methyl)acrylate (**1**) (Fig. 3b). In addition, aiming to develop an inexpensive and efficient methodology to generate carbamoyl radicals from formamide, we decided to employ the sono-Fenton process, which makes use of hydrogen peroxide and iron (II).

Considering that our goal is to develop a robust and fast synthetic methodology for indolines (Target: a 60 s reaction in an open flask), a comparison between a reaction under silent condition (magnetic stirring: 1500 rpm, 60 s reaction) and under ultrasonic irradiation (60 s reaction) were performed (Scheme 1). A solution of 2-(((N-aryl)amino)methyl)acrylate (**1a**) in formamide was sonicated in the presence of Fenton reagents (FeSO₄·7H₂O, H₂O₂, and H₂SO₄) for 60 s. The product

Table 2Exploitation of pulsed ultrasonic irradiation on the production of **2a**.^a

Entry	Time(s)	Pulse ON:OFF (s) ^d	Conversion ^b
1	15	–	4
2	30	–	84
3	60	–	98 (90) ^c
4	15	1.0:1.0	38
5	30	1.0:1.0	87
6	60	1.0:1.0	99 (97) ^c
7	60	0.5:0.5	94
8	60	2.0:2.0	98
9	60	1.0:2.0	26
10	60	2.0:1.0	70

^a **1a** (0.15 mmol), FeSO₄·7H₂O (1 mol%), H₂SO₄ (0.15 mmol), H₂O₂ (0.30 mmol) and formamide (3 mL).^b Determined by GC–MS analysis.^c Isolated yields of **2a** in parentheses.^d US amplitude = 60%.**Table 3**Exploitation of Fenton reagent concentrations for the production of **2a** under pulsed ultrasonic irradiation.^a

Entry	FeSO ₄ ·7H ₂ O(mol%)	H ₂ SO ₄ (eq.)	H ₂ O ₂ (eq.)	Conversion ^b
1	1.0	0.5	2	98(79) ^c
2	1.0	1.0	1	96(34) ^c
3	1.0	1.0	2	96(97) ^c

^a **1a** (0.15 mmol) and formamide (3 mL).^b Determined by GC–MS analysis.^c Isolated yields of **2a** in parentheses.

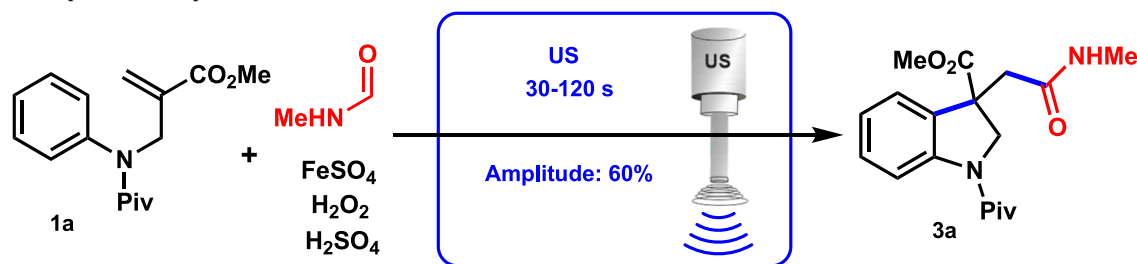
was obtained in excellent yield (90% and 98% conversion). On the other hand, when the reaction was performed without ultrasonic irradiation, under magnetic stirring (1500 rpm, 60 s reaction), the desired product was not detected.

Additional experiments to elucidate the role of ultrasonic irradiation on the preparation of indolines were performed. In addition, a set of experiments was designed to demonstrate the relevance of each reaction component (Scheme 2).

First, 2-((*N*-aryl)amino)methylacrylate (**1a**) was sonicated in the presence of formamide, Scheme 2 (a), and indoline (**2a**) was not detected; instead, only the starting material was observed. Under sonication at 20 kHz with an ultrasonic horn ($\varnothing = 12.7$ mm), as we can see in Scheme 2 (b), the sole use of water as a source of hydroxyl radicals did not provide the desired product. Low-frequency sonication is less efficient to produce hydroxyl radicals due to the generation of large

transient cavitation bubbles formed during irradiation [39]. This system can be responsible for entrapping hydroxyl radicals, avoiding their migration into the bulky media, and consequently avoiding their contact with other organic compounds, such as reagents or radical acceptors [39].

The complete removal of the catalyst, oxidant, or acid provided a poor conversion to the indoline (**2a**), as shown in Scheme 2 (c), (d) and (e), respectively. However, after adding all the reaction components and exposing the reaction mixture to the ultrasonic irradiation, it was possible to synthesize the desired indoline (**2a**) in excellent conversion, Scheme 2 (f). The combination of ultrasonic irradiation with the Fenton reaction can promote effective Fe(II) regeneration in the Fe(II)/Fe(III) redox cycle, increasing hydroxyl radical production [34–38], and consequently the generation of carbamoyl radicals (for more details, see reaction mechanism). In addition, we can expect improved mixing and

Table 4Exploitation of US amplitude on the production of 2a.^a

Entry	Time(s)	Amplitude (%)	Conversion ^b
1	30	40	7
2	60	40	82
3	60	50	98 (85) ^c
4	30	60	84
5	60	60	98 (91) ^c
6	30	80	–
7	60	80	36

^a **1a** (0.15 mmol), FeSO₄·7H₂O (1 mol%), H₂SO₄ (0.15 mmol), H₂O₂ (0.30 mmol) and formamide (3 mL).^b Determined by GC–MS analysis.^c Isolated yields of **2a** in parentheses.

contact between the hydroxyl radicals and 2-(((N-aryl)amino)methyl)acrylates, yielding desired indolines **2** in only 1 min.

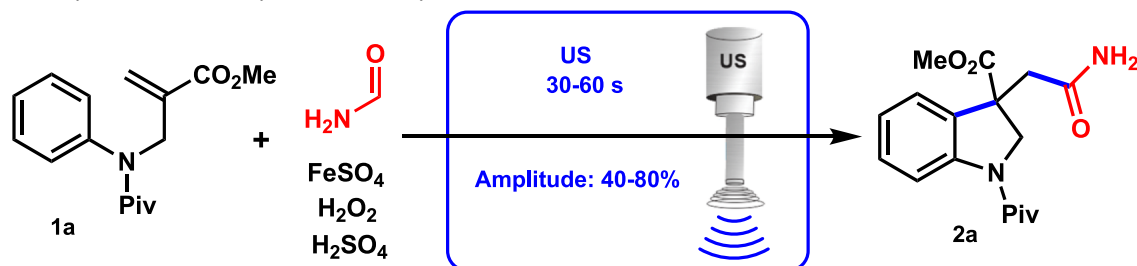
Our next step was to exploit pulsed ultrasonic irradiation on the reaction system to produce indoline (**2a**) Table 2.

Continuous sonication mode provided excellent yield for indoline (**2a**) after 60 s of reaction, as depicted in Table 2, entry 3. Shorter reaction times revealed lower product yields (Table 2, entries 1 and 2). We then decided to explore the reaction under pulsed mode. As depicted in Table 2, entry 4, sonication of the mixture in pulsed mode for 15 s led to higher conversion than continuous mode. The use of 60 s of pulsed US (Pulse ON:OFF = 1 s:1 s) provided full conversion of **1a** to **2a** with the excellent isolated yield of 97% as shown in Table 2, entry 6, which was chosen as the best condition to produce the desired indoline (**2a**). We can point that the application of pulsed ultrasound enables a short reaction time, and also increases the life of the transducers [40,41].

Then, we decided to verify the effects of the pulse time range in the

reaction, as depicted in Table 2, entries 7 and 8. The decrease in the pulse time led to a slight decrease in conversion, while increasing the pulse time range to 2 s on/off did not lead to significant changes in the conversion. When the probe was on for 1 s and off for 2 s, as shown in Table 2, entry 9, the conversion decreased significantly (26%). It was therefore suggested that when the probe is pulsed ON:OFF (1 s:1 s), the solution temperature increases rapidly and does not allow a significant decrease in temperature. However, the use of *probe on* for 2 s and *off* for 1 s leads to moderated conversion as shown in Table 2 entry 10. In this experiment, we believe that the time off is too short, which leads to intense mechanical vibration.

Once the pulsation effects were studied, we decided to analyze the components of our reaction and their stoichiometry over the conversion and yield. First, by decreasing the amount of acid, we observed a slight decrease in the isolated yield (Table 3, entry 1). Additionally, removing 1 equivalent of the oxidant led to a poor isolated yield (Table 3, entry

Table 5Exploitation of *N*-methylformamide for the synthesis of *N*-methylacetamide-indoline (**3a**) under ultrasonic irradiation.^a

Entry	Time(s)	Pulse ON:OFF (s)	Conversion ^b
1	30	–	–
2	60	–	5
3	120	–	99
4	30	1.0:1.0	24
5	45	1.0:1.0	85
6	60	1.0:1.0	98 (68) ^c
7	120	1.0:1.0	99 (75) ^c

^a **1a** (0.15 mmol), FeSO₄·7H₂O (1 mol%), H₂SO₄ (0.15 mmol), H₂O₂ (0.30 mmol) and *N*-methylformamide (3 mL). ^b Determined by GC–MS analysis.^c Isolated yield of **3a** in parenthesis.

2), and this experiment showed the crucial role of the oxidant in our system to achieve higher isolated yields of **2a** (Table 3, entry 3).

3.2. Amplitude of the ultrasound

The amplitude of the ultrasound was screened for the reaction, and as depicted in Table 4, entries 1–2, the use of 40% of the amplitude for 30 s led to a poor conversion to product **2a**, while 60 s reaction provided the desired product in 82% conversion. An increase in amplitude (50%) leads to 98% conversion, Table 4, entry 3. Additionally, when 60% of the amplitude was applied for 60 s, 98% conversion was achieved, Table 4, entry 5. Therefore, the determination of the isolated yield of entries 3 and 5 were performed, as both showed higher conversions. The best isolated yield occurred when 60% of the amplitude was applied, entry 5. Amplitudes above 60% led to intense mechanical vibration of the reaction mixture, as a result, poor conversions were obtained, as shown in Table 4 entries 6–7. After evaluating the effect of amplitude of the ultrasound in the synthesis of indoline **2a**, it was possible to verify that the higher conversion and isolated yield was achieved in entry 5 when 60% of the amplitude and 60 s were applied to the reaction.

3.3. Exploitation of *N*-methylformamide as a solvent and reagent for the synthesis of functionalized indolines

After the optimization of the indoline synthesis from formamide, the exploitation of *N*-methylformamide as a source of carbamoyl radicals

was also studied. Initially, the use of continuous ultrasonic irradiation for a 60 s reaction did not provide full conversion of the starting material **1a** as observed for formamide, Table 5, entry 2. However, a 2 min reaction under continuous ultrasonic irradiation provided full conversion to **3a**, as shown in Table 5, entry 3.

After applying the continuous mode, pulsed ultrasonic irradiation was studied for indoline synthesis from *N*-methylformamide. As depicted in Table 5, entries 4 and 5, with 30 and 45 s of pulsed US irradiation, was possible to detect the desired product. Increasing the reaction time led to full conversion with a 60 s reaction, and all the starting material was consumed. As exhibited in Table 5, entry 6, pulsed ultrasonic mode for the synthesis of indolines from *N*-methylformamide enables the same reaction time as that required for the synthesis of indolines from formamide. Although the reaction performed with 2 min under pulsed mode provided a higher isolated yield, 75% as shown in Table 5, entry 7, entry 6 was chosen, as it leads to the highest productivity.

3.4. Reaction scope with formamide

With the best set of conditions in hand, syntheses of indolines from a wide scope of substituted 2-((*N*-aryl)amino)methylacrylates were performed. Reactions with formamide to generate carbamoyl radicals were carried out within 60 s using pulsed ultrasonic irradiation, which led to a total of 30 s of effective irradiation. Under the conditions depicted in Table 2, entry 6, the model substrate (**1a**) containing no substituent provided an excellent isolated yield of 97% (Fig. 4, **2a**). The

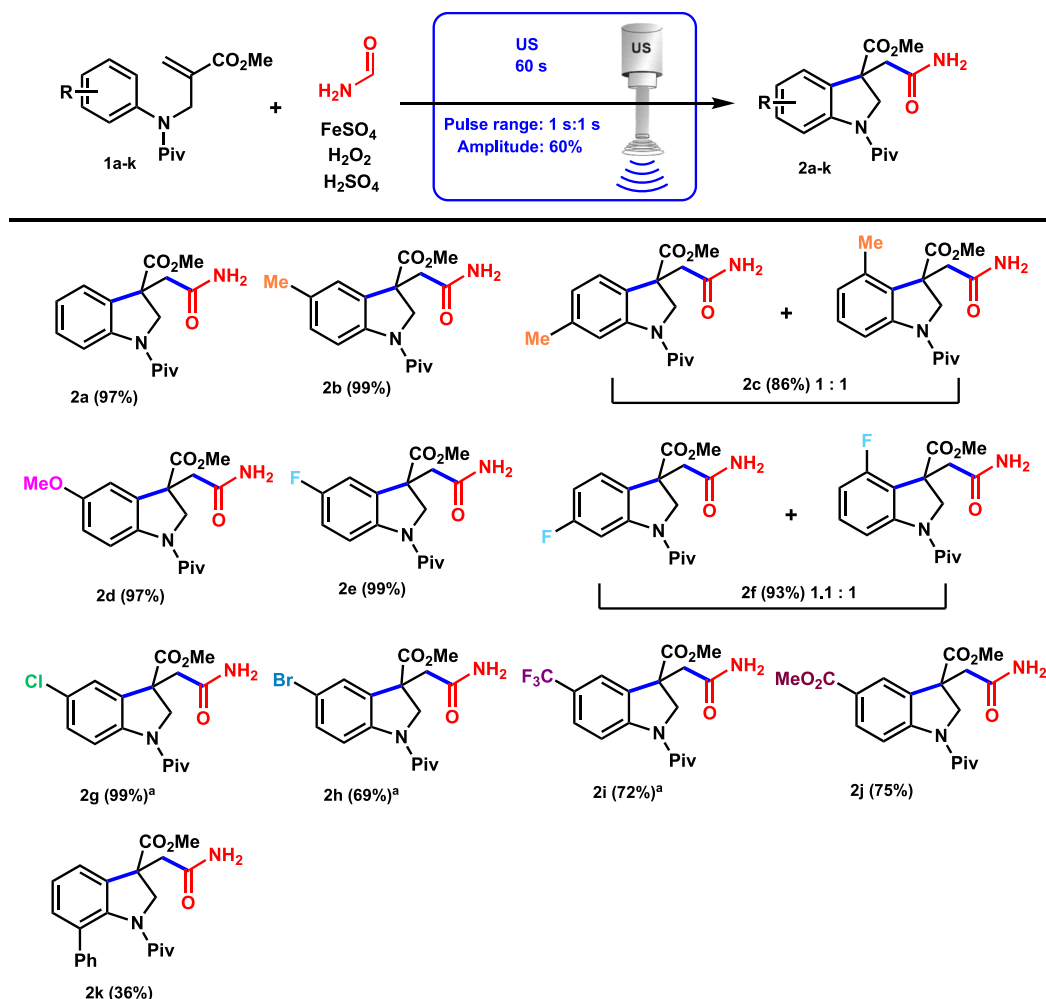
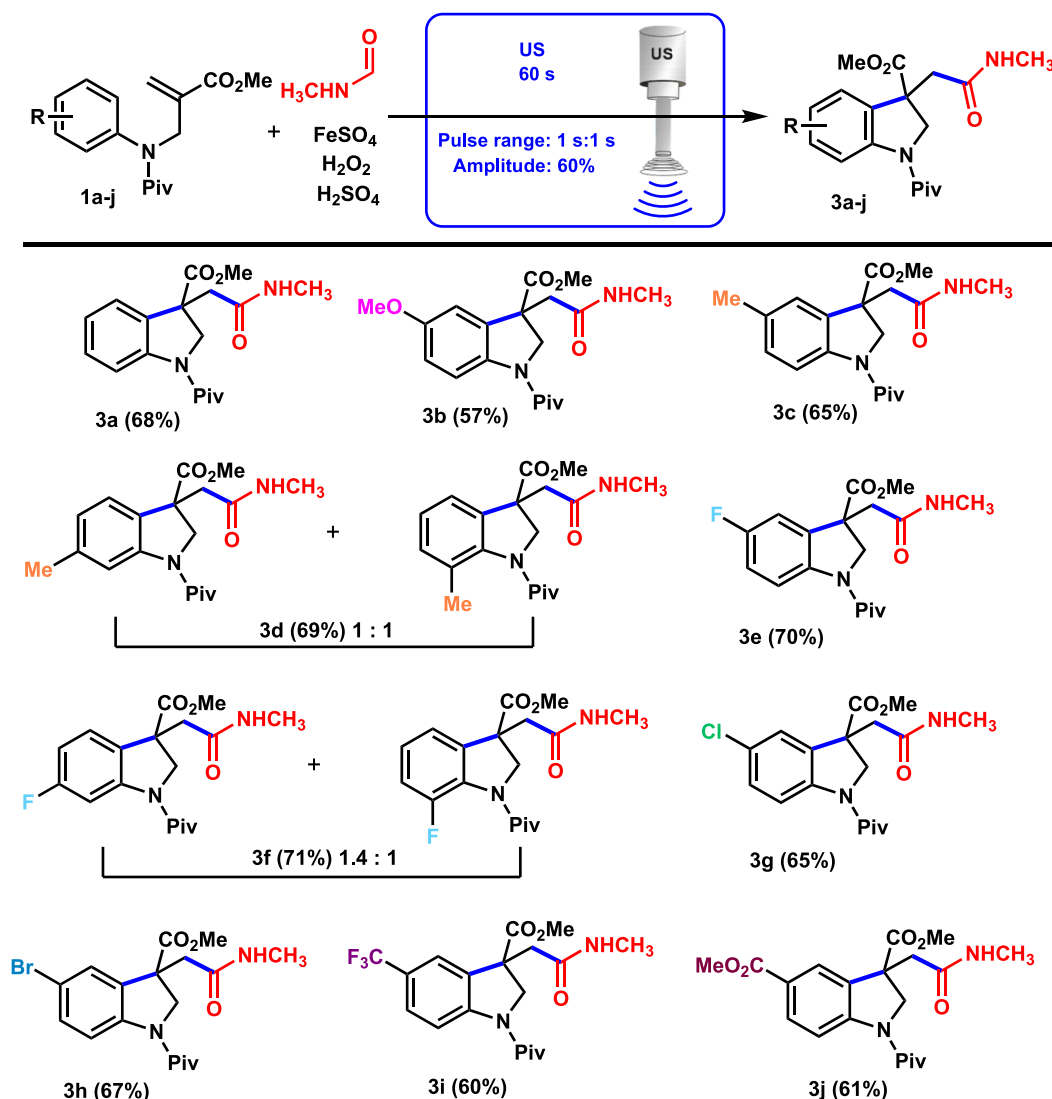


Fig. 4. Substrate scope for formamide. ^a *t*-BuOH (0.9 mL), formamide (2.1 mL), 2 min.

Fig. 5. Substrate scope for *N*-methylformamide.

isolated yields of the indolines containing electron donating substituents at the para position of the aromatic ring, such as *p*-Me and *p*-OMe, were excellent, giving 99% and 97% yield, respectively (Fig. 4, **2b** and **2d**). The isolated yields of the indolines containing electron-withdrawing groups such as *p*-F and *p*-Cl were also excellent (Fig. 4, **2e** and **2g**). For the preparation of indolines **2g-i**, the reactions were performed with 30% of *t*BuOH as a cosolvent for total solubilization of the starting material. A 2 min reaction was applied to achieve high conversion, as well as higher isolated yields (Fig. 4). When meta substituents were studied, both weak electron-donating groups and electron-withdrawing groups, such as *m*-Me and *m*-F gave slightly lower isolated yields (Fig. 4, **2c** and **2f**, 86% and 93 %, respectively), and a mixture of regioisomers was obtained. The reaction performed with the *ortho*-substituted starting material provided the desired indoline in poor isolated yield (Fig. 4, **2k**).

3.5. Reaction scope with *N*-methylformamide

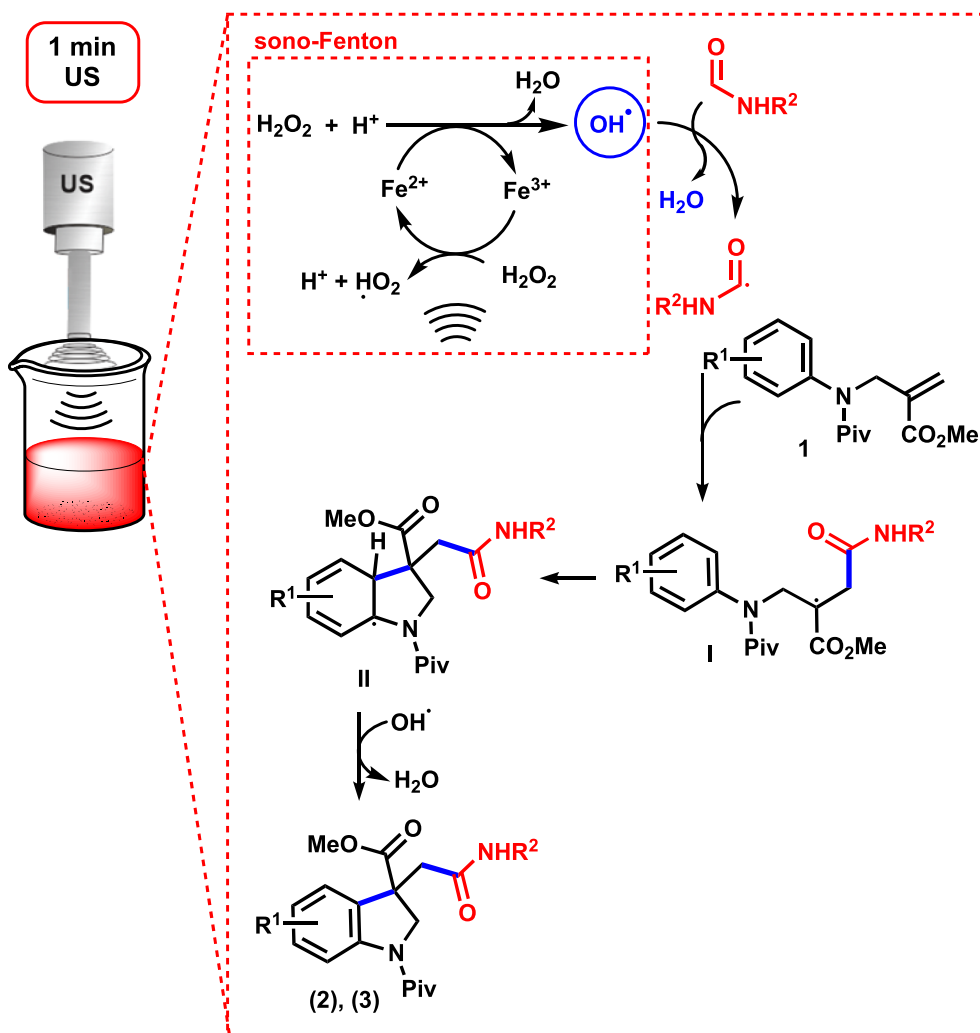
With the optimal conditions for the synthesis of indolines from *N*-methylformamide in hand, as depicted in Table 5, entry 6, by applying pulsed ultrasonic irradiation, a wide scope of methyl 3-(2-(methyl-amino)-2-oxoethyl)-1-pivaloylindoline-3-carboxylates was studied. As shown in Fig. 5, the isolated yields were moderated to high when electron-donating groups were applied (**3b**: 57%, **3c**: 65%, **3d**: 69%).

When 2-(((*N*-aryl)amino)methyl)acrylates **1** had electron-withdrawing groups on their aromatic ring, the yields for indolines **3e-h** were comparable with those obtained for model compound **3a**. In the case of strong electron-withdrawing groups attached to the aromatic ring, the isolated yield slightly decreased, as observed in Fig. 5, **3i-j**.

The proposed reaction mechanism starts with the reaction between H_2O_2 and Fe^{2+} for the generation of hydroxyl radicals under acidic conditions (Scheme 3) [34–38]. Then, the hydroxyl radicals react with formamide, abstracting hydrogen to generate carbamoyl radicals. The former radical attacks the carbon–carbon double bond of the acrylic ester moiety of 2-(((*N*-aryl)amino)methyl)acrylate (**1**) to generate radical intermediate **I**, which undergoes intramolecular trapping by the aromatic ring, generating intermediate **II**, which can be readily oxidized to give indolines **2** and **3**. Regeneration of the Fe^{2+} species can occur in the rearomatization step or by the reaction of Fe^{3+} and H_2O_2 to provide an $\text{Fe}-\text{O}_2\text{H}^{2+}$ complex, which provides Fe^{2+} and $\cdot\text{HO}_2$, a reaction that is enhanced under ultrasound irradiation [36,37].

4. Conclusion

In conclusion, a straightforward and easy-to-implement methodology for the synthesis of indolines via radical cascade reactions under ultrasonic irradiation was developed. When the reaction was performed



Scheme 3. Proposed reaction mechanism.

without ultrasonic irradiation, under magnetic stirring (1500 rpm), no indoline formation was observed. On the other hand, ultrasonic irradiation was essential to enable the fast regeneration of Fe(II) catalyst, improving carbamoyl radicals generation, consequently, indoline production. Our instrumentation was based on the use of US equipment (US Horn; 20 kHz), which can be found in several chemistry laboratories. The use of the sono-Fenton process in the presence of formamides and 2-(((N-aryl)amino)methyl)acrylates afforded a broad range of functionalized indolines in high yields (up to 99%; a 60 s reaction). We can expect further applications of ultrasonic irradiation for radical cascade reactions, aiming for high productivity and a fast process, as we have observed.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors are grateful for the Conselho Nacional de Desenvolvimento Científico e Tecnológico (National Council for Scientific and Technological Development, CNPq, grant no. 312751/2018-4 and 132280/2018-3), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education

Personnel, CAPES), and Fundação de Amparo à Pesquisa do Estado de São Paulo (The São Paulo Research Foundation, FAPESP, grant nos. 2018/07152-4, 2019/10762-1 and 14/50316-7) for financial support. We would also like to thank Prof. Dr. Massuo Jorge Kato and Dr. Lydia F. Yamagushi for helping with the HRMS analysis. We thank Prof. Dr. Alcindo dos Santos and Marcos Vinicio Archilha for helping with melting points measurements.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ultsonch.2021.105778>.

References

- [1] W.T. Richards, A.L. Loomis, The Chemical Effects Of High Frequency Sound Waves: I. A Preliminary Survey, *J. Am. Chem. Soc.* 49 (1927) 3086–3100, <https://doi.org/10.1021/ja01411a015>.
- [2] B. Banerjee, Recent developments on ultrasound assisted catalyst-free organic synthesis, *Ultrason. Sonochem.* 35 (2017) 1–14, <https://doi.org/10.1016/j.ultsonch.2016.09.023>.
- [3] G. Chatel, R.S. Varma, Ultrasound and microwave irradiation: contributions of alternative physicochemical activation methods to green chemistry, *Green Chem.* 21 (2019) 643–650, <https://doi.org/10.1039/C9GC02534K>.
- [4] Z. Li, T. Zhuang, J. Dong, L. Wang, J. Xia, H. Wang, X. Cui, Z. Wang, Sonochemical fabrication of inorganic nanoparticles for applications in catalysis, *Ultrason. Sonochem.* 71 (2021), 105384, <https://doi.org/10.1016/j.ultsonch.2020.105384>.
- [5] B.L. Gadilohar, D.V. Pinjari, G.S. Shankarling, An Energy Efficient Sonochemical Selective Oxidation of Benzyl Alcohols to Benzaldehydes by Using Bio-TSIL Choline

- Peroxydisulfate, *Ind. Eng. Chem. Res.* 55 (2016) 4797–4802, <https://doi.org/10.1021/acs.iecr.6b00731>.
- [6] M.T. Nazeri, A. Shaabani, B. Notash, Chemoselective synthesis of fully substituted pyrroles via a one-pot four-component isocyanide-based reaction, *19* (2021) 127112, <https://doi.org/10.1016/j.bmcl.2020.127112>.
 - [7] R. Venkateshwarlu, S.N. Singh, V. Siddaiah, H. Ramamohan, R. Dandela, K. A. Hossain, P.V. Babu, M. Pal, Ultrasound assisted rapid synthesis of mefenamic acid based indole derivatives under ligand free Cu-catalysis: Their pharmacological evaluation, *Bioorg. Med. Chem. Lett.* 30 (2020) 5333–5338, [https://doi.org/10.1016/S0040-4020\(01\)82382-6](https://doi.org/10.1016/S0040-4020(01)82382-6).
 - [8] R. Shashi, N.S. Begum, A.K. Panday, A Rapid Ultrasound Synthesis of Xanthenediones Catalyzed by Boric acid in Ethanol-Water Medium: Single Crystal, DFT and Hirshfeld Surface Analysis of Two Representative Compounds, *J. Mol. Struct.* 1228 (2021), 129794, <https://doi.org/10.1016/j.molstruc.2020.129794>.
 - [9] G. Cravotto, P. Cintas, Harnessing mechanochemical effects with ultrasound-induced reactions, *Chem. Sci.* 3 (2012) 295–307, <https://doi.org/10.1039/C1SC00740H>.
 - [10] G. Cravotto, P. Cintas, Power ultrasound in organic synthesis: moving cavitation chemistry from academia to innovative and large-scale applications, *Chem. Soc. Rev.* 35 (2006) 180–196, <https://doi.org/10.1039/B503848K>.
 - [11] T. Kimura, Application of Ultrasound to Organic Synthesis, in: F. Grieser, N. Enomoto, K. Okitsu, P.-K. Choi, H. Harada, K. Yasui (Eds.), *Elsevier, Sonochemistry and the acoustic bubble*, 2015, pp. 187–206, <https://doi.org/10.1016/C2013-0-18886-1>.
 - [12] M.C. Dewathe, P.R. Gogate, Ultrasound assisted intensified synthesis of 1-benzyloxy-4-nitrobenzene in the presence of phase transfer catalyst, *Chem. Eng. Sci.* 346 (2018) 438–446, <https://doi.org/10.1016/j.ces.2018.04.027>.
 - [13] G. Cravotto, E. Borretto, M. Oliverio, A. Procopio, A. Penoni, Organic reactions in water or biphasic aqueous systems under sonochemical conditions. A review on catalytic effects, *Catal. Commun.* 63 (2015) 2–9, <https://doi.org/10.1016/j.catcom.2014.12.014>.
 - [14] C. Wu, L.-H. Lu, A.-Z. Peng, G.-K. Jia, C. Peng, X. Cao, Z. Tang, W.-M. He, X. Xu, Ultrasound-promoted Brønsted acid ionic liquid-catalyzed hydrothiocyanation of activated alkynes under minimal solvent conditions, *Green Chem.* 20 (2018) 3683–3688, <https://doi.org/10.1039/C8GC00491A>.
 - [15] A. Maleki, J. Rahimi, O.M. Demchuk, A.Z. Wilczewska, R. Jasiński, Green in water sonochemical synthesis of tetrazolopyrimidine derivatives by a novel core-shell magnetic nanostructure catalyst, *Ultrason. Sonochem.* 43 (2018) 262–271, <https://doi.org/10.1016/j.ultsonch.2017.12.047>.
 - [16] S. Majhi, Cations of ultrasound in total synthesis of bioactive natural products: A promising green tool, *Ultrason. Sonochem.* 77 (2021), <https://doi.org/10.1016/j.ultsonch.2021.105665>.
 - [17] G. Cravotto, A. Procopio, M. Oliverio, L. Orio, D. Carnaroglio, Simple sonochemical protocols for fast and reproducible Grignard reactions, *Green Chem.* 13 (2011) 3806–3809, <https://doi.org/10.1039/C1GC15756F>.
 - [18] S.V. Sancheti, P.R. Gogati, Intensification of heterogeneously catalyzed Suzuki-Miyaura cross-coupling reaction using ultrasound: Understanding effect of operating parameters, *Ultrason. Sonochem.* 40 (2018) 30–39, <https://doi.org/10.1016/j.ultsonch.2017.01.037>.
 - [19] M.H. Islam, O.S. Burheim, J.-Y. Hihn, B.G. Pollet, High intensity ultrasound-promoted reformatsky reactions, *Ultrason. Sonochem.* 73 (2021), 105474, <https://doi.org/10.1016/j.ultsonch.2021.105474>.
 - [20] D.R. Araújo, Y.R. Lima, A.M. Barcellos, M.S. Silva, R.G. Jacob, E.J. Lenardão, L. Bagnoli, C. Santi, G. Perin, Ultrasound-Promoted Radical Synthesis of 5-Methylselenyl-4,5-dihydroisoxazoles, *Eur. J. Org. Chem.* 2020 (2020) 586–592, <https://doi.org/10.1002/ejoc.201901611>.
 - [21] L. Abenante, F. Penteado, M.M. Vieira, G. Perin, D. Alves, E.J. Lenardão, Ultrasound-enhanced Ag-catalyzed decarboxylative coupling between α -keto acids and disulfides for the synthesis of thioesters, *Ultrason. Sonochem.* 49 (2018) 41–46, <https://doi.org/10.1016/j.ultsonch.2018.07.014>.
 - [22] S. Merouani, O. Hamdaoui, Y. Rezgui, M. Guemini, Sensitivity of free radicals production in acoustically driven bubble to the ultrasonic frequency and nature of dissolved gases, *Ultrason. Sonochem.* 22 (2015) 41–50, <https://doi.org/10.1016/j.ultsonch.2014.07.011>.
 - [23] A. Székely, M. Klusmann, Molecular Radical Chain Initiators for Ambient- to Low-Temperature Applications, *Chem.: Asian J.* 15 (2019) 105–115, <https://doi.org/10.1002/asia.201801636>.
 - [24] T.G. McKenzie, F. Karimi, M. Ashokkumar, G.G. Qiao, Ultrasound and Sonochemistry for Radical Polymerization: Sound Synthesis, *Chem. Eu. J.* 25 (2019) 5372–5388, <https://doi.org/10.1002/chem.201803771>.
 - [25] E.M. Hussein, K.S. Khairou, Sonochemistry: Synthesis of Bioactive Heterocycles, *Synth. Commun.* 44 (2014) 2155–2191, <https://doi.org/10.1080/00397911.2014.893360>.
 - [26] B. Banerjee, Recent developments on ultrasound-assisted one-pot multicomponent synthesis of biologically relevant heterocycles, *Ultrason. Sonochem.* 35 (2017) 15–35, <https://doi.org/10.1016/j.ultsonch.2016.10.010>.
 - [27] M. Draye, G. Chatel, R. Duwald, Ultrasound for Drug Synthesis: A Green Approach, *Pharmaceuticals* 13 (2020) 23, <https://doi.org/10.3390/ph1302023>.
 - [28] P.M. Dewick, *Medicinal Natural Products: A Biosynthetic Approach*, Wiley (2009) 366–378.
 - [29] J.T. Ndongo, J.N. Mbing, M.F. Tala, A. Montellier, D.E. Pegnyemby, M. Cuendet, H. Laatsch, *Phytochem.* 144 (2017) 189–196, <https://doi.org/10.1016/j.phytochem.2017.09.013>.
 - [30] K.-H. Lim, O. Hiruka, K. Komiyama, T.-S. Kam, Jerantianines A–G, Cytotoxic Aspidosperma Alkaloids from *Tabernaemontana corymbosa*, *J. Nat. Prod.* 71 (2008) 1591–1594, <https://doi.org/10.1021/np800435c>.
 - [31] S. Zeeli, T. Weill, E. Finklin-Groner, C. Bejar, M. Melamed, S. Furman, M. Zhenin, A. Nudelman, M. Weinstock, Synthesis and Biological Evaluation of Derivatives of Indoline as Highly Potent Antioxidant and Anti-inflammatory Agents, *J. Med. Chem.* 61 (2018) 4004–4019, <https://doi.org/10.1021/acs.jmedchem.8b00001>.
 - [32] F. Brucelle, P. Renaud, Synthesis of Indolines, Indoles, and Benzopyrrolizidinones from Simple Aryl Azides, *Org. Lett.* 14 (2012) 3048–3051, <https://doi.org/10.1021/ol301120w>.
 - [33] T. Fujita, S. Sanada, Y. Chiba, K. Sugiyama, J. Ichikawa, Two-Step Synthesis of Difluoromethyl-Substituted 2,3-Dihydrobenzoheteroles, *Org. Lett.* 16 (2014) 1398–1401, <https://doi.org/10.1021/ol5001582>.
 - [34] G. Harichandran, S. Prasad, SonoFenton degradation of an azo dye, *Direct Red*, *Ultrason. Sonochem.* 29 (2016) 178–185, <https://doi.org/10.1016/j.ultsonch.2015.09.005>.
 - [35] N.N. Mahamuni, Y.G. Adewuyi, Advanced oxidation processes (AOPs) involving ultrasound for waste water treatment: A review with emphasis on cost estimation, *Ultrason. Sonochem.* 17 (6) (2010) 990–1003, <https://doi.org/10.1016/j.ultsonch.2009.09.005>.
 - [36] L. Jih-Gao, M. Ying-Shih, Oxidation of 2-Chlorophenol in Water by Ultrasound/Fenton Method, *J. Environ. Eng.* 126 (2000) 130–137, [https://doi.org/10.1061/\(ASCE\)0733-9372\(2000\)126:2\(130\)](https://doi.org/10.1061/(ASCE)0733-9372(2000)126:2(130)).
 - [37] B. Nappolian, H. Jung, H. Choi, J.H. Lee, J.-W. Kang, Sonolytic degradation of methyl tert-butyl ether: the role of coupled fenton process and persulphate ion, *Water Res.* 36 (2002) 4699–4708, [https://doi.org/10.1016/S0043-1354\(02\)00211-7](https://doi.org/10.1016/S0043-1354(02)00211-7).
 - [38] M. Pirsaeheb, N. Moradi, Sonochemical degradation of pesticides in aqueous solution: investigation on the influence of operating parameters and degradation pathway—a systematic review, *RCS Adv.* 10 (2020) 7396–7423, <https://doi.org/10.1039/C9RA11025A>.
 - [39] L. Somaglino, G. Bouchoux, J.-L. Mestas, C. Lafon, Validation of an acoustic cavitation dose with hydroxyl radical production generated by inertial cavitation in pulsed mode: Application to in vitro drug release from liposomes, *Ultrason. Sonochem.* 18 (2011) 577–588, <https://doi.org/10.1016/j.ultsonch.2010.07.009>.
 - [40] S.V. Sancheti, P.R. Gogati, A review of engineering aspects of intensification of chemical synthesis using ultrasound, *Ultrason. Sonochem.* 36 (2017) 527–543, <https://doi.org/10.1016/j.ultsonch.2016.08.009>.
 - [41] H.D. Raskar, D.N. Avhad, V.K. Rathod, Ultrasound assisted production of daunorubicin: Process intensification approach, *Chem. Eng. Process.* 77 (2014) 7–12, <https://doi.org/10.1016/j.ces.2013.12.008>.