Regioselective synthesis and antibacterial evaluation of a new class of substituted pyrazolo[3,4-*b*]pyridines

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New derivatives of polyfunctional pyrazolo[3,4-*b*]pyridines were synthesised *via* a regioselective one-pot three-component reaction of 3- (cyanoacetyl)indole, 5-amino-3-methylpyrazole and arylaldehydes in excellent yields using Fe^{3+}-montmorillonite as a reusable catalyst under conventional conditions and ultrasonic irradiation. In particular, valuable features of this method include high reaction rate, employment of a reusable catalyst, straightforward procedure, the easy work-up of the products and mild reaction conditions. The antibacterial activities of the synthesised products were examined which showed promising activities.

Keywords: pyrazolo[3,4-*b*]pyridine, pyrazole, indole, Fe^{3+}-montmorillonite, ultrasound, antibacterial activity

Aminopyrazoles belong to a very important class of heterocycles due to their biological and pharmacological activities.[1,2] Moreover, they are used as key starting materials for the synthesis of heterocycles containing a pyrazole structural unit. Many such compounds display a broad spectrum of pharmacological and biological activities, such as antimicrobial,[3] antifungal[4] and antitumour properties.[5]

Combination of the pyrazole moiety with various heterocyclic ring systems has resulted in interesting biological and pharmacological properties.[6–9] Pyrazolo[3,4-*b*]pyridine skeletons possess diverse biological properties, including antioxidant, antibacterial and antitubercular activities.[10–14] Some derivatives exhibit potential antimalarial properties,[15] fungicidal activities[16] and also used as vasodilators.[17]

Following our continued interest in the development of synthetic strategies to obtain functionalised heterocycles of biological importance,[18–23] also guided by the observation that the presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably,[18] and considering the important biological properties of indole containing heterocycles, we now describe a novel and clean synthesis of indole-sustituted pyrazolopyridine derivatives through a three-component condensation reaction of 3-cyanoacetylindole (**1**), 5-amino-3-methylpyrazole (**2**) and arylaldehydes (**3**) in the presence of Fe^{3+}-montmorillonite (Fe^{3+}@Mont.) as a reusable catalyst in ethanol under reflux conditions and ultrasonic irradiations (Scheme 1).

Result and discussion

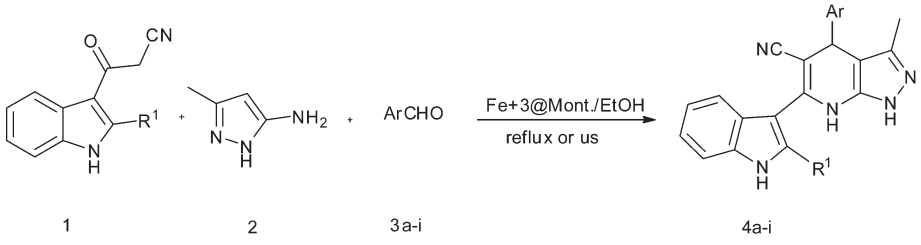
Synthesis of 4-(2,4-dichlorophenyl)-6-(1*H*-indol-3-yl)-3-methyl-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**4a**), by the reaction of equimolar amounts of 3- (cyanoacetyl)indole (**1**), 5-amino-3-methylpyrazole (**2**) and 2,4-dichlorobenzaldehyde (**3a**) in the presence of Fe^{3+}@Mont. was selected as model reaction. Different solvents and catalysts were screened for the synthesis of **4a**. The results are summarised in Tables 1 and 2. It is evident from the results that EtOH (Table 1, entry 5) and Fe^{3+}@Mont. (Table 2, entry 2), are the most effective solvent and catalyst respectively, resulting in the highest yield and shortest reaction time among the solvents and catalysts selected.

We also verified the amount of catalyst needed for the preparation of **4a**, and the best result was obtained using 0.05 g Fe^{3+}@Mont./1 mmol substrate in EtOH (5 mL) (Table 3).

The catalyst was recycled and reused in the preparation of **4a** as model compound. After each run, the catalyst was simply filtered, washed and activated at 120 °C. The result showed that after three successive runs, catalytic activity of the catalyst was retained without significant loss of activity (Table 4).

The plausible mechanism for the formation of **4a–i** is outlined in Scheme **2**. The formation of these products can be visualised by initial Knoevenagel condensation of aldehyde (**3**) and 3-cyanoacetylindoles (**2**). The Fe^{3+}@Mont. activated arylidene intermediate, seems to be a good acceptor for the Michael addition of **2** *via* attack of the nucleophilic C-4 of the pyrazole, followed by cyclisation and loss of H_2O to furnish the desired pyrazolopyridines **4a–i**.

The regioselectivity observed in this reaction may be rationalised by hard–soft–acid–base interaction in the reaction intermediate, in which the nitrogen group prefer carbonyl group functionality rather than the CN group. The result of the reaction between 3- (cyanoacetyl)indole (**1**), 3-amino-5-methylpyrazole (**2**), and various aryl aldehydes (**3**) in the



R[1]: H, Me

Ar: 3-HOC_6H_4, 2,4-$Cl_2C_6H_3$, 3-$MeOC_6H_4$, 2,6-$ClFC_6H_3$, 3-$O_2NC_6H_4$, 4-$CH_3C_6H_4$

Scheme 1 Synthesis of indolylpyrazolo[3,4-*b*]pyridine derivatives **4a–i**.

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Table 1 Synthesis of **4a** in the presence of Fe^{3+}@Mont. (0.05 g /L mmol substrate) in several solvents

Entry	Solvent	Time/min	Yield/%[a]
1	Ethylenglycol	60	75
2	MeOH	70	68
3	DMF	90	62
4	THF	100	55
5	EtOH	25	89
6	AcOH	150	45
7	CH_3CN	180	40
8	CH_2Cl_2	210	35
9	H_2O	240	30

[a]Isolated yield.

Table 2 Effect of various catalysts in the synthesis of **4a**[a]

Entry	Catalyst	Time/min	Yield/%[b]
1	K10	45	75
2	Fe^{3+}@Mont.	25	89
3	*p*-TSA	40	80
4	KSF	45	70
5	L-proline	50	80
6	Cellulose–sulfuric acid	50	75
7	AcOH	55	75
8	–	60	75

[a]EtOH as a solvent.
[b]Isolated yield.

Table 3 Optimisation of the amount of catalyst in the synthesis of **4a**

Entry	Amount of catalyst/g	Time/min	Yield/%[a]
1	0.02	35	80
2	0.05	25	89
3	0.1	25	85

[a]Isolated yield.

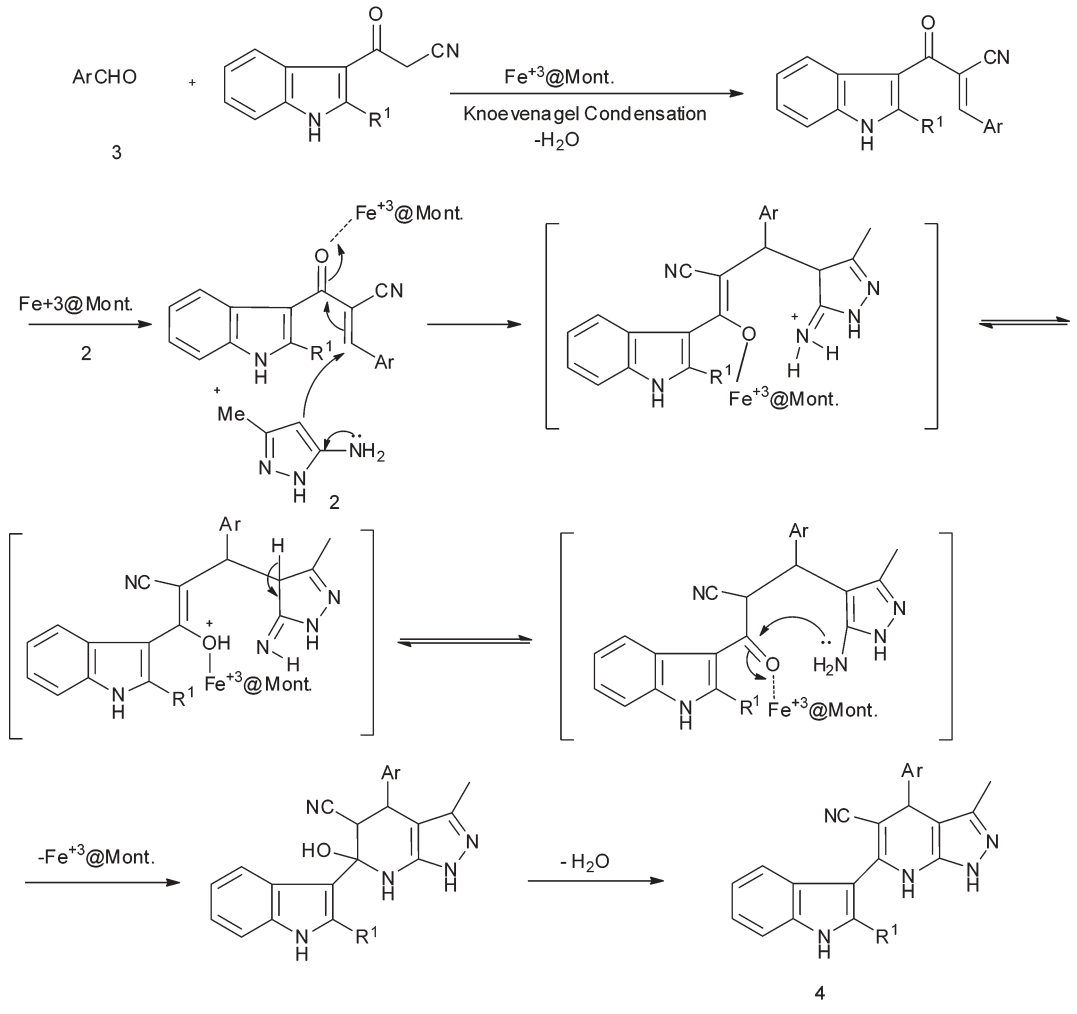
Table 4 Reusability of Fe^{3+}@Mont. in the preparation of **4a** under ultrasonic irradiation

Entry	No. of runs	Time/min	Yield/%[a]
1	First	4	98
2	Second	4	95
3	Third	4	89
4	Fourth	4	73
5	Fifth	4	64

[a]Isolated yield.

presence of Fe^{3+}@Mont. in refluxing ethanol under optimised conditions has been summarised in Table 5. The aromatic aldehydes bearing electron-donating groups as well as electron withdrawing groups underwent reactions successfully.

Recently, organic chemists have tried to develop green and environmentally benign routes for the preparation of organic



Scheme 2 Plausible mechanism of synthesis of indolylpyrazolo[3,4-*b*]pyridines **4a–i**.

Table 5 Synthesis of products **4a–i** using Fe^{3+}@Mont. in refluxing EtOH and under ultrasonic irradiations at 60 °C

Entry	Product	R^1	Ar	Classical method		Sonochemical method	
				Time /min	Yield/%[a]	Time /min	Yield/%[a]
1	**4a**	H	2,4-$Cl_2C_6H_3$	25	89	4	98
2	**4b**	H	3-HOC_6H_4	30	90	5	98
3	**4c**	H	3-$MeOC_6H_4$	30	80	5	90
4	**4d**	H	3-$O_2NC_6H_4$	20	85	3	95
5	**4e**	H	4-$CH_3C_6H_4$	40	80	7	85
6	**4f**	H	2,6-$ClFC_6H_3$	25	90	3	98
7	**4g**	Me	2,4-$Cl_2C_6H_3$	25	90	3	98
8	**4h**	Me	3-HOC_6H_4	25	90	4	98
9	**4i**	Me	2,6-$ClFC_6H_3$	25	90	3	98

[a]Isolated yield.

compounds of synthetic and biological values. In this area, the use of ultrasound has gained popularity compared to conventional heating.[24] We have used ultrasonic irradiation in the synthesis of potent compounds with medicinal values[18–20,25,26] which has encouraged us to explore the use of this methodology in the synthesis of pyrazolopyridinones. We therefore investigated the effect of ultrasonic irradiation on the synthesis of novel fused pyrazolopyrines (**4a–i**). An equimolar mixture of reactants in the presence of Fe^{3+}@Mont. (0.05 g) in EtOH (5 mL) were placed in a pyrex-glass open vessel and irradiated at 60 °C by ultrasonic irradiation (40 kHz) to furnish the desired products (**4a–i**) in very short reaction times (3–7 min) and excellent yields (85–98%) (Table 5).

To extend the synthetic potential of this protocol to other cyanoacetyl substrates, the synthesis of pyrrole substituted pyrazolo[3,4-*b*]pyridine derivatives was studied. We investigated the reaction between 2- (cyanoacetyl)-*N*-methylpyrrole, 5-amino-3-methylpyrazole (**2**) and arylaldehyde (**3j**), in the presence of Fe^{3+}@Mont., using the optimised conditions described above and obtained 1-methyl-1*H*-pyrrol-2-yl)-4,7-dihydro-1*H*-pyrazolo[3,4-*b*]pyridine (**4j**) (Fig. 1) in 120 min and 70% yield under classic conditions. Under ultrasonic irradiation, the reaction was completed in 20 min with 73% yield.

The structures of all the products were fully characterised by spectroscopic (IR, ^{1}H NMR, ^{13}C NMR) and elemental analyses.

The antibacterial activity of synthesised compounds **4a–j** was examined using *Escherichia coli* (EC), *Bacillus subtilis* (BS), *Pseudomonas Aeruginosa* (A), *Salmonella enterica* (SE) and *Staphylococcus aureu*s (SA). For comparison, two routinely used antibiotics, erythromycin and nalidixic acid, were also used. The results revealed that most of the products (**4a–i**) exhibit strong activities towards both Gram-negative and Gram-positive bacteria, as revealed by the diameters of their inhibition zones. Among the tested compounds, **4j** shows very strong inhibitory effects on both types of bacterium. The results of this study are listed in Table 6.

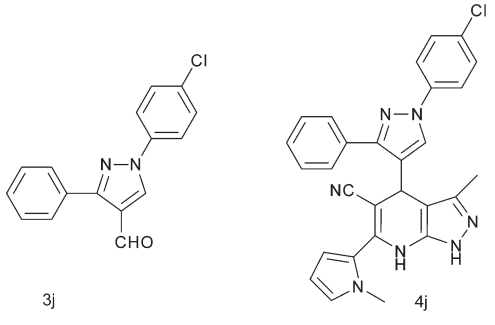


Fig. 1 Structures of **3j** and **4j**.

Experimental

Melting points were measured on an electrothermal 9100 apparatus. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz Bruker DRX-400 in DMSO-d_6 as solvent and TMS as an internal standard. Chemical shifts on ^{1}H and ^{13}C NMR were expressed in ppm downfield from tetramethylsilane. Sonication was performed in Elmasonic S 40H ultrasonic cleaning unit (40 kHz). Elemental analyses were done on a Carlo-Erba EA1110CNNO-S analyser and agreed with the calculated values. All the chemicals were purchased from Merck and used without further purification. All solvents used were dried and distilled according to standard procedures.

*Synthesis of (**4a–j**); general procedure*

A mixture of 3-amino-5-methyl pyrazole (1 mmol), 3- (cyanoacetyl)-indole[27] (**1**) (1 mmol), arylaldehyde (1 mmol) and Fe^{3+}@ Mont. (0.05 g) in EtOH (5 mL) was heated under reflux or by ultrasonic irradiation using Elmasonic S 40H ultrasonic cleaning unit (40 kHz) at 60 °C. The progress of the reaction was monitored by TLC (EtOAc/petroleum ether 8:4). After completion of the reaction, the catalyst was removed by filtration, and the filtrate was evaporated under reduced pressure to remove the solvent. The residue was purified by column chromatography (EtOAc/petroleum ether 8:4) to provide the pure desired products.

Synthesis of Fe^{3+}@Mont.[28]

A total of 1% suspension of montmorillonite (K10) in a 1.5 mole dm^{-3} solution of $FeCl_3.6H_2O$ was stirred overnight. On settling, the supernatant solution was discarded and the hhexchange process repeated three times. The ion-exchanged material was filtered and washed free of chloride ion (checked by 0.1M $AgNO_3$) with deionised water and dried in air.

(2,4-Dichlorophenyl)-6-(1H-indol-3-yl)-3-methyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4a**): Cream powder; m.p. >300 °C. IR (KBr) (ν_{max}/cm^{-1}): 3396, 3050, 2926, 2858, 2189, 1649, 1591, 1514, 1384, 1099, 802, 744. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.83 (3H, s, CH_3), 5.45 (1H, s, CH), 7.17–7.09 (2H, m, ArH), 7.54–7.41 (4H, m, ArH), 7.63 (1H, s, ArH), 7.73 (1H, s, ArH), 9.83 (1H, br., s, NH), 11.76 (1H, br., s, NH), 12.08 (1H, br., s, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 9.8, 29.5, 77.1, 100.1, 109.4, 112.4, 120.0, 120.6, 122.2, 122.6, 125.6, 127.6, 128.6, 129.2, 132.4, 132.8, 133.1, 135.6, 136.3, 142.4, 147.2, 156.6 ppm. Anal. Calcd for $C_{22}H_{15}Cl_2N_5$ (420.29): C, 62.87; H, 3.60; N, 16.66. Found: C, 62.75; H, 3.49; N, 16.50%.

4-(3-Hydroxyphenyl)-6-(1H-indol-3-yl)-3-methyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4b**): Cream powder; m.p. 260–263 °C. IR (KBr) (ν_{max}/cm^{-1}): 3353, 3188, 3068, 2955, 2199, 1650, 1602, 1539, 1504, 1383, 1271, 876, 741. ^{1}H NMR (DMSO-d_6, 400 MHz): δ 1.87 (3H, s, CH_3), 4.82 (1H, s, CH), 6.64 (1H, ddd, *J* = 7.2, 2.4, 0.8 Hz, ArH), 6.72 (1H, t, *J* = 1.8 Hz, ArH), 6.76 (1H, d, *J* = 7.6 Hz, ArH), 7.08–7.19 (3H, m, ArH), 7.46 (1H, d, *J* = 8.4 Hz, ArH), 7.54 (1H, d, *J* = 7.6 Hz, ArH), 7.72 (1H, s, ArH), 9.38 (1H, br. s, OH), 9.60 (1H, br., s, NH), 11.62 (1H, br. s, NH), 11.89 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d_6, 100 MHz): δ 10.0, 33.2, 79.2, 101.4, 109.7, 112.4, 114.1, 114.9, 118.7, 120.0, 120.6, 122.2, 123.3, 125.7, 127.4, 129.7, 136.3, 138.6, 146.2, 148.2, 156.8, 158.0 ppm. Anal. Calcd for $C_{22}H_{17}N_5O$ (367.40): C, 71.92; H, 4.66; N, 19.06. Found: C, 71.75; H, 4.60; N, 19.00%.

Table 6 Antimicrobial activity of the compounds **4a–j**

Compound	Conc. of compound µg/well	Antimicrobial activity (Zone of inhibition in mm)				
		Staphylococcus aureus	*Salmonella*	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Escherichia coli*
4a	6.25	17 (16)[a] (17)[b]	16 (17)[a]	18 (17)[a] (17)[b]	14	15
4b	6.25	15	16 (16)[a]	16 (16)[a]	17 (16)[a]	14
4c	6.25	14	15	17 (17)[a]	12	18 (19)[a]
4d	6.25	13	14	15	16 (17)[a]	15
4e	6.25	15	16 (16)[a]	16 (15)[a]	14	17 (18)[a]
4f	6.25	13	15	14	15	14
4g	6.25	16 (17)[a]	14	16 (15)[a] (16)[b]	13	15
4h	6.25	14	16 (16)[a]	16 (17)[a]	13	15
4i	6.25	15	13	14	16 (17)[a]	15
4j	6.25	20 (21)[a] (20)[b]	25 (24)[a] (26)[b]	23 (22)[a] (24)[b]	23 (23)[a] (21)[b]	24 (23)[a] (24)[b]
Erythromycin	15	21	25	25	17	18
Nalidixic acid	30	30	27	20	19	20

[a] Data of duplicated experiments.
[b] Data of triplicated experiments.

6-(1H-Indol-3-yl)-4-(3-methoxyphenyl)-3-methyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4c**): Cream powder; m.p. 252–254 °C. (KBr) (ν_{max}/cm^{-1}): 3350, 3050, 2920, 2190, 1645, 1600, 1540, 1510, 1485, 1455, 1420, 1380, 1258, 1040, 875, 740, 698. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.88 (3H, s, CH$_3$), 3.75 (3H, s, OMe), 4.91 (1H, s, CH), 6.83 (1H, dd, *J* = 7.8, 2.2 Hz, ArH), 6.88 (1H, s, ArH), 6.90 (1H, d, *J* = 7.6 Hz, ArH), 7.05–7.21 (3H, m, ArH), 7.47 (1H, d, *J* = 8.0 Hz, ArH), 7.53 (1H, d, *J* = 8.0 Hz, ArH) 7.73 (1H, s, ArH), 9.64 (1H, br. s, NH), 11.65 (1H, br. s, NH), 11.92 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 10.0, 31.7, 55.8 (OMe), 77.6, 101.6, 111.4, 111.9, 112.4, 114.9, 117.7, 120.0, 120.6, 121.0, 121.3, 122.4, 125.0, 127.4, 129.4, 139.3, 139.4, 148.4, 158.9, 161.9 ppm. Anal. Calcd for $C_{23}H_{19}N_5O$ (381.43): C, 72.42; H, 5.02; N, 18.36. Found: C, 72.30; H, 4.89; N, 18.24%.

6-(1H-Indol-3-yl)-3-methyl-4-(3-nitrophenyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4d**): Yellow powder; m.p. 266–268 °C. (KBr) (ν_{max}/cm^{-1}): 3360, 3250, 3050, 2910, 2198, 1650, 1600, 1505, 1470, 1455, 1520, 1345, 1380, 800, 740, 725, 700. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.87 (3H, s, CH$_3$), 5.23 (1H, s, CH), 7.10 (1H, td, *J* = 7.46, 0.8 Hz, ArH), 7.18 (1H, td, *J* = 7.73, 0.8 Hz, ArH), 7.47 (1H, d, *J* = 8.0, ArH), 7.53 (1H, d, *J* = 8.00 Hz, ArH), 7.71 (1H, t, *J* = 8.0 Hz, ArH), 7.76 (1H, s, ArH), 7.83 (1H, dt, *J* = 7.60, 1.2 Hz, ArH), 8.15 (1H, ddd, *J* = 8.0, 2.4, 0.8 Hz, ArH), 8.17 (1H, s, ArH), 9.82 (1H, br. s, NH), 11.68 (1H, br. s, NH), 12.04 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 9.9, 28.4, 78.0, 100.4, 109.4, 112.4, 113.3, 120.1, 120.5, 122.2, 124.4, 125.0, 125.6, 127.7, 130.7, 135.7, 136.2, 136.3, 147.0, 148.5, 148.8, 155.5 ppm. Anal. Calcd for $C_{22}H_{16}N_6O_2$ (396.40): C, 66.66; H, 4.07; N, 21.20. Found: C, 66.51; H, 3.92; N, 21.25%.

6-(1H-Indol-3-yl)-3-methyl-4-(p-tolyl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4e**): Cream powder; m.p. >300 °C. (KBr) (ν_{max}/cm^{-1}): 3350, 3100, 3060, 2900, 2850, 2190, 1650, 1558, 1540, 1505, 1430, 1380, 820, 785, 740. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.84 (3H, s, CH$_3$), 2.30 (3H, s, CH$_3$), 4.88 (1H, s, CH), 7.07–7.24 (4H, m, ArH), 7.46 (2H, t, *J* = 8.0 Hz, ArH), 7.50–7.53 (2H, m, ArH), 7.71 (1H, s, ArH), 9.63 (1H, br. s, NH), 11.74 (1H, br. s, NH), 12.02 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 10.0, 21.5, 29.5, 79.4, 98.4, 101.4, 119.9, 120.5, 121.0, 122.1, 125.7, 127.9, 129.1, 129.4, 129.5, 136.0, 136.3, 136.8, 142.7, 152.7, 155.5 ppm. Anal. Calcd for $C_{23}H_{19}N_5$ (365.43): C, 75.59; H, 5.24; N, 19.16. Found: C, 75.43; H, 5.10; N, 19.25%.

4-(2-Chloro-6-fluorophenyl)-6-(1H-indol-3-yl)-3-methyl-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4f**): Cream powder; m.p. 260–263 °C. (KBr) (ν_{max}/cm^{-1}): 3350, 3280, 3065, 2920, 2195, 1647, 1600, 1560, 1570, 1520, 1450, 1380, 1135, 1080, 895, 780, 740; ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.86 (1H, s, CH$_3$), 5.66 (1H, s, CH), 7.09 (1H, td, *J* = 7.2, 0.8 Hz, ArH), 7.16 (1H, td, *J* = 7.40, 1.2 Hz, ArH), 7.37 (2H, t, *J* = 6.40 Hz, ArH), 7.46 (2H, d, *J* = 8.0 Hz, ArH), 7.53–7.57 (1H, m, ArH), 7.70 (1H, s, ArH), 9.75 (1H, br. s, NH), 11.67 (1H, br. s, NH), 11.94 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 9.5, 24.4, 98.8, 109.6, 110.0, 112.4, 112.6, 113.0, 118.4, 120.0, 121.2, 122.1, 122.7, 123.1, 126.0, 126.4,127.2, 129.3, 136.3, 137.0, 143.0, 147.1, 156.0, 161.1 (d, $^1J_{C\text{-}F}$ = 240 Hz) ppm. Anal. Calcd for $C_{22}H_{15}ClFN_5$ (403.84): C, 65.43; H, 3.74; N, 17.34. Found: C, 65.36; H, 3.61; N, 17.25%.

4-(2,4-Dichlorophenyl)-3-methyl-6-(2-methyl-1H-indol-3-yl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4g**): Cream powder; m.p. >300 °C. (KBr) (ν_{max}/cm^{-1}): 3350, 3300, 3050, 2900, 2200, 1645, 1590, 1514, 1460, 1340, 1100, 830, 800, 740. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.83 (3H, s, CH$_3$-pyrazole), 2.37 (3H, s, CH$_3$-indole), 5.45 (1H, s, CH), 7.32–7.35 (2H, m, ArH), 7.40–7.53 (4H, m, ArH), 7.64 (1H, s, ArH), 9.79 (1H, br. s, NH), 11.42 (1H, br. s, NH), 11.96 (1H, br., s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 9.7, 13.1, 29.4, 76.2, 100.2, 106.9, 111.1, 119.7, 119.8, 121.4, 121.5, 125.3, 127.2, 129.0, 130.3, 133.0, 133.1, 136.2, 136.4, 142.2, 147.2, 157.1 ppm. Anal. Calcd for $C_{23}H_{17}Cl_2N_5$ (434.32): C, 63.60; H, 3.95; N, 16.12. Found: C, 63.51; H, 3.84; N, 16.01%.

4-(3-Hydroxyphenyl)-3-methyl-6-(2-methyl-1H-indol-3-yl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4h**): Cream powder; m.p. 242–245 °C. (KBr) (ν_{max}/cm^{-1}): 3355, 3250, 3050, 2930, 2910, 2198, 1650, 1600, 1558, 1510, 1485, 1455, 1380, 1260, 875, 740, 690. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.87 (3H, s, CH$_3$-pyrazole), 2.37 (3H, s, CH$_3$-indole), 4.83 (1H, s, CH), 6.63 (1H, ddd, *J* = 7.20, 2.4, 0.8 Hz, ArH), 6.72 (1H, s, ArH), 6.77 (1H, d, *J* = 8.0 Hz, ArH), 7.01–7.16 (3H, m, ArH), 7.34 (1H, d, *J* = 8.0 Hz, ArH), 7.43 (1H, d, *J* = 8.0 Hz, ArH), 9.53 (1H, br. s, OH), 9.61 (1H, br. s, NH), 11.39 (1H, br. s, NH), 11.88 (1H, br. s, NH) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 9.9, 13.1, 32.7, 78.9, 101.4, 107.0, 111.3,114.0, 114.8, 114.9, 118.6, 119.7, 121.3, 122.7, 122.9, 127.2, 127.3, 129.7,135.3, 136.3, 146.1, 148.3, 155.7, 157.9 ppm. Anal. Calcd for $C_{23}H_{19}N_5O$ (381.43): C, 72.42; H, 5.02; N, 18.36. Found: C, 72.31; H, 4.89; N, 18.45%.

4-(2-Chloro-6-fluorophenyl)-4,7-dihydro-3-methyl-6-(2-methyl-1H-indol-3-yl)-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4i**): Cream powder; m.p. 234–236 °C. (KBr) (ν_{max}/cm^{-1}): 3350, 3280, 3065, 2920, 2195, 1600, 1560, 1570, 1520, 1450, 1380, 1135, 1080, 895, 780, 740. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 1.87 (3H, s, CH$_3$-pyrazole), 2.36 (3H, s, CH$_3$-indole), 5.66 (1H, s, CH), 6.99–7.12 (2H, m, ArH), 7.22–7.46 (5H, m, ArH), 9.74 (1H, br. s, NH), 11.39 (1H, br.s, NH), 11.89 (1H, br. s, NH) ppm. Anal. Calcd for $C_{23}H_{17}ClFN_5$ (417.87): C, 66.11; H, 4.10; N, 16.76. Found: C, 66.01; H, 4.03; N, 16.65%

4-[1-(4-Chlorophenyl)-3-phenyl-1H-pyrazol-4-yl]-3-methyl-6-(1-methyl-1H-pyrrol-2-yl)-4,7-dihydro-1H-pyrazolo[3,4-b]pyridine-5-carbonitrile (**4j**): White powder; m.p. 245–247 °C. (KBr) (ν_{max}/cm^{-1}): 3300, 3050, 2920, 2200, 1635, 1537, 1520, 1500, 1420, 1385, 1085, 800, 757, 730, 690. ^{1}H NMR (DMSO-d$_6$, 400 MHz): δ 2.10 (3H, s, CH$_3$-pyrazole), 3.92 (3H, s, CH$_3$-pyrrole), 5.23 (1H, s, CH), 6.18 (1H, dd, *J* = 4.0, 2.8 Hz, ArH), 6.31 (1H, dd, *J* = 4.8, 2.0 Hz, ArH), 6.81 (1H, dd, *J* = 3.6, 1.6 Hz, ArH), 7.22 (1H, t, *J* = 7.6 Hz, ArH), 7.41 (2H, d, *J* = 8.4 Hz, ArH), 7.48 (2H, d, *J* = 8.4 Hz, ArH), 7.62 (2H, t, *J* = 7.6 Hz, ArH), 7.80 (2H, d, *J* = 8.0 Hz, ArH), 8.06 (1H, s, ArH), 9.12 (1H, br. s, N–H), 13.84 (1H, br. s, N–H) ppm. ^{13}C NMR (DMSO-d$_6$, 100 MHz): δ 9.9, 21.2, 36.6, 82.2, 101.2, 108.0, 111.1, 114.7, 115.2, 118.5, 119.0, 127.7, 128.5, 128.9, 129.4, 130.3, 130.9, 131.4, 133.6, 139.4, 143.1, 144.0, 149.3, 152.3, 152.4 ppm. Anal. Calcd for $C_{28}H_{22}ClN_7$ (491.97): C, 68.36; H, 4.51; N, 19.93. Found: C, 68.22; H, 4.39; N, 19.78%.

Determination of antimicrobial activity: The antibacterial activity of the synthesised compounds (**4a–j**) was examined using EC, BS, PS, *Salmonell*a and SA. All media were prepared according to manufacturers' instructions. A colony of each test organism was subcultured from nutrient agar plates into nutrient broth and incubated at 37 °C for 18 h. Mueller–Hinton agar plates were prepared and four plates were inoculated with bacteria from nutrient broth cultures. The antibacterial activity was performed by well diffusion technique. A concentration of 100 μg mL^{-1} of sample was prepared in DMSO. A sterilised glass tube (5 mm diameter) was used to aseptically scoop out the solid medium from the plate to create wells and 40 μL of the sample solution (6.25 μg/well) was aseptically added. The plates were incubated at 37 °C for 24 h. After incubation, zone of inhibition was measured.

Conclusions

In summary, we have demonstrated a clean, efficient and versatile approach for the synthesis of novel and highly functionalised derivatives of indole substituted pyrazolo[3,4-*b*]pyridines (**4a–j**) *via* one-pot three-component reactions, in a regiochemical reaction, using Fe^{3+}@ Mont. as reusable and eco-friendly solid acid catalyst under ultrasonic irradiation and conventional conditions. The reaction induced by ultrasound offered better yields and much lower reaction times than conventional heating. This protocol has distinct advantages such as good to excellent yields, short reaction times, easy operation and mild reaction conditions. These products were also evaluated for their antibacterial activities. Most of the compounds exhibited excellent antibacterial activity against both Gram-negative and Gram-positive bacteria. Further synthetic applications of this methodology and biological screening of the novel heterocycles thus generated are in progress in our laboratory.

We are grateful to the Research Council of University of Guilan for financial support of this research work.

Received 2 May 2013; accepted 3 June 2013
Paper1301922 *doi: 10.3184/174751913X13735444714766*
Published online: 9 August 2013

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