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Indium bromide catalysed, ultrasound-assisted, regio-selective synthesis of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates

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Abstract A series of pyrazole-4-carboxylates have been synthesised using indium bromide catalyst and the cyclisation of respective 3-substituted-isoquinolinylhydrazines **1** into their corresponding ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoates **3** in ethanol solvent under ultrasonic irradiation at 90 °C for 30 min. The regio-selective cyclisation products were efficiently provided by indium bromide catalyst and are confirmed by nuclear Overhauser effect spectroscopy–nuclear magnetic resonance (NOESY–NMR) studies.

Keywords Ultrasonic irradiation · Pyrazole-4-carboxylates · 1-(3-Substituted-isoquinolin-1-yl) hydrazines · Microwave · Indium bromide · Cyclisation · Regio-selectivity

Introduction

Pyrazoles occupied an important position as bio-active drugs in the pharmaceutical industry [1], in both lead identification and lead optimisation processes [2].

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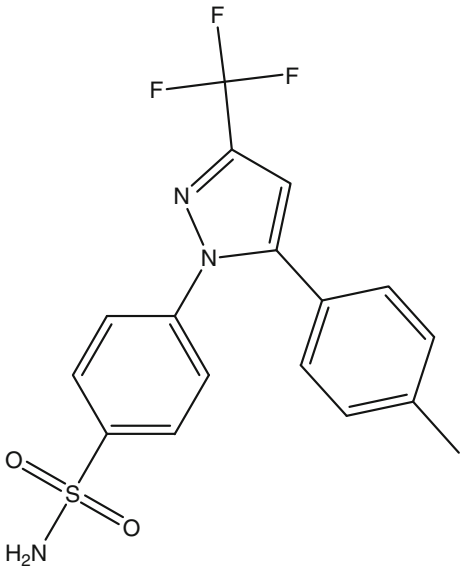
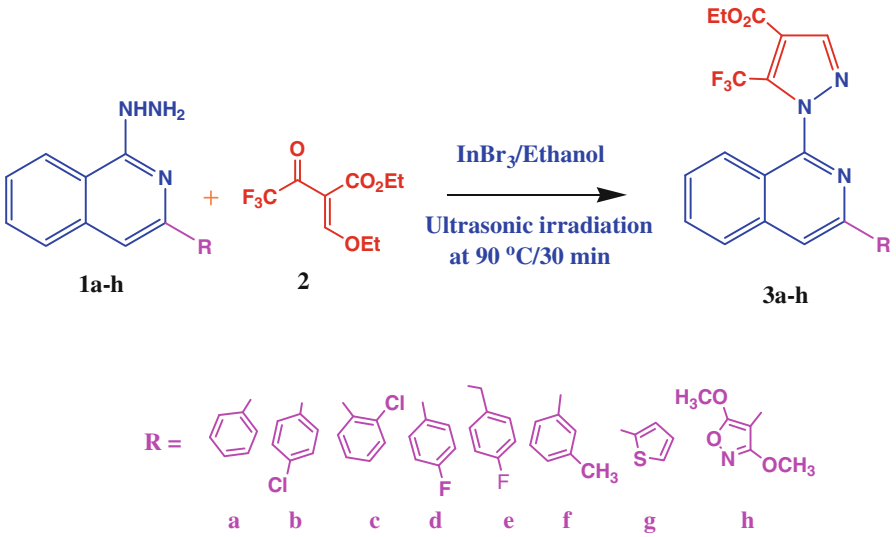
Pyrazoles are well established in the literature as important biologically effective heterocyclic compounds [3]. Pyrazole derivatives had demonstrated potential pharmacological activities such as anti-inflammatory [4], anti-pyretic [5], anti-microbial [6], anti-viral [7], anti-tumour [8], anti-convulsant [9], anti-histaminic [10] and anti-depressant activities [11]. It has been proved that those 1*H*-pyrazole-4-carboxylic acids and their esters had potential as in vitro anti-bacterial agents against Gram-positive bacteria. Pyrazole carboxylic acid derivatives provided important building blocks in organic and medicinal chemistry. Celecoxib [12] (Fig. 1) is the first-to-market drug of a number of selective cyclo-oxygenase 2 (COX-2) inhibitors, which are promising anti-inflammatory and analgesic agents.

In recent years, various synthetic methods have been introduced, including microwave irradiation or sonication conditions, with the aim of increasing the efficiency of the reactions, catalysts and reagents used in these reactions. Further attempts were made to save time, solvent quantity and safe handling, and in achieving economically and environmentally benign reaction conditions. The synthesis of simple pyrazole and their carboxylic acid derivatives [13–17] were also attempted with the above methodologies. However, most of these methods involved were multi-step synthesis with longer reaction times and lesser yields. Here, an efficient ultrasound-assisted regio-selective synthesis of a series of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates using indium bromide catalyst in the presence of ethanol at 90 °C for 30 min under ultrasonic conditions is reported.

Fig. 1 Celecoxib





Scheme 1 Synthesis of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates **3**

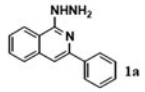
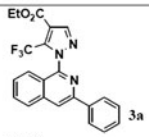
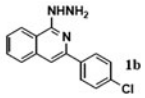
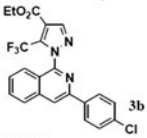
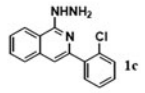
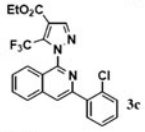
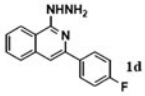
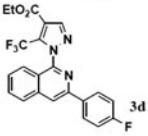
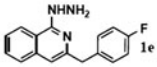
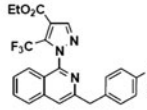
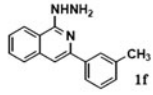
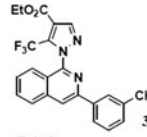
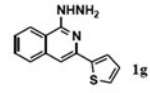
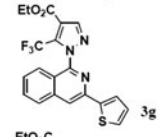
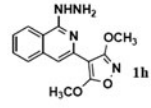
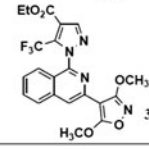
Results and discussion

In our continued interest of research on isoquinolines and related compounds [18–38], in this communication, an efficient, ultrasound-assisted and indium bromide catalysed synthesis of a series of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates is reported. The reaction of various 1-hydrazino-3-substituted-isoquinolines **1** with ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate **2** in absolute ethanol solvent in the presence of indium bromide catalyst and ultrasonic irradiation at 90 °C for 30 min afforded ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates **3** in excellent yields and high purity (Scheme 1; Table 1).

By choosing cyclisation of 1-hydrazino-3-phenylisoquinoline **1a** and ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate **2** as a model reaction (Scheme 2), the optimisation of cyclisation was carried out by screening different acidic catalysts as reported in Table 2. The results suggested that the cyclisation proceeds well with indium bromide catalyst (Table 2, entry 6) with an excellent yield and purity. However, other acidic catalysts such as Con. HCl, MK-10, Amberlyst 15 (H) and $HClO_4$–SiO_2 produced moderate yields (Table 2, entries 2, 4, 5, 8 and 9), and rest of the catalysts were found to be less effective.

The influence of the catalyst load was then investigated using **1a** and **2** (Table 3). The results indicated that an increasing amount of indium bromide enhanced the reaction yield until 15 mol%; however, further increases did not significantly improve the yield (see Table 3, entries 6–10). The effect of solvents in the cyclisation reaction of **1a** and **2** was also explored (Table 4). Among all of the solvents tested,

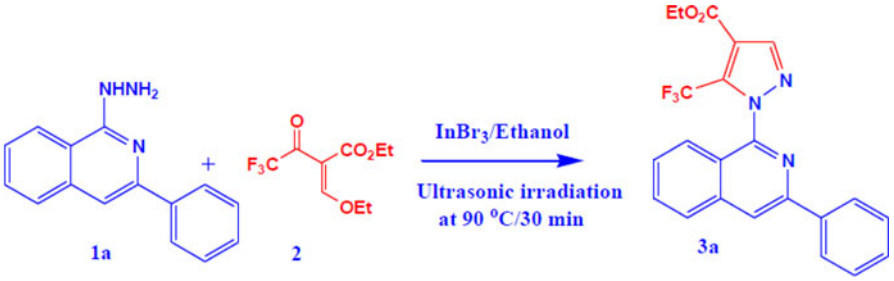
Table 1 Cyclisation of 1-hydrazino-3-substituted-isoquinolines **1** and ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate, **2**

Entry	1-hydrazino-3-substituted isoquinoline, **1**	Product, **3**	Yield[a] (%)
1	 **1a**	 **3a**	93
2	 **1b**	 **3b**	88
3	 **1c**	 **3c**	89
4	 **1d**	 **3d**	91
5	 **1e**	 **3e**	82
6	 **1f**	 **3f**	92
7	 **1g**	 **3g**	87
8	 **1h**	 **3h**	83

Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), indium bromide (20 mol%), ethanol (8 mL) in ultrasonic irradiation at 90 °C for 30 min

[a] Isolated yield

absolute ethanol proved to be an efficient solvent under ultrasonic irradiation at 90 °C (Table 4, entry 4), while other solvents, 1,4-dioxane, 2-methyl THF, 2-propanol and toluene, were found to be moderate solvents (Table 4, entries 5–8).



Scheme 2 Synthesis of ethyl-5-(trifluoromethyl)-l-(3-phenylisoquinolin-1-yl)-l*H*-pyrazole-4-carboxylate **3a**

Table 2 Effect of catalyst in the reaction of **1a** and **2**

Entry	Catalyst	Yield[a] (%)
1	No catalyst	50
2	CH_3COOH	68
3	PTSA	35
4	Montmorillonite K-10	85
5	Con. HCl	72
6	$InBr_3$	94
7	$HClO_4$–SiO_2	66
8	MK-SF	68
9	Amberlyst 15 (H)	70

Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), catalyst (20 mol%), absolute ethanol (8 mL) in ultrasonic irradiation at 90 °C for 30 min

[a] Isolated yield

Table 3 Optimisation of catalyst load in the reaction of **1a** and **2**

Entry	Indium bromide (mol%)	Yield[a] (%)
1	1	55
2	3	60
3	6	68
4	9	72
5	12	88
6	15	92
7	18	92
8	21	93
9	24	93
10	27	93

Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), indium bromide catalyst, absolute ethanol (8 mL) in ultrasonic irradiation at 90 °C for 30 min

[a] Isolated yield

In continuation, the ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates **3** were synthesised using microwave heating, as well as by ultrasonic irradiation, and were compared as shown in Table 5. It should be noted that conventional heating offered lesser yields of desired products after

Table 4 Effect of solvent in the reaction of **1a** and **2**

Entry	Solvent	Yield[a] (%)
1	DMF	62
2	DMSO	60
3	THF	68
4	Absolute ethanol	93
5	1,4-Dioxane	75
6	2-Methyl THF	73
7	2-Propanol	83
8	Toluene	80

Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), catalyst indium bromide (20 mol%), ethanol (8 mL) in ultrasonic irradiation at 90 °C for 30 min

[a] Isolated yield

Table 5 Comparison of conventional microwave heating and ultrasonic irradiation of **1** and **2**

Entry	Hydrazine, **1**	Microwave irradiation, **3** yield[a] (%)	Ultrasonic irradiation, **3** yield[a] (%)
1	1a	50	93
2	1b	61	88
3	1c	63	89
4	1d	68	91
5	1e	52	82
6	1f	67	92
7	1g	60	87
8	1h	57	83

Reaction conditions: **1** (0.1 mmol), **2** (0.11 mmol), indium bromide catalyst (20 mol%), ethanol (8 mL) at 90 °C for 30 min

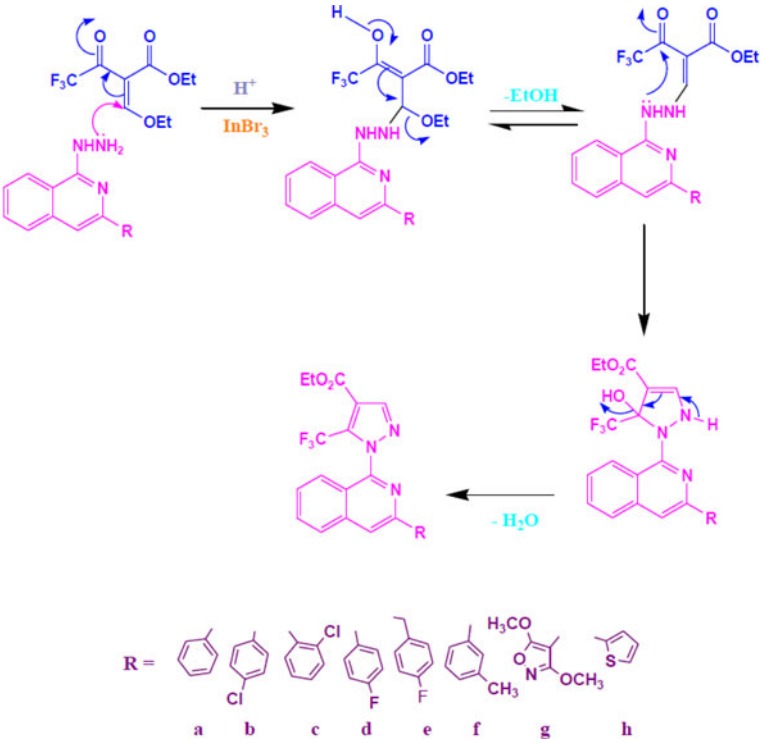
[a] Isolated yield

prolonged reaction. The result indicated that the ultrasonic-assisted reaction gave an excellent yield in comparison to conventional and microwave heating.

It should be noted that, although microwave-assisted reaction often takes place quickly compared to ultrasonic condition, in the present study, ultrasonic condition offered better results of the desired products under the optimised reaction time of 30 min.

With the optimised result in hand, various ethyl-5-(trifluoromethyl)-1-(3 substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates **3** were regio-selectively synthesised, as depicted in Scheme 1 and Table 1. The desired product **3a**–**h** were obtained in high yield and purity and were characterised by different spectral techniques, including 1H, 13C, LC–MS and elemental analysis. The proposed mechanism of the regio-selective reaction is depicted in Scheme 3.

Further, the nuclear Overhauser effect spectroscopy–nuclear magnetic resonance (NOESY–NMR) technique was utilised in confirming the regio-selective isomer. In the pyrazole cyclisation, the –CF3 group and –H position were confirmed by the NOESY–NMR technique using compound **3d** (Fig. 2). The NOESY study was performed in a one-dimensional fashion by pre-selecting individual resonances. Initially, the spectra read with the pre-selected H from the **1c** position in pyrazole gave a large negative signal, while there were no weaker positive signals. However, in order to confirm this further, the next singlet proton from the **4** position in NMR



Scheme 3 Mechanism of the reaction

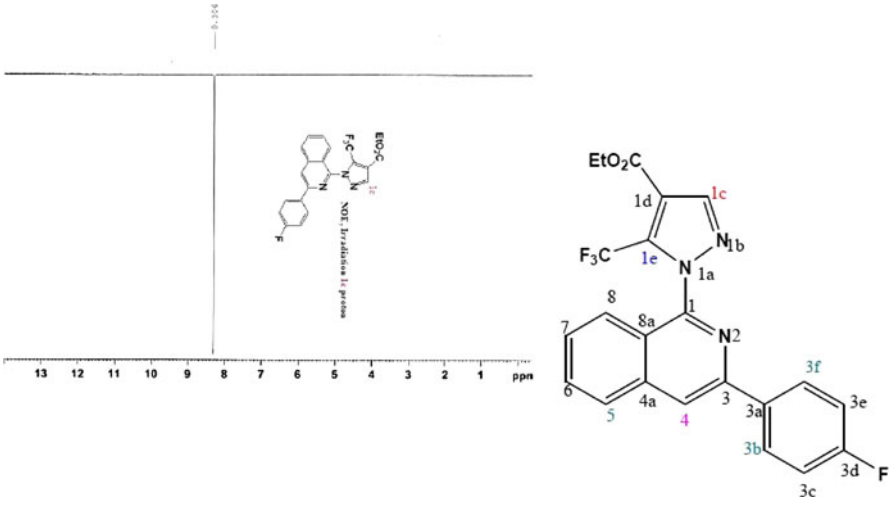


Fig. 2 NOE spectrum of **3d**

was pre-selected, which showed a large negative signal and two weaker positive signals corresponding to –2H (from the **3b**, **3f** positions) and –1H (from the **5** position). Based on the above NOESY result, it is suggested that the –CF3 group is in the **5** position and the –H group is in the **3** position of the pyrazole ring moiety.

Experimental

All reagents purchased from Sigma-Aldrich, Lancaster and Qualigens were used without further purification. Ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoates were purchased from Lancaster and used as received. Infrared (IR) spectra were recorded using Avatar 330 apparatus equipped with a DTGS detector. The NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz). Mass spectra were obtained using Agilent mass spectrometry. Sonication was performed in a Sonics Vibra-Cell VC 130 ultrasonic processor with an operating frequency of 20 kHz and a power output 0–130 Watt. Melting points were determined in open capillaries.

The starting material hydrazine derivatives were synthesised and characterised by 1H NMR, 13C NMR, FTIR, LC–MS and elemental analysis techniques.

1a: Yellow solid, mp 182–183 °C, IR (cm^{-1}) 3,283, 3,185, 3,054, 2,922, 1,949, 1,617, 1,595, 1,565, 1,504, 1,441, 1,422, 1,378, 1,325, 1,183, 1,140, 1,073, 1,030, 960, 914, 842, 818, 797, 766, 747, 683, 642, 574, 520, 411. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.80 (bs, 1H), 8.26–8.22 (m, 3H), 7.82–7.80 (d, $J = 8.0$ Hz, 1H), 7.65–7.61 (t, $J = 7.6$ Hz, 1H), 7.57 (s, 1H), 7.50–7.44 (m, 3H), 7.40–7.37 (t, $J = 7.6$ Hz, 1H), 4.64 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 156.9, 148.0, 140.0, 137.8, 2 × 130.4, 2 × 128.8, 128.5, 127.5, 126.8, 126.0, 123.1, 117.1, 106.3. LC–MS: m/e 236.1, $C_{15}H_{13}N_3$ requires Mol. Wt.: 235.11. Elemental analysis, calculated: C, 76.57; H, 5.57; N, 17.86%. Found: C, 76.49; H, 5.51; N, 17.78%.

1b: Yellow solid, mp 220–221.5 °C, IR (cm^{-1}) 3,251, 2,973, 2,261, 2,183, 2,130, 2,043, 2,020, 1,991, 1,957, 1,655, 1,616, 1,568, 1,510, 1,442, 1,417, 1,381, 1,325, 1,197, 1,143, 1,099, 1,067, 1,034, 958, 870, 841, 806, 750, 669, 618, 514. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.75–8.91 (bs, 1H), 8.27–8.24 (d, $J = 8.6$ Hz, 2H), 8.20–8.18 (d, $J = 8.3$ Hz, 1H), 7.79–7.77 (d, $J = 7.7$ Hz, 1H), 7.64–7.60 (t, $J = 8.0$ Hz, 1H), 7.58 (s, 1H), 7.52–7.51 (d, $J = 9.3$ Hz, 2H), 7.49–7.43 (t, $J = 8.8$ Hz, 1H), 7.41–6.80 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 151.4, 149.0, 138.5, 136.4, 135.1, 133.3, 131.4, 129.6, 128.9, 128.4, 128.1, 127.3, 126.5, 126.0, 116.1. LC–MS: m/e 270.0, $C_{15}H_{12}ClN_3$ requires Mol. Wt.: 269.73. Elemental analysis, calculated: C, 66.79; H, 4.48; Cl, 13.14; N, 15.58%. Found: C, 66.72; H, 4.46; N, 15.54%.

1c: Yellow solid, mp 107–108 °C, IR (cm^{-1}) 3,251, 2,973, 2,261, 2,183, 2,130, 2,043, 2,020, 1,991, 1,957, 1,655, 1,616, 1,568, 1,510, 1,442, 1,417, 1,381, 1,325, 1,197, 1,143, 1,099, 1,067, 1,034, 958, 870, 841, 806, 750, 669, 618, 514. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.85 (bs, 1H), 8.24–8.22 (d, $J = 8.4$ Hz, 1H), 7.80–7.75 (m, 2H), 7.67–7.63 (t, $J = 7.2$ Hz, 1H), 7.57–7.38 (m, 4H), 7.22 (s, 1H), 7.20–6.60 (bs, 2H). ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 156.8, 148.1, 140.2, 137.8, 137.0, 132.2, 131.8, 130.5, 129.6, 127.5, 127.0, 126.5, 123.0, 116.7, 111.0.

LC–MS: m/e 269.8, $C_{15}H_{12}ClN_3$ requires Mol. Wt.: 269.73. Elemental analysis, calculated: C, 66.79; H, 4.48; Cl, 13.14; N, 15.58%. Found: C, 66.72; H, 4.39; N, 15.51%.

1d: Yellow solid, mp 201–202 °C, IR (cm^{-1}) 3,085, 2,913, 2,177, 2,129, 2,061, 2,026, 2,001, 1,964, 1,895, 1,692, 1,653, 1,600, 1,566, 1,505, 1,408, 1,366, 1,323, 1,277, 1,215, 1,156, 1,131, 1,093, 1,044, 1,013, 964, 883, 823, 779, 754, 682, 663, 614, 587, 531, 505. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.70–8.90 (bs, 1H), 8.30–8.27 (m, 2H), 8.21–8.19 (d, $J = 8.0$ Hz, 1H), 7.80–7.78 (d, $J = 8.0$ Hz, 1H), 7.65–7.61 (t, $J = 7.2$ Hz, 1H), 7.54 (s, 1H), 7.47–7.43 (t, $J = 8.0$Hz, 1H), 7.31–7.27 (t, $J = 8.8$ Hz, 2H), no clear NH_2 peak appeared. ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 164.0, 161.5, 156.9, 147.0, 137.8, 136.5, 130.52, 128.8, 128.7, 127.4, 126.1, 123.1, 116.9, 115.7, 106.1. LC–MS: m/e 254.1, $C_{15}H_{12}FN_3$ requires Mol. Wt.: 253.1 Elemental analysis, calculated: C, 71.13; H, 4.78; F, 7.50; N, 16.59%. Found: C, 71.07; H, 4.69; N, 16.52%.

1e: Yellow solid, mp 162–163 °C, IR (cm^{-1}) 3,280, 2,912, 1,778, 1,616, 1,592, 1,561, 1,499, 1,447, 1,422, 1,391, 1,322, 1,237, 1,211, 1,175, 1,156, 1,087, 959, 852, 820, 787, 743, 583, 550, 503. ^{1}H NMR (400 MHz, DMSO-D6, ppm): 8.13–8.11 (d, $J = 8.0$ Hz, 1H), 7.62–7.53 (m, 2H), 7.42–7.36 (m, 3H), 7.13–7.08 (t, $J = 9.2$ Hz, 2H), 6.72 (s, 1H), 3.98 (s, 2H). ^{13}C NMR(100 MHz, DMSO-D6, ppm): δ 162.4, 160.0, 156.6, 152.1, 137.5, 136.8, 131.2, 131.2, 130.3, 126.5, 125.5, 123.0, 116.3, 115.4, 108.1, 43.2. LC–MS: m/e 267.7, $C_{16}H_{14}FN_3$ requires Mol. Wt.: 267.12. Elemental analysis, calculated: C, 71.89; H, 5.28; F, 7.11; N, 15.72%. Found: C, 71.88; H, 5.27; N, 15.76%.

1f: Yellow solid, mp 161–162.5 °C, IR (cm^{-1}) 3,184, 3,043, 2,148, 1,966, 1,614, 1,583, 1,564, 1,509, 1,422, 1,375, 1,323, 1,172, 1,090, 966, 943, 814, 786, 745, 646. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.75 (bs, 1H), 8.20–8.18 (d, $J = 8.4$ Hz, 1H), 8.06 (s, 1H), 8.04–8.02 (d, J= 8.0 Hz, 1H), 7.80–7.78 (d, $J = 8.0$ Hz, 1H), 7.64–7.60 (t, $J = 8.0$ Hz, 1H), 7.54 (s, 1H), 7.46–7.42 (t, $J = 8.4$ Hz, 1H), 7.37–7.33 (t, $J = 7.6$ Hz, 1H), 7.20–7.18 (d, $J = 7.2$ Hz, 1H), 6.96–5.95 (bs, 2H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 156.8, 148.1, 2 × 139.9, 137.8, 130.4, 129.2, 128.7, 127.4, 127.3, 126.0, 124.0, 123.1, 117.0, 106.3, 21.7. LC–MS: m/e: 249.8, $C_{16}H_{15}N_3$ requires Mol. Wt.: 249.13. Elemental analysis, calculated: C, 77.08; H, 6.06; N, 16.85%. Found: C, 77.03; H, 6.12; N, 16.76%.

1g: Yellow solid, mp 180–181.5 °C, IR (cm^{-1}) 3,291, 3,191, 3,046, 2,530, 2,420, 2,443, 2,290, 2,225, 2,143, 1,897, 1,842, 1,613, 1,585, 1,566, 1,556, 1,527, 1,453, 1,391, 1,323, 1,229, 1,182, 1,140, 1,080, 1,020, 956, 897, 855, 811, 749, 704, 657, 635, 572. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ 8.84 (bs, 1H), 8.17–8.15 (d, $J = 8.0$ Hz, 1H), 7.77–7.73 (m, 2H), 7.63–7.59 (t, $J = 7.6$Hz, 1H), 7.56–7.54 (d, $J = 6.0$ Hz, 1H), 7.44–7.40 (m, 2H), 7.16–7.14 (t, $J = 4.8$ Hz, 1H). ^{13}CNMR (100 MHz, DMSO-D6, ppm): δ 156.6, 146.3, 144.0, 137.6, 130.7, 128.5, 127.1, 127.0, 125.8, 124.0, 123.2, 116.9, 104.4. LC–MS: m/e 242.1, $C_{13}H_{11}N_3S$ requires Mol. Wt.: 241.07. Elemental analysis, calculated: C, 64.70; H, 4.59; N, 17.41; S, 13.29%. Found: C, 64.64; H, 4.51; N, 17.37; S, 13.22%.

1h: Yellow solid, mp 153–154.5 °C, IR (cm^{-1}) 3,292, 3,037, 2,330, 2,290, 2,251, 1,896, 1,833, 1,616, 1,561, 1,520, 1,461, 1,407, 1,321, 1,237, 1,200, 1,143, 1,104, 964, 893, 828, 793, 749, 653.6, 596, 564. ^{1}H NMR (400 MHz, DMSO-D6, ppm): δ

8.98–8.70 (bs, 1H), 8.21-8.19 (d, $J = 8.0$Hz, 1H), 7.79–7.77 (d, $J = 8.0$ Hz, 1H), 7.66–7.62 (t, $J = 7.2$ Hz, 1H), 7.49–7.45 (t, $J = 8.0$ Hz,1H), 7.10 (s, 1H), 2.65 (s, 3H), 2.47 (s, 3H). The NH_2 peak does not appear. ^{13}C NMR (100 MHz, DMSO-D6, ppm): δ 167.0, 159.0, 156.9, 141.9, 137.4, 130.5, 127.1, 126.2, 123.0, 116.4, 116.3, 109.1, 13.1, 12.3. LC–MS: m/e 255.1, $C_{14}H_{14}N_4O_3$ requires Mol. Wt.: 286.11. Elemental analysis, calculated: C, 58.73; H, 4.93; N, 19.57; O, 16.77%. Found: C, 58.64; H, 4.91; N, 19.61%.

General procedure for the synthesis of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates, (**3a**–**h**)

A mixture of 1-hydrazino isoquinoline **1** (0.1 mmol), ethyl-2-(ethoxymethylene)-4,4,4-trifluoro-3-oxobutanoate **2** (0.11 mmol), indium bromide catalyst (10 mol%) and ethanol (8.0 mL) and the resulting mixture was subjected to ultrasonic irradiation by immersing the probe directly into the reaction mixture for 30 min. The operating frequency was 15 kHz and the output power was 100 Watt through manual adjustment. The reaction was monitored by TLC. After completion of the reaction, the resulting solution was concentrated in vacuo. The crude products were subjected to silica-gel (230–400 mesh) flash column chromatography using hexane–ethyl acetate (90:10) as an eluent to afford the pure products **3**, which were characterised by 1H NMR, 13C NMR, FTIR, LC–MS and elemental analysis techniques.

3a: Yellow solid, mp 90–91 °C, IR (cm^{-1}) 2,913, 2,185, 2,113, 2,036, 2,019, 1,991, 1,950, 1,906, 1,716, 1,627, 1,561, 1,465, 1,419, 1,391, 1,330, 1,297, 1,235, 1,195, 1,152, 1,033, 953, 881, 846, 769, 745, 680, 589, 565. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.28–8.27 (2H, d, $J = 6.4$), 8.14–8.12 (2H, d, $J = 8.4$), 8.01–7.99 (1H, d, $J = 8.4$), 7.79–7.73 (2H, m), 7.63–7.59 (1H, t, $J = 7.6$), 7.52–7.48 (2H, t, $J = 7.2$), 7.45–7.41 (1H, t, $J = 7.2$), 4.46–4.4 (2H, q), 1.44–1.41 (3H, t, $J = 6.8$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.0, 149.5, 149.0, 142.8, 139.3, 137.7, 131.4, 129.1, 128.8, 128.6, 127.3, 126.9, 124.4, 122.9, 118.5, 117.8, 116.8, 61.3, 14.1. LC–MS: m/e 412.2, $C_{22}H_{16}F_3N_3O_2$ requires Mol. Wt.: 411.12. Elemental analysis, calculated: C, 64.23; H, 3.92; F, 13.85; N, 10.21; O, 7.78%. Found: C, 64.19; H, 3.86; N, 10.12%.

3b: Yellow solid, mp 108–110 °C, IR (cm^{-1}) 3,050, 2,913, 2,850, 2,495, 2,216, 2,162, 2,135, 2,042, 2,018, 1,979, 1,947, 1,717, 1,641, 1,629, 1,600, 1,546, 1,468, 1,339, 1,305, 1,267, 1,202, 1,164, 1,109, 1,034, 905, 868, 826, 782, 743, 683, 617, 523. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.28 (1H, s), 8.23 (1H, s), 8.09–8.06 (2H, d, $J = 8.4$), 8.01–7.99 (1H, d, $J = 8.4$), 7.80–7.74 (2H, m), 7.65–7.60 (1H, t, $J = 8.0$), 7.48–7.45 (2H, d, $J = 9.2$), 4.46–4.41 (2H, q), 1.44–1.41 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.9, 149.1, 148.2, 142.8, 139.3, 136.1, 135.3, 2 × 131.6, 2 × 129.0, 128.8, 128.1, 2 × 127.3, 2 × 124.5, 123.0, 118.4, 116.9, 61.4, 14.1. LC–MS: m/e 446.2, $C_{22}H_{15}ClF_3N_3O_2$ requires Mol. Wt.: 445.08. Elemental analysis, calculated: C, 59.27; H, 3.39; Cl, 7.95; F, 12.78; N, 9.43; O, 7.18%. Found: C, 59.23; H, 3.32; N, 9.36%.

3c: Yellow semisolid, mp 34–35 °C, IR (cm^{-1}) 2,989, 2,908, 2,318, 2,232, 2,182, 2,130, 2,086, 2,051, 2,001, 1,958, 1,715, 1,622, 1,588, 1,557, 1,464, 1,394,

1,325, 1,261, 1,235, 1,144, 1,033, 944, 883, 827, 773, 747, 692, 566, 511. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.27 (2H, s), 8.03–8.01 (1H, d, $J = 8.4$), 7.83–7.79 (1H, m), 7.73–7.70 (1H, dd, $J = 9.6, 2.0$), 7.69–7.66 (2H, m), 7.53–7.50 (1H, dd, $J = 9.6, 1.6$), 7.41–7.33 (2H, m), 4.44–4.38 (2H, q), 1.42–1.39 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.9, 149.0, 148.3, 142.9, 138.4, 137.5, 132.4, 132.0, 131.5, 130.3, 2 × 129.7, 129.2, 127.4, 2 × 127.1, 124.1, 124.1, 123.1, 116.7, 61.3, 14.0. LCMS: m/e 446.2, $C_{22}H_{15}ClF_3N_3O_2$ requires Mol. Wt.: 445.08. Elemental analysis, calculated: C, 59.27; H, 3.39; Cl, 7.95; F, 12.78; N, 9.43; O, 7.18%. Found: C, 59.23; H, 3.32; N, 9.38%.

3d: Yellow solid, mp 86–87.5 °C, IR (cm^{-1}) 2,959, 2,279, 2,224, 2,182, 2,157, 2,132, 2,056, 2,038, 2,017, 1,971, 1,723, 1,637, 1,600, 1,564, 1,476, 1,453, 1,427, 1,337, 1,306, 1,271, 1,223, 1,156, 1,111, 1,073, 1,043, 1,026, 1,001, 923, 881, 839, 793, 714, 711, 680, 648, 613, 577, 525. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.3 (1H, s), 8.2 (1H, s), 8.15–8.10 (2H, m), 8.00–7.98 (1H, d, $J = 8.0$), 7.79–7.73 (2H, m), 7.63–7.59 (1H, t, $J = 8.0$), 7.20–7.15 (2H, t, $J = 10.0$), 4.46–4.40 (2H, q), 1.44–1.41 (3H, t, $J = 6.8$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 162.4, 160.9, 149.0, 148.5, 142.8, 139.4, 133.9, 131.5, 128.7, 128.7, 127.3, 124.4, 122.8, 118.2, 116.9, 115.9, 115.7, 61.4, 29.7, 14.1. LC–MS: m/e 430.2, $C_{22}H_{15}F_4N_3O_2$ requires Mol. Wt.: 429.11. Elemental analysis, calculated: C, 61.54; H, 3.52; F, 17.70; N, 9.79; O, 7.45%. Found: C, 61.48; H, 3.47; N, 9.70%.

3e: Yellow oily liquid, mp 34–35 °C, IR (cm^{-1}) 2,989, 2,908, 2,318, 2,232, 2,182, 2,130, 2,086, 2,051, 2,001, 1,958, 1,715, 1,622, 1,588, 1,557, 1,464, 1,394, 1,325, 1,261, 1,235, 1,144, 1,033, 944, 883, 827, 773, 747, 692, 566, 511. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.25 (1H, s), 7.84–7.82 (1H, d, $J = 8.0$), 7.74–7.70 (1H, m), 7.59–7.54 (3H, m), 7.28–7.25 (2H, m), 7.02–6.98 (2H,t, $J = 8.8$), 4.44–4.38 (2H, q), 4.27 (2H, s), 1.42–1.39 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.9, 152.9, 148.9, 142.8, 2 × 139.0, 134.6, 131.3, 130.7, 130.6, 2 × 128.4, 126.6, 2 × 124.1, 122.6, 121.3, 116.6, 115.5, 115.2, 61.3, 42.8, 14.1. LC–MS: m/e 444.0, $C_{23}H_{17}F_4N_3O_2$ requires Mol. Wt.: 443.13. Elemental analysis, calculated: C, 62.30; H, 3.86; F, 17.14; N, 9.48; O, 7.22%. Found: C, 62.27; H, 3.79; N, 9.41%.

3f: Yellow solid, mp 93–94.5 °C, IR (cm^{-1}) 3,068, 2,983, 2,925, 1,961, 1,728, 1,628, 1,566, 1,470, 1,443, 1,413, 1,324, 1,299, 1,268, 1,237, 1,085, 1,038, 959, 898, 854, 754, 689, 523. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.28–8.25 (2H, d, $J = 12.0$), 8.00–7.90 (3H, m), 7.78–7.71 (2H, m,), 7.62–7.58 (1H, m), 7.40–7.36 (1H, t, $J = 7.6$), 7.25–7.23 (1H, d, $J = 8.4$), 4.46–4.40 (2H, q), 2.45 (3H, s), 1.44–1.41 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 161.0, 149.6, 148.9, 142.8, 139.3, 138.5, 137.6, 131.3, 129.9, 128.7, 128.5, 127.6, 127.3, 124.4, 124.0, 122.9, 120.5, 118.5, 116.8, 61.4, 29.7, 21.5, 14.1. LC–MS: m/e 426.2, $C_{23}H_{18}F_3N_3O_2$ requires Mol. Wt.: 425.41. Elemental analysis, calculated: C, 64.94; H, 4.26; F, 13.40; N, 9.88; O, 7.52%. Found: C, 64.90; H, 4.19; N, 9.82%.

3g: Yellow solid, mp 128–129 °C, IR (cm^{-1}) 2,989, 2,908, 2,318, 2,232, 2,182, 2,130, 2,086, 2,051, 2,001, 1,958, 1,715, 1,622, 1,588, 1,557, 1,464, 1,394, 1,325, 1,261, 1,235, 1,144, 1,033, 944, 883, 827, 773, 747, 692, 566, 511. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.27(1H, s), 8.09 (1H, s), 7.95–7.93 (1H, d, $J = 8.0$), 7.76–7.71 (3H, m), 7.58–7.55 (1H, t, $J = 7.2$), 7.41–7.40 (1H, d, $J = 5.2$),

7.15–7.13 (1H, t, $J = 4.8$), 4.46–4.40 (2H, q), 1.44–1.40 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 160.9, 148.8, 145.0, 143.1, 142.8, 139.3, 134.7, 134.3, 131.6, 128.2, 127.6, 127.0, 125.3, 124.6, 122.7, 120.4, 117.7, 116.6, 61.4, 14.1. LC–MS: m/e 418.2, $C_{20}H_{14}F_3N_3O_2S$ requires Mol. Wt.: 417.41. Elemental analysis, calculated: C, 57.55; H, 3.38; F, 13.65; N, 10.07; O, 7.67; S, 7.68%. Found: C, 57.49; H, 3.32; N, 10.01; S, 7.65%.

3h: Yellow solid, mp 106–108 °C, IR (cm^{-1}) 3,726, 3,623, 3,345, 2,984, 2,904, 2,190, 2,153, 1,964, 1,713, 1,625, 1,563, 1,468, 1,397, 1,326, 1,270, 1,240, 1,150, 1,041, 958, 903, 842, 753, 716, 688, 605, 539, 453, 403. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.29 (1H, s), 8.19 (1H, s), 7.99–7.97 (1H, d, $J = 8.4$ Hz), 7.85 (1H, s), 7.83–7.79 (1H, t, $J = 8.0$), 7.66–7.59 (1H, m), 4.45–4.40 (2H, q), 2.61 (3H, s), 2.47 (3H, s), 1.43–1.40 (3H, t, $J = 7.2$). ^{13}C NMR (100 MHz, $CDCl_3$ ppm): δ 168.0, 160.8, 158.7, 149.4, 143.0, 142.7, 138.9, 134.9, 131.8, 129.0, 126.9, 124.3, 122.9, 121.5, 116.7, 114.8, 113.4, 61.4, 14.0, 12.4, 11.5. LC–MS: m/e 463.2, $C_{21}H_{17}F_3N_4O_5$ requires Mol. Wt.: 462.12. Elemental analysis, calculated: C, 54.55; H, 3.71; F, 12.33; N, 12.12; O, 17.30%. Found: C, 54.50; H, 3.65; N, 12.05%.

Conclusion

In conclusion, an efficient method for the regio-selective synthesis of series of ethyl-5-(trifluoromethyl)-1-(3-substituted-isoquinolin-1-yl)-1*H*-pyrazole-4-carboxylates using indium bromide catalyst in the presence of absolute ethanol solvent is reported under the ultrasonic irradiation method.

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