Res Chem Intermed (2012) 38:615–627
DOI 10.1007/s11164-011-0375-y

An efficient 2-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate (TBTU)-mediated synthesis of 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinoline-1-yl)-1*H*-pyrazole-4-carboxamides

K. Prabakaran · F. Nawaz Khan · Jong Sung Jin

Received: 2 August 2011 / Accepted: 25 August 2011 / Published online: 13 September 2011

Abstract A series of 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinoline-1-yl)-1*H*-pyrazole-4-carboxamides **4** has been effectively achieved in high yield and purity from the reaction of pyrazole carboxylic acid **2** with amines **3** in the presence of TBTU as a catalyst and diisopropyl ethylamine as a base in acetonitrile at room temperature.

Keywords Isocoumarins · TBTU · Pyrazole-4-carboxamide · 1,3-Disubstituted isoquinoline

Introduction

Pyrazole derivatives are an important class of heterocyclic compounds [1], some of which are depicted in Fig. 1. Pyrazoles with carboxamide moieties and trifluoromethane group (e.g., pyrazosulfuron-ethyl, tebufenpyrad and tolfenpyrad, the active pyrazole carboxamides) have demonstrated their potential in the agrochemical industry [2–5]. Also, pyrazole carboxylic acids represent important building blocks in organic and medicinal chemistry [6, 7]. For example, celecoxib, a first-to-market drug of a number of selective cyclo-oxygenase 2 (COX-2) inhibitors, is a promising

Electronic supplementary material The online version of this article (doi: 10.1007/s11164-011-0375-y) contains supplementary material, which is available to authorized users.

K. Prabakaran · F. N. Khan (✉)
Organic and Medicinal Chemistry Research Laboratory, Organic Chemistry Division, School of Advanced Sciences, VIT University, Vellore 632 014, Tamil Nadu, India
e-mail: nawaz_f@yahoo.co.in

F. N. Khan · J. S. Jin
Division of High Technology Materials Research, Busan Center, Korea Basic Science Institute (KBSI), Busan 618 230, Korea
e-mail: jsjin@kbsi.re.kr

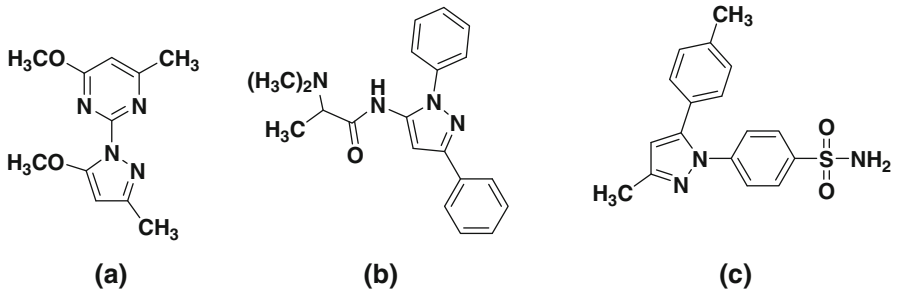


Fig. 1 **a** Mepirizole, **b** difenamizole, **c** cyclooxygenase-2 (COX-2) inhibitor Celecoxib

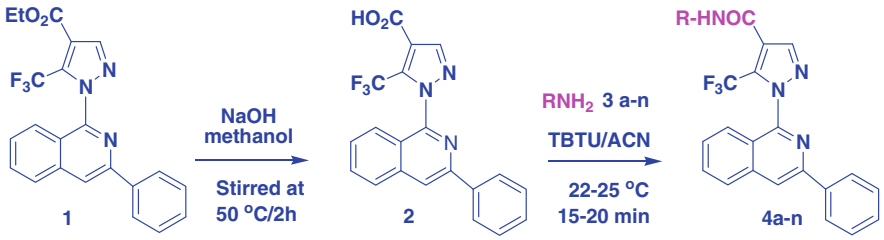
anti-inflammatory and analgetic agent [8, 9]. Pyrazole-substituted epothilone derivative showed strong anti-tumour activity through the stabilisation of microtubules by binding with tubulin [10].

Isoquinolines are useful intermediates in organic synthesis, and have demonstrated their potential in heterocycles construction [11–15] through palladium-catalysed annulations, electrophilic cyclisations, etc. More importantly, 1,3-disubstituted isoquinoline skeleton with pharmaceutically important properties [16–20], such as chiral ligands for the transition metal catalysts [21], and their iridium complexes in organic light emitting diodes (OLEDs) [22], has been achieved. A number of methods have been developed for the synthesis of 1,3-disubstituted isoquinolines, including palladium-catalysed cross-coupling [23], copper-catalysed tandem reaction [24] and others [25–29]. Synthesis of disubstituted isoquinolines have been reported [30, 31] in which 1,3-disubstituted derivatives showed an extensive range of biological activities including potent thrombin inhibitory and anti-bacterial activity [32, 33]. In our continued research interest on isocoumarins and isoquinolines [34–55], the present article envisioned the efficient methodology for a series of 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinoline-1-yl)-1*H*-pyrazole-4-carboxamides in high yield and purity.

Results and discussion

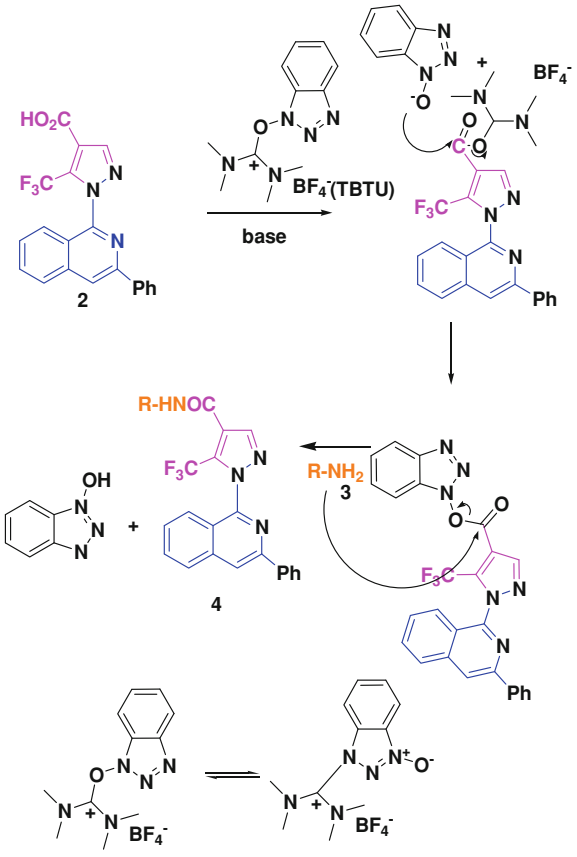
Reactions of 5-(trifluoromethyl)-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxylic acid **2** with primary amines **3** in the presence of TBTU as a catalyst and *N*,*N*-diisopropylethylamine as a base in acetonitrile afforded 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxamides **4** (Scheme 1; Tables 1, 2, 3, 4 and 5) in excellent yields (Table 5). Compound **2** was synthesised in 97% yield from hydrolysis of **1** with sodium methoxide in methanol (Scheme 1).

The advantages of this reaction include low toxicity of by-products, ease of separation of products and simple work-up. A proposed mechanism for the formation of **4** is depicted in Scheme 2. The optimisation of reaction condition was carried out by choosing acid **2** and amine **3a** using different coupling reagents and diisopropyl ethylamine in acetonitrile at room temperature. The result obtained is recorded in Table 1. The reaction works very well in TBTU (entry 4). However,



Scheme 1 Synthesis of 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxamide **4**

Scheme 2 A possible mechanism for the amidation of **2** in the presence of TBTU



coupling reagents such as HBTU and T_3P produced moderate yields (Table 1, entries 1 and 3), and other reagents were found to be less effective.

The quantities of both TBTU and DIPEA were varied to maximise the yield of **4a** from reaction of **2** with **3a** (Table 2). The results indicated that the optimised condition involves use of 1.1 equivalents of TBTU and at least 2.0 equivalents of DIPEA (Table 2, entry 10). The effect of base on the reaction was also investigated (Table 3). It was found that reactions involving the use of aliphatic amines such as methyl, ethyl, 1-phenyl ethyl and *n*-hexyl amines do not require the use of diisopropylethyl amine as a base. However,

Table 1 Effect of coupling reagents in the amidation of **2** and **3a**

Entry	Coupling reagent	Yield[a] (%)
1	HATU	72
2	EDC.HCl/HOBt	48
3	T_3P	70
4	TBTU	90
5	DCC	52

Reaction conditions: a mixture of **2** (1.0 eq), amine **3** (1.1 eq), diisopropyl ethyl amine (2.0 eq, only for acrylic and aromatic amines) and coupling reagent (1.1 eq) in acetonitrile solvent (8 mL) was stirred at ambient temperature for 20–30 min

[a] Isolated yield

Table 2 Effect of amount of TBTU and diisopropyl ethyl amine loading in the amidation of **2** and **3a**

Entry	TBTU (eq)	DIPEA (eq)	Yield[a] (%)
1	0.5	1.0	62
2	0.75	1.0	70
3	1.0	1.0	72
4	1.1	1.0	72
5	1.2	1.0	72
6	1.1	1.2	75
7	1.1	1.4	80
8	1.1	1.6	83
9	1.1	1.8	87
10	1.1	2.0	90
11	1.1	2.2	90
12	1.1	2.4	90

Reaction conditions: a mixture of **2** (1.0 eq), amine **3** (1.1 eq) in acetonitrile solvent (8 mL) was stirred at ambient temperature for 20–30 min

[a] Isolated yield

it must be noted that the reaction completes within 15–20 min in every case and therefore the effect of base in reactions **2** and **3i** was also investigated (Table 3). The results suggested that decreasing the quantity of base gradually increases the yield in which aliphatic amine **3i** itself acted as a base and facilitated the reaction. The effect of solvent in reactions **2** and **3i** was investigated and the results are recorded in Table 4. The results revealed that solvents such as acetonitrile and tetrahydrofuran (Table 4, entries 1 and 2) gave good yields in comparison to solvents like 2-methyltetrahydrofuran, dichloromethane and *N*,*N*-dimethyl formamide. Several amines **3** were tested in reactions described in Scheme 1 under the optimised condition. The yields of **4a–n** were in the range of 84–93% with high purity (Table 5). The products were characterised by different spectral techniques including ^{1}H NMR, ^{13}C NMR, IR and MS.

Experimental

All reagents were purchased from Sigma-Aldrich, Lancaster, and Qualigens, India, and used without further purification. TBTU purchased from Spectrochem, India,

Table 3 Effect of loading of diisopropylethyl amine in **2** and **3i**

Entry	DIPEA (eq)	Yield[a] (%)
1	2.0	25
2	1.7	30
3	1.4	36
4	1.1	55
5	0.8	62
6	0.5	67
7	0.2	75
8	Nil	91

Reaction conditions: a mixture of **2** (1.0 eq), amine **3** (1.1 eq), diisopropylethyl amine and TBTU (1.1 eq) in acetonitrile solvent (8 mL) was stirred at ambient temperature for 20–30 min

[a] Isolated yield

Table 4 Effect of solvent in the amidation reaction of **2** and **3i**

Entry	Solvent	Yield[a] (%)
1	Acetonitrile	91
2	Tetrahydrofuran	88
3	2-methyl THF	85
4	Dichloromethane	76
5	*N,N*-dimethyl formamide	70

Reaction conditions: a mixture of **2** (1.0 eq), amine **3** (1.1 eq), diisopropyl ethyl amine (2.0 eq, only for acylic and aromatic amines) and TBTU (1.1 eq) in solvent (8 mL) was stirred at ambient temperature for 20–30 min

[a] Isolated yield

and used as received. Infrared (IR) spectra were recorded using Avatar 330 equipped with DTGS detector. The NMR spectra were recorded on a Bruker Spectrospin Avance DPX400 Ultrashield (400 MHz for ^{1}H and 100 MHz for ^{13}C). Mass spectra were obtained using Agilent mass spectrometry. Melting points were determined in open capillaries.

Synthesis of 5-(trifluoromethyl)-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxylic acid **2**

A mixture of ethyl-5-(trifluoromethyl)-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxylate **1** (30 g, 72.97 mmol), sodium hydroxide (pellets, 3.21 g, 1.1 eq) in methanol/water (3:1) mixture were stirred vigorously for 2 h. The reaction completion was monitored by TLC analysis, the reaction mixture concentrated to remove methanol and the remaining aqueous layer further diluted with 300 mL water and the pH adjusted to 3–4 range. The solid precipitate was filtered off and dried under high vacuum for 2 h at 50–55 °C to afford pure 5-(trifluoromethyl)-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxylic acid **2** (27 g, 96.6%) as light yellow crystals: mp 209–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 13.55(bs, 1H), 8.80 (s, 1H), 8.46 (s, 1H), 8.26–8.24 (d, $J = 8.4$ Hz, 1H), 8.20–8.19 (d, $J = 7.6$ Hz, 2H), 7.97–7.93 (t, $J = 6.8$ Hz, 1H), 7.78–7.72 (q, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.50–7.47 (app. t, $J = 7.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.1,

Table 5 Synthesis of **4** according to Scheme 1

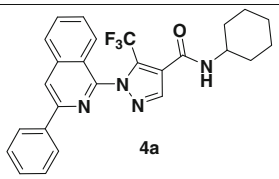
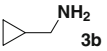
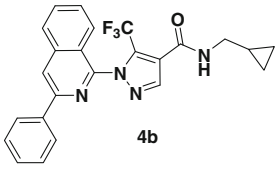
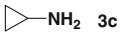
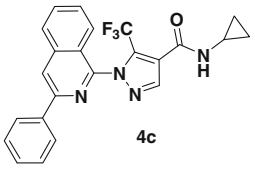
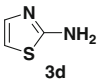
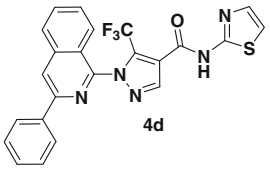
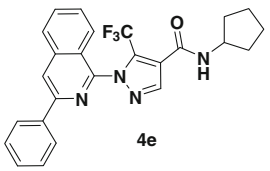
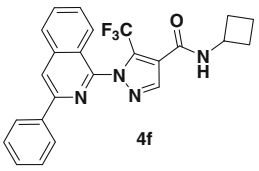
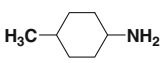
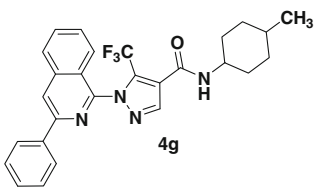
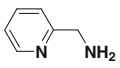
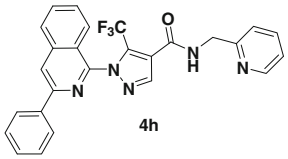
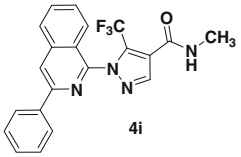
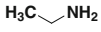
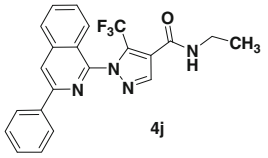
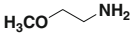
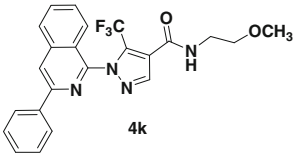
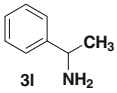
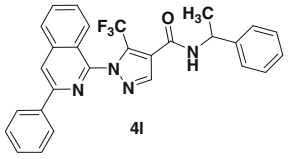
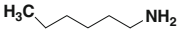
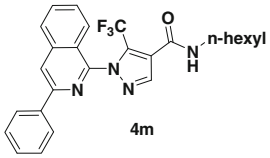
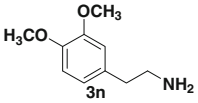
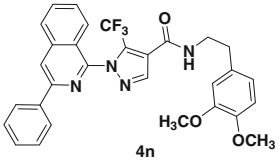
Entry	Amines **3**	Product **4**	Yield[a] (%)
1	 **3a**	 **4a**	90
2	 **3b**	 **4b**	89
3	 **3c**	 **4c**	92
4	 **3d**	 **4d**	88
5	 **3e**	 **4e**	84
6	 **3f**	 **4f**	87
7	 **3g**	 **4g**	93

Table 5 continued

Entry	Amines **3**	Product **4**	Yield[a] (%)
8	 **3h**	 **4h**	85
9	 **3i**	 **4i**	91
10	 **3j**	 **4j**	90
11	 **3k**	 **4k**	87
12	 **3l**	 **4l**	90
13	 **3m**	 **4m**	86
14	 **3n**	 **4n**	87

Reaction conditions: a mixture of 2 (1.0 eq), amine 3 (1.1 eq), diisopropyl ethyl amine (2.0 eq, only for acylic and aromatic amines) and TBTU (1.1 eq) in acetonitrile solvent (8 mL) was stirred at ambient temperature for 20–30 min.

[a] Isolated yield

149.0, 148.5, 143.6, 139.5, 137.5, 133.1, 132.5, 129.8, 129.5, 128.1, 126.9, 124.5, 122.7, 119.5, 118.2; IR (cm^{-1}) 3,366, 3,094, 2,921, 2,853, 2,249, 1,699, 1,638, 1,595, 1,505, 1,481, 1,413, 1,307, 1,227, 1,154, 1,100, 1,009, 922, 879, 850, 823, 743, 679, 631, 606, 549, 523, 503; LC–MS: *m/z* 384.2, $C_{20}H_{12}F_3N_3O_2$ requires 383.09. Calcd C, 62.67; H, 3.16; N, 10.96%. Found: C, 62.59; H, 3.08; N, 10.87%.

General procedure for the synthesis of 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinolin-1-yl)-1*H*-pyrazole-4-carboxamide **4**

To a 20-mL vial TBTU (0.46 g, 1.43 mmol) and diisopropyl ethylamine (0.336 g; 2.60 mmol; in case of aliphatic amines not necessary to add additional base) were added to a mixture of **2** (0.5 g; 1.30 mmol), amine **3** (1.43 mmol), acetonitrile (8 mL) at room temperature under nitrogen atmosphere. This reaction mixture was stirred vigorously for 20–30 min and its completion was monitored by TLC analysis. The reaction mixture was quenched by the addition of water (15 mL) and the solid precipitate was filtered off and dried under vacuum for 2 h to give **4a–4n** in high yields (Table 5).

The analysis data of **4a–n** are given below.

4a. Yield: 90% of white solid; mp 206–207 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (s, 1H), 8.50 (d, $J = 7.6$ Hz, 1H), 8.33 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (t, $J = 8.4$ Hz, 1H), 7.79–7.72 (m, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.49 (app. t, $J = 8.4$ Hz, 1H), 3.78 (bs, 1H), 1.89–1.74 (m, 4H), 1.62 (d, $J = 12.8$ Hz, 1H), 1.39–1.15 (m, 5H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 159.6, 148.9, 148.4, 140.6, 139.5, 137.6, 132.46, 129.8, 129.7, 129.4, 128.2, 126.9, 124.6, 122.8, 122.5, 119.2, 48.7, 32.6, 25.6, 25.1; IR (cm^{-1}) 3,225, 3,056, 2,983, 2,930, 2,854, 2,185, 1,984, 1,637, 1,585, 1,544, 1,493, 1,468, 1,407, 1,325, 1,289, 1,247, 1,158, 1,089, 1,043, 956, 887, 850, 750, 694, 566, 522, 452; LC–MS: *m/z* 465.1, 466.1. $C_{26}H_{23}F_3N_4O$ requires 464.18. Anal Calcd for $C_{26}H_{23}F_3N_4O$: C, 67.23; H, 4.99; N, 12.06%. Found: C, 67.20; H, 4.99; N, 12.01%.

4b: Yield: 406 mg (89%) of white solid; mp 210–211 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78–8.75 (m, 2H), 8.36 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 8.0$ Hz, 1H), 7.79–7.72 (m, 2H), 7.58–7.54 (t, $J = 8.4$ Hz, 2H), 7.48 (app. t, $J = 7.2$ Hz, 1H), 3.21–3.18 (t, $J = 6.0$ Hz, 2H), 1.06 (m, 1H), 0,51–0.46 (m, 2H), 0.29–0.27 (m, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.4, 148.9, 148.4,140.6, 139.5, 137.6, 132.4, 129.8, 129.7, 129.5, 128.2, 126.9, 124.6, 122.8,122.2, 119.3, 43.7, 11.2, 3.7; IR (cm^{-1}) 3,213, 3,055, 2,866, 1,666, 1,639, 1,589, 1,544, 1,490, 1,469, 1,406, 1,328, 1,279, 1,248, 1,164, 1,075, 1,043, 957, 886, 852, 749, 692; LC–MS: m/z 437.1, 438.1. $C_{24}H_{19}F_3N_4O$ requires 436.15. Anal Calcd for $C_{24}H_{19}F_3N_4O$: C, 66.05; H, 4.39; N, 12.84%. Found: C, 66.02; H, 4.40; N, 12.81%.

4c: Yield: 406 mg (92%) of white solid; mp 223–224 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (s, 1H), 8.70 (d, $J = 4.0$ Hz, 1H), 8.33 (s, 1H), 8.26–8.20 (m, 3H), 7.94 (app. t, $J = 7.2$ Hz, 1H), 7.76 (app. t, $J = 8.0$ Hz, 1H), 7.70 (d, $J = 8.4$ Hz, 1H), 7.58–7.54 (t, $J = 7.6$ Hz, 2H), 7.48 (app. t, $J = 7.2$ Hz, 1H), 2.87 (m, 1H), 0.78–0.73 (m, 2H), 0.61–0.57 (m, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 161.1, 148.5, 148.0, 140.3, 139.1, 137.1, 132.0, 129.3, 129.3, 129.0, 127.8, 126.4, 124.1, 122.3, 121.6, 118.90, 22.8, 5.8; IR (cm^{-1}), 3,226, 3,053, 2,921, 2,851, 2,267,

2,184, 2,139, 2,029, 2,013, 1,986, 1,960, 1,661, 1,636, 1,587, 1,549, 1,493, 1,470, 1,406, 1,380, 1,325, 1,292, 1,251, 1,162, 1,044, 1,022, 954, 888, 795, 751, 727, 694, 661, 564, 521, 500, 449; LC–MS: *m/z* 423.1, 424.1. $C_{23}H_{17}F_3N_4O$ requires 422.14. Anal Calcd for $C_{23}H_{17}F_3N_4O$: C, 65.40; H, 4.06; N, 13.26%. Found: C, 65.37; H, 4.06; N, 12.27%.

4d: Yield: 428 mg (88%) of yellow solid; mp 235–236 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 12.99 (bs, 1H), 8.81 (s, 1H), 8.71 (s, 1H), 8.27 (d, $J = 8.4$ Hz, 1H), 8.23–8.21 (d, $J = 8.4$ Hz, 2H), 7.97 (app. t, $J = 8.0$ Hz, 1H), 7.81–7.73 (m, 2H), 7.62–7.55 (m, 3H), 7.49 (app. t, $J = 7.2$ Hz, 1H), 7.36 (d, $J = 3.6$ Hz, 1H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 159.4, 148.8, 148.5, 141.5, 139.5, 137.5, 132.5, 129.8, 129.5, 128.2, 126.9, 124.5, 122.7, 119.5, 114.5; IR (cm^{-1}), 3,459, 3,122, 3,017, 2,969, 2,944, 1,740, 1,676, 1,625, 1,552, 1,491, 1,463, 1,407, 1,286, 1,262, 1,224, 1,155, 1,039, 956, 917, 884, 858, 793, 758, 718, 685, 618, 521; LC–MS: *m/z* 466.0, 468.0. $C_{23}H_{14}F_3N_5OS$ requires 465.09. Anal Calcd for $C_{23}H_{14}F_3N_5OS$: C, 59.35; H, 3.03; N, 15.05; S, 6.89%. Found: C, 59.32; H, 3.03; N, 15.07; S, 6.89%.

4e: Yield: 395 mg (84%) of white solid; mp 237–238 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (s, 1H), 8.58 (d, $J = 7.2$ Hz, 1H), 8.34 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 8.0$ Hz, 1H), 7.79–7.71 (m, 2H), 7.58–7.55 (t, $J = 7.6$ Hz, 2H), 7.49 (app. t, $J = 7.2$ Hz, 1H), 4.23 (m, 1H), 1.96–1.92 (m, 2H), 1.78 (bs, 2H), 1.57 (bs, 4H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.1, 148.9, 148.4, 140.6, 139.5, 137.6, 132.4, 129.8, 129.7, 129.4, 128.2, 126.9, 124.6, 122.8, 122.5, 119.2, 51.3, 32.5, 24.0; IR (cm^{-1}), 3,229, 3,052, 2,930, 2,852, 1,637, 1,585, 1,544, 1,493, 1,468, 1,407, 1,325, 1,289, 1,247, 1,169, 1,099, 1,045, 956, 889, 850, 754, 695, 566, 523, 452; LC–MS: *m/z* 451.1, 452.1. $C_{25}H_{21}F_3N_4O$ requires 450.17. Anal. Calcd for $C_{25}H_{21}F_3N_4O$: C, 66.66; H, 4.70; N, 12.44%. Found: C, 66.63; H, 4.69; N, 12.39%.

4f: Yield: 397 mg (87%) of white solid; mp 236–237 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.88 (d, $J = 7.6$ Hz, 1H), 8.77 (s, 1H), 8.37 (s, 1H), 8.26–8.19 (m, 3H), 7.94 (app. t, $J = 8.0$ Hz, 1H), 7.79–7.70 (m, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.48 (app. t, $J = 7.2$ Hz, 1H), 4.42 (m, 1H), 2.31–2.24 (m, 2H), 2.10–2.04 (m, 2H), 1.74–1.71 (m, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 159.4, 148.9, 148.4, 140.6, 139.5, 137.5, 132.4, 129.8, 129.7, 129.5, 128.2, 126.9, 124.5, 122.7, 122.1, 119.3, 44.8, 30.4, 15.2; IR (cm^{-1}), 3,228, 3,053, 2,928, 2,851, 2,028, 2,013, 1,985, 1,960, 1,660, 1,636, 1,586, 1,549, 1,493, 1,470, 1,406, 1,380, 1,325, 1,292, 1,251, 1,163, 1,045, 1,023, 954, 888, 852, 795, 751, 727, 694, 661, 564, 521, 500, 449; LC–MS: *m/z* 437.1, 438.1. $C_{24}H_{19}F_3N_4O$ requires 436.15. Anal Calcd for $C_{24}H_{19}F_3N_4O$: C, 66.05; H, 4.39; N, 12.84%. Found: C, 66.06; H, 4.36; N, 12.81%.

4g: Yield: 465 mg (93%) of white solid; mp 180–181 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (s, 1H), 8.47 (app. t, $J = 9.0$ Hz, 1H), 8.33 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 8.4$ Hz, 1H), 7.80–7.71 (m, 2H), 7.59–7.54 (t, $J = 8.4$ Hz, 2H), 7.49 (app. t, $J = 7.6$ Hz, 1H), 3.99–3.98 (bs, 1H), 1.90 (d, $J = 10.4$ Hz, 1H), 1.74–1.70 (m, 2H), 1.62–1.54 (m, 3H), 1.53–1.31 (m, 2H), 1.07 (t, $J = 7.2$ Hz, 1H), 0.95–0.94 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.1, 159.7, 148.9, 148.4, 140.7, 140.6, 139.5, 137.6, 132.4, 129.8, 129.7, 129.5, 128.2, 126.9, 124.6, 122.8, 119.2, 48.8, 46.5, 34.0, 32.5, 29.9, 28.7, 22.6; IR (cm^{-1}), 3,228, 3,058, 2,983, 2,935, 2,855, 1,637, 1,585, 1,545, 1,495, 1,468, 1,407, 1,322, 1,289, 1,247, 1,158, 1,089, 1,043, 956, 887, 852, 750, 694, 566, 522, 452;

LC–MS: *m/z* 479.1, 480.2. $C_{27}H_{25}F_3N_4O$ requires 478.2. Anal Calcd for $C_{27}H_{25}F_3N_4O$: C, 67.77; H, 5.27; N, 11.7%. Found: C, 67.76; H, 5.27; N, 11.69%.

4h: Yield: 465 mg (85%) of white solid; mp 198–199 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 9.32 (t, $J = 6.0$ Hz, 1H), 8.79 (s, 1H), 8.56 (d, $J = 4.8$ Hz, 1H), 8.48 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 8.0$ Hz, 1H), 7.84–7.73 (m, 3H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.50–7.42 (m, 2H), 7.31 (app. t, $J = 7.2$ Hz, 1H), 4.63–4.62 (d, $J = 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.6, 158.6, 149.4, 148.9, 148.5, 140.8, 139.5, 137.5, 137.2, 132.5, 132.1, 129.8, 129.5, 128.2, 126.9, 124.6, 122.7, 122.7, 121.7, 121.5, 121.2, 119.3, 118.5; IR (cm^{-1}), 3,459, 3,019, 2,966, 1,742, 1,676, 1,625, 1,550, 1,492, 1,463, 1,407, 1,289, 1,262, 1,224, 1,150, 1,040, 956, 917, 884, 858, 793, 758, 718, 685, 618; LC–MS: *m/z* 474.1, 475.1. $C_{27}H_{25}F_3N_4O$ requires 473.15. Anal Calcd for $C_{26}H_{18}F_3N_5O$: C, 65.96; H, 3.83; N, 14.79%. Found: C, 65.97; H, 3.83; N, 14.78%.

4i: Yield: 377 mg (91%) of white solid; mp 218–219 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (s, 1H), 8.65 (d, $J = 4.0$ Hz, 1H), 8.35 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 7.2$ Hz, 1H), 7.79–7.70 (m, 2H), 7.58–7.47 (m, 3H), 2.84–2.83 (d, $J = 4.4$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.8, 148.9, 148.5, 140.7, 139.5, 137.6, 132.4, 129.8, 129.7, 129.5, 128.2, 126.9, 124.5, 122.7, 122.1, 119.3, 118.5, 26.9; IR (cm^{-1}), 3,230, 3,054, 2,930, 2,851, 2,029, 2,015, 1,984, 1,636, 1,660, 1,588, 1,549, 1,495, 1,470, 1,405, 1,380, 1,325, 1,295, 1,251,, 1,163, 1,023, 954, 852, 795, 751, 727, 694, 661, 564, 521, 500; LC–MS: *m/z* 397.1, 398.1. $C_{21}H_{15}F_3N_4O$ requires 396.12. Anal Calcd for $C_{21}H_{15}F_3N_4O$: C, 63.63; H, 3.81; N, 14.14%. Found: C, 63.66; H, 3.81; N, 14.12%.

4j: Yield: 377 mg (90%) of white solid; mp 208–209 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (bs, 1H), 8.67 (t, $J = 5.6$ Hz, 1H), 8.35 (bs, 1H), 8.32–8.20 (m, 3H), 7.95 (app. t, $J = 8.4$ Hz, 1H), 7.79–7.71 (m, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.48 (app. t, $J = 7.2$ Hz, 1H), 3.35–3.29 (q, 2H), 1.19–1.15 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.2, 148.9, 148.4, 140.6, 139.5, 137.6, 132.4, 129.8, 129.7, 129.5, 128.2, 126.9,124.5, 122.7, 122.3, 119.3, 34.4, 15.0; IR (cm^{-1}), 3,232, 3,055, 2,932, 2,852, 1,636, 1,588, 1,549, 1,495, 1,470, 1,405, 1,380, 1,325, 1,295, 1,251,, 1,163, 1,023, 954, 852, 795, 751, 727, 694, 661, 564, 521, 500; LC–MS: *m/z* 411.1, 412.1. $C_{22}H_{17}F_3N_4O$ requires 410.14. Anal Calcd for $C_{22}H_{17}F_3N_4O$: C, 64.39; H, 4.18; N, 13.65%. Found: C, 64.39; H, 4.19; N, 13.66%.

4k: Yield: 400 mg (87%) of white solid; mp 135–137 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78–8.75 (m, 2H), 8.37 (s, 1H), 8.26–8.20 (q, 3H), 7.95 (app. t, $J = 6.8$ Hz, 1H), 7.79–7.71 (m, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.49 (app. t, $J = 7.2$ Hz, 1H), 3.52–3.46 (m, 4H), 3.32 (s, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.5, 148.9, 148.4, 140.7, 139.5, 137.6, 132.4, 129.8, 129.7, 129.5, 128.2,126.9, 124.5, 122.8, 122.0, 119.3, 70.8, 58.4; 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; LC–MS: *m/z* 441.1, 442.1. $C_{23}H_{19}F_3N_4O_2$ requires 440.15. Anal Calcd for $C_{23}H_{19}F_3N_4O_2$: C, 62.72; H, 4.35; N, 12.72%. Found: C, 62.69; H, 4.33; N, 12.72%.

4l: Yield: 400 mg (90%) of white solid; mp 175–176 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 9.11–9.09 (d, $J = 8.0$ Hz, 2H), 8.78 (bs, 1H), 8.45 (bs, 1H), 8.26–8.20 (m, 3H), 7.94 (app. t, $J = 7.6$ Hz, 1H), 7.79–7.72 (m, 2H), 7.58–7.54 (t,

$J = 7.6$ Hz, 2H), 7.49 (d, $J = 7.2$ Hz, 1H), 7.46–7.44 (d, $J = 7.6$ Hz, 2H), 7.39–7.36 (t, $J = 7.6$ Hz, 2H), 7.27 (app. t, $J = 7.2$ Hz, 1H), 5.18 (t, $J = 7.2$ Hz, 1H), 1.52–1.50 (d, $J = 7.2$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 159.7, 148.9, 148.5, 144.7, 140.8, 139.5, 137.6, 132.4, 129.8, 129.7, 129.4, 128.7, 128.2, 127.2, 126.9, 126.5, 124.6, 122.8, 122.1, 119.3, 48.9, 22.7; IR (cm^{-1}), 3,283, 3,185, 3,054, 2,922, 1,949, 1,595, 1,617, 1,565, 1,504, 1,422, 1,378, 1,325, 1,441, 1,183, 1,140, 1,073, 1,030, 960, 914, 842, 818, 797, 766, 747, 683, 642, 574, 520, 411; LC–MS: *m/z* 487.1, 488.1. $C_{28}H_{21}F_3N_4O$ requires 486.17. Anal Calcd for $C_{28}H_{21}F_3N_4O$: C, 69.13; H, 4.35; N, 11.52%. Found: C, 69.13; H, 4.33; N, 11.49%.

4m: Yield: 400 mg (86%) of white solid; mp 143–144 °C; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78 (bs, 1H), 8.65 (t, $J = 5.6$ Hz, 1H), 8.34 (bs, 1H), 8.26–8.24 (d, $J = 8.0$ Hz, 1H), 8.22–8.20 (d, $J = 8.8$ Hz, 2H), 7.95 (app. t, $J = 8.0$ Hz, 1H), 7.79–7.72 (m, 2H), 7.58–7.54 (t, $J = 7.2$ Hz, 2H), 7.48 (app. t, $J = 7.2$ Hz, 1H), 3.32–3.26 (m, 2H), 1.58–1.51 (q, 2H), 1.38–1.23 (m, 6H), 0.91–0.87 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.3, 148.9, 148.4, 140.6, 139.5, 137.6, 132.4, 131.6, 129.8, 129.7, 129.49, 128.2, 126.9, 124.6, 122.7, 122.3, 121.2, 119.3, 31.4, 29.3, 26.5, 22.5, 14.3; IR (cm^{-1}), 3,233, 3,058, 2,936, 2,851, 2,026, 2,015, 1,984, 1,636, 1,650, 1,588, 1,549, 1,495, 1,470, 1,405, 1,388, 1,325, 1,295, 1,251, 1,163, 1,023, 954, 852, 795, 751, 727, 694, 661, 564, 521, 500; LC–MS: *m/z* 467.1, 468.1. $C_{26}H_{25}F_3N_4O$ requires 466.2. Anal Calcd for $C_{26}H_{25}F_3N_4O$: C, 66.94; H, 5.40; N, 12.0%. Found: C, 66.92; H, 5.39; N, 11.99%.

4n: Yield: 400 mg (87%) of yellow liquid; ^{1}H NMR (400 MHz, DMSO-D_6) δ 8.78–8.74 (m, 2H), 8.31 (s, 1H), 8.26–8.20 (m, 3H), 7.95 (app. t, $J = 8.0$ Hz, 1H), 7.79–7.70 (m, 2H), 7.58–7.55 (t, $J = 7.6$ Hz, 2H), 7.49 (app. t, $J = 7.6$ Hz, 1H), 6.91–6.87 (m, 2H), 6.80 (d, $J = 8.0$ Hz, 1H), 3.77–3.72 (m, 8H), 2.83–2.80 (m, 2H); ^{13}C NMR (100 MHz, DMSO-D_6) δ 160.3, 149.1, 148.9, 148.5, 147.8, 140.6, 139.5, 137.5, 132.4, 132.2, 129.8, 129.5, 128.2, 126.9, 124.5, 122.7, 122.2, 121.0, 119.3, 113.0, 112.4, 56.0, 55.8, 41.3, 38.7, 34.9; IR (cm^{-1}), 3,292, 3,037, 2,330, 2,290, 2,251, 2,198, 2,222, 2,181, 2,160, 2,142, 2,119, 2,059, 2,025, 2,013, 1,986, 1,968, 1,963, 1,955, 1,942, 1,896, 1,861, 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, 596, 564; LC–MS: *m/z* 547.1. $C_{30}H_{25}F_3N_4O_3$ requires 546.19. Anal Calcd for $C_{30}H_{25}F_3N_4O_3$: C, 65.93; H, 4.61; N, 10.25%. Found: C, 65.91; H, 4.59; N, 10.22%.

Conclusion

An efficient, simple and high yielding method for the synthesis of various 5-(trifluoromethyl)-*N*-alkyl-1-(3-phenylisoquinoline-1-yl)-1*H*-pyrazole-4-carboxamides from pyrazole carboxylic acid and primary amines in the presence of TBTU was established. The procedure involves simple work-up, ease of separation of products and low toxicity of by-products.

Acknowledgment The authors wish to express their gratitude to the Management, VIT University, India for their support and facilities.

References

1. J. Elguero, In Pyrazoles, ed. by A.R. Katritzky, C.W. Rees, E.F.V. Scriven. Comprehensive heterocyclic chemistry II, vol 3 (Elsevier Science, Oxford, 1996), pp. 1–75
2. H. Suzuki, Y. Iwasawa, T. Satoh, T. Ikari, T. Oguchi, Japanese Kokai Tokkyo (Nissan Chemical Co., Chiyoda Ku, 1994), JP 06-56792
3. I. Okada, S. Okui, T. Tanaka, Y. Takahashi, Japanese Kokai Tokkyo (Mitsubishi Chemical Co., Minato-ku), JP 64-25763
4. I. Okada, S. Okui, M. Wada, Y. Takahashi, Japanese Kokai Tokkyo (Mitsubishi Chemical Co., Minato-ku), JP 03-81266
5. F. Bruce, S. Christopher, Pestic. Sci. **50**, 324 (1997)
6. T. Van Herk, J. Brussee, A.M.C.H. van den Nieuwendijk, P.A.M. van der Klein, A.P. Ijzerman, C. Stannek, A. Burmeister, A. Lorenzen, J. Med. Chem. **46**, 3945 (2003)
7. F. Varano, D. Catarzi, V. Colotta, G. Filacchioni, A. Galli, C. Costagli, V. Carlá, J. Med. Chem. **45**, 1035 (2002)
8. G. Dannhardt, S. Laufer, Curr. Med. Chem. **7**, 1101 (2000)
9. T.J. Carty, A. Marfat, Curr. Opin. Anti Inflamm. Immunomod. Invest. Drugs **1**, 89 (1999)
10. K.C. Nicolaou, B.A. Pratt, S. Arseniyadis, M. Wartmann, A. ÒBrate, P. Giannakakou, Chem. Med. Chem. **1**, 41 (2006)
11. H. Matsuda, H. Shimoda, M. Yoshikawa, Bioorg. Med. Chem. **7**, 1445 (1999)
12. T. Furuta, Y. Fukuyama, Y. Asakawa, Phytochemistry. **25**, 517 (1986)
13. N. Asao, T. Nogami, K. Takahashi, Y. Yamamoto, J. Am. Chem. Soc. **124**, 764 (2002)
14. K.R. Roesch, R.C. Larock, J. Org. Chem. **63**, 5306 (1998)
15. A. Arcadi, S. Cacchi, F. Marinelli, Synthesis. 749 (1986)
16. Q. Huang, J.A. Hunter, R.C. Larock, Org. Lett. **3**, 2973 (2001)
17. A. Buske, S. Busemann, J. Mühlbacker, J. Schmidt, A. Porzel, G. Bringmann, G. Adam, Tetrahedron. **55**, 1079 (1999)
18. G. Bringmann, J. Holenz, R. Weirich, M. Rübenacker, C. Funke, Tetrahedron. **54**, 497 (1998)
19. D. Kletsas, W. Li, Z. Han, V. Papadopoulos, Biochem. Pharmacol. **67**, 1927 (2004)
20. K.W. Bentley, *The Isoquinoline Alkaloids*, vol. 1 (Hardwood Academic, Amsterdam, 1998)
21. F. Durola, J. -P. Saunage, O. S. Wenger, Chem. Commun. 171 (2006)
22. K.-H. Fang, L.-L. Wu, Y.-T. Huang, C.-H. Yang, I.-W. Sun, Inorg. Chim. Acta. **359**, 441 (2006)
23. Z. Huo, H. Tomeba, Y. Yamamoto, Tetrahedron Lett. **49**, 5531 (2008)
24. Y.-Y. Hu, J. Hu, X.-C. Wang, L.-N. Guo, X.-Z. Shu, Y.-N. Niu, Y.-M. Liang, Tetrahedron. **66**, 80 (2010)
25. P.J. Campos, M. Caro, A. Rodrĭguez, Tetrahedron Lett. **42**, 3575 (2001)
26. B.K. Ghorai, D. Jiang, J. Herndon, W. Org. Lett. **5**, 4261 (2003)
27. R. Alonso, P.J. Campos, B. Garcĭa, M.A. Rodrĭguez, Org. Lett. **8**, 3521 (2006)
28. Y.-N. Niu, Z.-Y. Yan, G.-L. Gao, H.-L. Wang, X.-Z. Shu, K.-G. Ji, Y.-M. Liang, J. Org. Chem. **74**, 2893 (2009)
29. Z. Huo, Y. Yamamoto, Tetrahedron Lett. **50**, 3651 (2009)
30. K. Tsugio, K. Shinjiro, T. Hiroshi, Chem. Lett. **13**, 1351 (1984)
31. H. Qinhua, C.L. Richard, Tetrahedron Lett. **43**, 3557 (2002)
32. L. Xin-Hua, Z. Jing, Z. An-na, S. Bao-An, Z. Hai-Liang, B. Shan, B. Pinaki, P. Chun-Xiu, Bioorg. Med. Chem. **17**, 1207 (2009)
33. B. Heike, W. Julia, A. Christain, L. Matthias, Develop. Comp. Immun. **30**, 410 (2006)
34. P. Manivel, F.N. Khan, J. Chil. Chem. Soc. **54**, 180 (2009)
35. P. Manivel, S.M. Roopan, R.S. Kumar, F.N. Khan, J. Chil. Chem. Soc. **54**, 183 (2009)
36. P. Manivel, F.N. Khan, Ind J. Chem. **48B**, 825 (2009)
37. F.N. Khan, P. Manivel, K. Prabakaran, V.R. Hathwar, M. Akkurt, Acta Cryst. **E66**, o1081 (2010)
38. F.N. Khan, P. Manivel, K. Prabakaran, V.R. Hathwar, M. Akkurt, Acta Cryst. E **66**, o1094 (2010)
39. N.T. Patil, F.N. Khan, Y. Yamamoto, Tetrahedron Lett. **45**, 8497 (2004)
40. P. Manivel, S.M. Roopan, F.N. Khan, Ind. J. Het. Chem. **18**, 21 (2008)
41. P. Manivel, S.M. Roopan, F.N. Khan, J. Chil. Chem Soc. **53**, 1609 (2008)
42. K. Prabakaran, P. Manivel, F.N. Khan, Tetrahedron Lett. **51**, 4340 (2010)
43. S.S. Tajudeen, F.N. Khan, Synth. Commun. **37**, 3649 (2007)
44. S.M. Roopan, T. Maiyalagan, F.N. Khan, Can. J. Chem. **86**, 1019 (2008)

45. V.R. Hathwar, P. Manivel, F.N. Khan, T.N.G. Row, Acta Cryst. E **63**, o3707 (2007)
46. V.R. Hathwar, P. Manivel, F.N. Khan, T.N.G. Row, Acta Cryst. E **63**, o3708 (2007)
47. S.M. Roopan, F.R.N. Khan, Arkivoc **13**, 161 (2009)
48. V.R. Hathwar, P. Manivel, F.N. Khan, T.N.G. Row, Cryst. Eng. Comm. **11**, 284 (2009)
49. F.N. Khan, P. Manivel, K. Prabakaran, V.R. Hathwar, S.W. Ng, Acta Cryst. **E66**, o370 (2010)
50. P. Manivel, F.N. Khan, V.R. Hathwar, Phosphorus Sulphur Silicon Relat. Elem. **185**, 1932 (2010)
51. K. Prabakaran, F.N. Khan, J.S. Jin, Tetrahedron Lett. **52**, 2566 (2011)
52. F.N. Khan, P. Manivel, K. Prabakaran, V.R. Hathwar, S.W. Ng, Acta Cryst. **E65**, o2732 (2009)
53. F.N. Khan, P. Manivel, K. Prabakaran, V.R. Hathwar, S.W. Ng, Acta Cryst. **E66**, o488 (2010)
54. P. Manivel, F.N. Khan, Phosphorus Sulphur Silicon Relat. Elem. **184**, 2910 (2009)
55. S.M. Roopan, T.R.S. Sri, B.R. Reddy, F.N. Khan, Ind. J. Heterocycl. Chem. **19**, 77 (2009)