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An environmentally friendlier approach—ionic liquid catalysed, water promoted and grinding induced synthesis of highly functionalised pyrazole derivatives

Cite this: DOI: 10.1039/c3ra42493f

Received 21st May 2013,
Accepted 22nd July 2013

DOI: 10.1039/c3ra42493f

www.rsc.org/advances

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Grinding induced synthesis of highly functionalised pyrazoles derivatives by use of malanonitrile, phenyl hydrazine and diversified aldehyde. Ionic liquid is used as a catalyst with water, and no by-products form. A high yield is obtained and simple handling are the benefits of the adopted route, and this route fulfils all shades of green chemistry.

The current interest of the organic chemist is to synthesise biodynamic heterocyclic molecules with the maintenance of green chemistry protocols.[1] This involves all factors like easy handling, atom economy, energy saving, cost effectiveness and the use of non-renewable resources.

In addition, Mechanochemistry[2a] involving mechanical action and mechanical energy is a good alternative synthesis approach for chemists. Out of several methods which fall in this type of chemistry, one of the fascinating methods is 'grinding induced reaction'.[2b] This method carries a pool of advantages,[2c] one of them being that the reactant particles break down[2d] to smaller particles and thus provide a larger surface area for the reactions to occur. In literature many examples of reaction in which the reaction was mostly carried out at room temperature[2e] using pestle and mortar are available such as Reformatsky reaction,[3a] Grignard reaction,[3b] Dickmann condensation,[3c] Reduction,[3d] Aldol condensation[3e] *etc*.

Multicomponent reaction is now being paid extraordinary[4a] attention since it involves a liquid which also behaves as a catalyst. Moreover, it involves the formation of more than one bond[4b] in a single step which encourages atom economy and easy handling. In contrast, a multi step reaction involves a catalyst which may be highly toxic and may at times be difficult to be removed from the reaction mixture.[4c] A multi step reaction may require purification at each individual step.[4d] It also saves the environment from the hazardous effects of organic solvents.

Ionic liquids are considered to be good solvents[5a] for organic synthesis because (1), they are liquid at room temperature and (2), can dissolve a wide range of polar and non polar organic and inorganic molecules. Many types of reactions reported in literature are promoted by different types of ionic liquids including alkylation,[5b] condensation,[5c] esterification,[5d] hydrogenation,[5e] hydroformylation,[5f] oxidation,[5g] with excellent yield. They have also other properties like non-inflammably and extremely low vapour pressure which maintains their fluidity and volume.[13] Thus an ionic liquid serves as a better solvent and catalyst as compared to most organic solvents.

With the above mentioned aspects in our mind we performed and studied the reaction which is grinding induced and employs an ionic solvent which plays a great role in catalysis. We have chosen pyrazole moiety due to its importance in the field of pharmaceutical chemistry and agriculture.

Pyrazole framework occurs in many natural products and shows a large range of pharmacological activities like antitumor,[6a] antimicrobial,[6b] anti-inflammatory,[6c] antiviral,[6d] and analgesic[6e] activities. pyrazoleoxime ethers have also proven to be very important, for example compound (A) of this class shows antitumor activity and compound (B) shows cytotoxic activity (Fig. 1).[7]

Pyrazole moiety Celebrex[8] is a drug used for arthritis. Similarly, Viagra[9] is used to treat pulmonary arterial hypertension (PAH), and Rimonabant[9b] is an anarectic anti-obesity drug. 5-Methylpyrazole–3-carboxylic acid[10a] shows anti-diabetic activity, deracoxib[10b] is a nonsteroidal veterinary medicine to treat osteoarthritis in dogs.

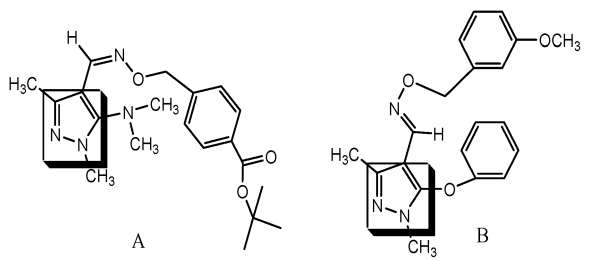

Fig. 1 Some examples of pyrazoleoxime ethers.

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Table 1 Optimization studies for solvent effect

Entry	Solvent	Yield (%)
1	H_2O	52
2	CH_3OH	54
3	CH_3CH_2OH	60
4	$C_6H_5CH_3$	16
5	THF	22

Well known wide spectrum qualities of pyrazoles motivated us to devise a new protocol for pyrazole derivatives. Recently many research groups reported the synthesis of pyrazole derivatives implementing various strategies. For example Glorius *et al.* synthesised pyrazoles using 2-methyl-3-(phenylamino)but-2-enoate and benzonitrile, catalysed by $Cu(OAC)_2$.[11a] Dembinski *et al.* used diketone and hydrazine.[11b] Yaziciet and co-workers have reported formation of hydrazone by α,β-unsaturated carbonyl compounds with hydrazine followed by intermolecular cyclization in the presence of $I_2/NaHCO_3$.[11c] Odam *et al.* reported $Ti(NMe_2)_2(PyPyr)_2$ catalysed pyrazoles synthesis using cyclohexylisonitrile, hydrazine and alkynes.[11d] Wang and co-workers synthesised pyrazoles from aldehyde, hydrazine and alkynes using PTSA as a catalyst.[11e] We synthesised the pyrazoles starting from easily available and simple starting materials aldehyde (**1**), malanonitrile (**2**) and phenylhydrazine (**3**), affording densely functionalized pyrazoles.[12]

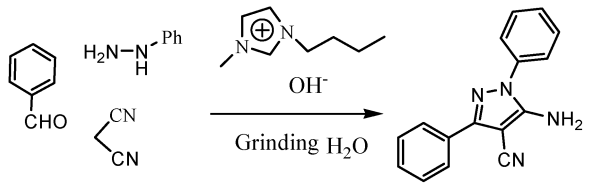
We mixed reagents **1**, **2** and **3** in stoichiometric amounts in mortar and ground the mixture with the help of a pestle. After the completion of the experiment, more than one pot is present on TLC plate. To overcome this problem we ground the mixture in a sequential manner.[13] We took **1** and **2** in mortar and ground the reactants until the completion of the reaction. This was followed by the addition of phenyl hydrazine and continuous grinding led to the formation of a single product. Next we performed the experiment twice—once by taking 1 ml water so as to make a paste of the reactants we were grinding and the second time by using ethanol instead of water. It was found that the reaction proceeded more smoothly[14] in the presence of ethanol than in water. We hence concluded that an increase in the polarity of the organic solvent reduces the reaction time and also increases the overall yield of the product (Table 1).

Our next approach was to study the scope of taking various types of ionic liquids as catalyst (20 mol%) during the time of grinding (Table 2, Scheme 1). This enhanced the yield to a great extent. The best result was obtained with (Bim)OH, the reason

Table 2 Effect of different types of ionic liquid as a catalyst

Entry	Solvent	Time (min)	Yield[a] (%)
1	(Bmim)OH	20	76
2	$(Hmim)H_2PO4$	40	60
3	$(Hmim)HSO_4$	35	65
4	(Bmim)Cl	50	62
5	(Bmim)PF6	45	56
6	(Bmim)BF4	47	58

[a] Is isolated yield



Scheme 1 Ionic liquid induced synthesis of highly functionalised pyrazole derivatives.

Table 3 Optimization of catalyst (Bim)OH

Entry	Amount (mol%)	Time (min)	Yield (%)
1	10	15	65
2	15	15	70
3	20	15	76
4	30	15	76
5	40	15	76
6	50	15	76
7	Catalyst system	15	90

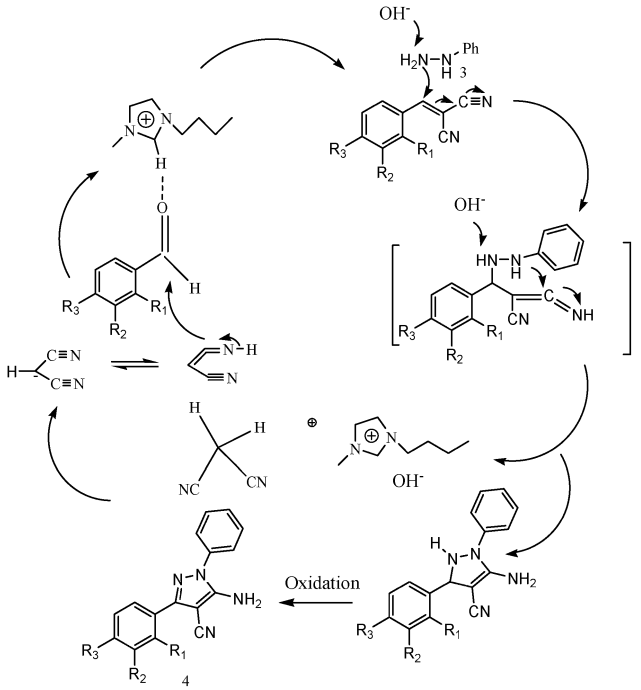
being that an ionic solvent of basic nature facilitates Knoevengal reaction, and also the second step which is Micheal addition. Only 20 mol% of (Bim)OH is sufficient for maximum yield. When the amount of catalyst was decreased from 20 mol% to 10 mol% and 15 mol% relative to substrate **1**, the yield of the product 4a is reduced, but the use of 30 mol%, 40 mol%, and 50 mol% of catalyst did not affect the yield (Table 3).

Moreover, cyclisation occurs with greater ease in a polar solvent.[14] Thus, using 1 ml water with ionic liquid gives dramatic improvement of the reaction in terms of yield and reaction rate.[15] We performed the experiment with different solvents with ionic liquid and the best result was obtained with basic ionic liquid with water[16] the yield of the product remarkably increases from 76% to 90% (Table 3, entry 3 and 7). Hence we prepared the ionic liquid and water system by taking 20 mol% of (Bim)OH and 1 ml water and performed the batch of reactions to achieve an insight into the role of electronic effect on the reaction. It was found that

Table 4 Synthesis of pyrazole derivatives[a]

Entry	R_1	R_2	R_3	2	3	Time	Yield[b] (%)
4a	H	H	H	2	3	15	90
4b	H	H	OCH_3	2	3	20	89
4c	H	OCH_3	H	2	3	22	88
4d	H	H	NO_2	2	3	12	96
4e	H	NO_2	H	2	3	12	96
4f	H	H	Cl	2	3	14	95
4g	Cl	H	H	2	3	15	95
4h	H	H	F	2	3	10	97
4i	H	OCH_3	OCH_3	2	3	30	85
4j	H	H	$N(CH3)_2$	2	3	24	82
4k	H	H	CH_3	2	3	25	80
4l	OH	H	H	2	3	30	75
4m	H	H	CN	2	3	16	88
4n	H	H	H	2	3(4 Cl)	25	86

[a] Time in min. [b] Yield of isolated of purified product.



Scheme 2 A plausible pathway for the synthesis of pyrazole derivatives.

aldehyde with an electron withdrawing substituent provided better results in comparison to those having an electron donating substituent. A withdrawing group (Table 4, entry 4h) present on aldehydes facilitates the first step of the reaction, *i.e.*, Knoevengeal reaction and basic nature of catalyst system also promotes this step (Scheme 2).

Conclusion

In summary, we have disclosed a mild and green procedure for the synthesis of novel pyrazole derivatives with the aim of causing no harmful effects to the environment and introducing the use of the ionic liquid with water in grinding fashion. The adopted route has many significant features like short time, simple handling and is an eco-friendly approach.

General methods

A. General information

Reagents were obtained from commercial suppliers (aldehydes by Sigma Aldrich, hydrazines by Loba Chemie and malanonitrile by Alfa Aesar) and used without further purification unless otherwise specified by a reference. All reactions were Performed using oven-dried glassware. Organic solutions were concentrated using a Buchi rotary evaporator. TLC was performed using silica gel GF254 (Merck) plates. Melting points were determined by open glass capillary method and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 993 IR spectrophotometer, ^{1}H NMR spectra were recorded on a Bruker AVII 400 spectrometer in $CDCl_3$ using TMS as internal reference with chemical shift value being reported in ppm. All coupling constants (J) are reported in Hertz (Hz). ^{13}C NMR spectra were recorded on the same instrument at 100 MHz in $CDCl_3$ and TMS was used as the internal reference. Mass (EI) spectra were recorded on a JEOL D-300 mass spectrometer.

B. General procedure for the synthesis of pyrazoles (4a to 4n)

Aldehyde (1 mmol), malanonitrile (1 mmol), (Bim)OH (20 mol%) and 1 ml water, were thoroughly ground with pestle and mortar. After the formation of Knoevengel adduct added phenyl hydrazine (1 mmol) and again thoroughly ground for an appropriate time (Table 4). When the reaction was complete (check by TLC) we added 5 ml water and the mixture was extracted with DCM (3 × 5 ml). The combined organic phase was dried over $MgSO_4$. Filtered and evaporated under reduced pressure. The resulting product was recrystallised by hot ethanol. Only 4g semisolid and 4h was liquid. After isolation of the product, the remaining mother liquid containing the ionic liquid was washed with DCM (3 × 5 ml) to remove any organic impurity. Dried under vacuum at 90 °C to afford (Bim)OH, which was used in subsequent runs without purification.

5-amino-1,3-diphenyl-1*H*-pyrazole-4-carbonitrile (4a). White solid, Melting point, 159–160 °C. IR (KBr) ν_{max}, 3483, 3344, 3081, 2357, 1589, 1422, 1251, 1124, 1110, 1065 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.2 Hz, 2H), 7.71 (s, 1H). 7.63 (s, 1H), 7.40 (t, J = 7.6 Hz, 2H), 7.36 (m, 3H), 7.16–7.29 (d, J = 7.6 Hz, 2H), 6.92 (t, J = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.52, 150.42, 146.09, 137.85, 135.77, 129.74, 128.05, 127.9, 126.64, 120.56, 113.25, 112.82, EIMS (m/z): 260 (M).$^+$

5-amino-3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4b). Light brown white solid, Melting point, 106–108 °C. IR (KBr) ν_{max}, 3350, 3270, 3030, 2820, 2630, 2215, 1540, 860 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.85 (m, 1H), 7.67 (s, 1H), 7.58–7.61 (m, 2H), 7.24–7.28 (m, 1H), 7.09 (d, J = 7.6, 2H), 7.00 (m, 1H), 6.89–6.93 (m, 2H), 6.83 (t, 1H) 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 160.03, 144.93, 143.44, 137.43, 128.10, 127.58, 127.10, 119, 114.11, 112.66, 99.98, 59.33, 55.35; EIMS (m/z) 290(M).$^+$

5-amino-3-(2-methoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4c). Red solid, Melting point 130–132 °C. IR (KBr) ν_{max}, 3480, 3410, 3120, 2830, 2545, 2238, 1650, 1580, 780, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.84 (m, 1H), 7.66 (s, 1H), 7.57–7.60 (m, 2H), 7.23–7.26 (m, 1H), 7.10 (d, J = 7.6, 2H), 7.01 (m, 1H), 6.89–6.93 (m, 2H), 6.85 (t, 1H) 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.01, 143.92, 143.37, 137.54, 137.40, 129.01, 127.30, 128.44, 125.84, 118.92, 112.89, 114.02, 56.01; EIMS (m/z) 290(M).$^+$

5-amino-3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4d). Red solid, Melting point 164–166 °C. IR (KBr) ν_{max}, 3465, 3355, 3105, 2354, 1610, 1417, 1456, 1345, 1256, 1133,1108, 1094 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), δ 8.25 (d, J = 7.6 Hz, 2H) 8.03 (s, 1H), 7.74–7.77 (m, 3H), 7.20–7.34 (m, 2H), 7.18 (d, J = 7.6 Hz, 2H), 6.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.53, 149.56, 145.26, 137.73, 135.32, 131.72, 130.93, 129.90, 122.78, 122.15, 123.47, 113.43, 112.36, EIMS (m/z) 305(M).$^+$

5-amino-3-(3-nitrophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4e). Saffron colour solid, Melting point 128–130 °C, IR (KBr) ν_{max}, 3455, 3321, 3111, 2355, 1592, 1477, 1445, 1343, 1328,1266, 1149, 1120, 1092 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H) 8.13 (d, J = 8.0 Hz,1H), 8.02 (d, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.75 (s, 1H) 7.57 (t, J = 7.6 Hz, 1H), 7.34 (t, J = 7.2 Hz, 2H), 7.17 (d, J = 8.4

Hz, 2H), 6.95 (t, J = 7.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.43, 149.26, 144.26, 137.73, 134.32, 131.82, 129.93, 129.87, 122.68, 122.10, 121.37, 113.43, 112.46; EIMS (m/z) 305 (M).$^+$

5-amino-3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4f). Cream colour solid, Melting point, 128–130 °C. IR (KBr) ν_{max}, 3460, 3380, 3130, 2520, 2253, 1660, 1570 cm^{-1}; ^{1}H NMR; (400 MHz, $CDCl_3$) δ 7.66 (s, 2H) 7.64 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 7.29–7.33 (m, 2H), 7.16 (d, J = 7.6 Hz, 2H), δ 6.95 (t, J = 7.4 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.23, 143.41, 142, 133, 130, 129, 127, 126, 119.41, 115.65; EIMS (m/z) 294(M^+), 296 (M + 2).$^+$

5-amino-3-(2-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4g). Semi solid, IR(KBr) ν_{max}, 3475, 3425, 3150, 2520, 2335, 1660, 1575,765, 720, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 2H) 7.58 (d, J = 8.4 Hz, 2H), 7.35 (d, J = 8.4 Hz, 2H), 7.28–7.32 (m, 2H), 7.15 (d, J = 7.6 Hz, 2H), δ 6.94 (t, J = 7.6 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.82, 144.87, 144.43, 139.44, 138.52, 137.90, 129.41, 128.54, 127.04, 119.34, 117.25, 112.84, 114.04, 99.48; EIMS (m/z) 294(m^+), 296(M + 2).$^+$

5-amino-3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4h). Yellow oil, IR (KBr) ν_{max}, 3465, 3410, 3143, 2545, 2220, 1650,1650, 1320, 840 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.96(m, 2H), 7.63 (s, 1H), 7.57–7.62 (m, 2H), 7.25–7.27 (m, 2 H),7.11 (d, J = 7.6, 1H), 6.90–6.93 (m, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.56, 144.93, 144.51, 136.32, 138.47, 130.56, 129.01, 128.31, 127.41, 119.32, 116.56, 115.67, 113.34; EIMS (m/z) 278(M^+).

5-amino-3-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4i). White solid, Melting point 120–123 °C. IR (KBr) ν_{max}, 3310, 3190, 3050, 2840, 2650, 2200, 1535, 1630, 874, 725 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (s, 1H), 7.68–7.69 (d, 1H, J = 2 Hz), 7.64 (s, 1H), 7.37–7.39 (m, 1H), 7.25–7.29 (m, 3H arom), 7.16 (s, 2H), 6.95–697 (d, 1H, J = 8.4), 3.77 (s, 3H), 3.79(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.45, 149.80, 148.02, 145.23, 144.46, 137.36, 129.43, 128.64, 127.36, 120.04, 115.48, 114.54, 112, 99.46, 56.10, 56.16; EIMS (m/z) 320 (M).$^+$

4-amino-1-(4-(dimethylamino)phenyl)-2,3-dihydro-3-phenyl-1*H*-pyrazole-5-carbonitrile (4j). Yellow solid, Melting point, 105–107 °C. IR (KBr) ν_{max}, 3430, 3320, 3180, 2810, 2545, 2230, 1640, 1580 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81–7.84 (m, arom, 4H), 7.65–7.69 (m, 2H), 7.61 (s,1H), 7.25–7.29 (m, 2H), 7.14 (s, 2H), 3.15 (s, 6H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 150.97, 145.03, 129.28, 128.18, 123.01, 127.82,115.11, 113.4, 59.01, 40.10; EIMS (m/z) 303(M).$^+$

5-Amino-1-phenyl-3-*p*-tolyl-1*H*-pyrazole-4-carbonitrile (4k). Pink powder, Melting point, 118–120 °C. IR (KBr) ν_{max}, 3484, 3318, 3098, 2927, 2358, 1598, 1418, 1255, 1125, 1123, 1094. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (s, 2H).7.58 (d, J = 7.6 Hz, 2H), 7.30–7.34 (m, 2H), 7.22 (d, J = 7.6 Hz, 2H),7.15 (d, J = 7.76 Hz, 2H), 6.91 (dd, J = 3.4 Hz and J = 7.6 Hz, 1H), δ 2.42 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.22, 150.95, 145.13, 129.26, 128.15, 123.11, 127.84, 115.11, 113.40, 104.65, 21.92; EIMS (m/z) 274 (M).$^+$

5-amino-3-(2-hydroxyphenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4l). Yellow solid, Melting Point, 160–162 °C, IR (KBr) ν_{max}, 3580, 3487, 3343, 3122, 2354, 2195, 1602, 1413, 1182, 1055 cm^{-1}; ^{1}H NMR (400 MHz, DMSO) δ 10.51 (s, 1H), 10.37 (s, 1H), 8.15 (s, 1H), 7.54 (dd, J = 1.6 Hz and J = 7.6 Hz, 1H), 7.24 (dd, J = 7.6 Hz and J = 8.4 Hz, 2H), 6.94 (d, J = 7.6 Hz, 2H), 7.14–7.18 (m,1H), 6.84–6.89 (m, 2H), 6.74 (t, J = 7.2 Hz, 1H), ^{13}C NMR (100 MHz, DMSO): δ 156.48, 152.20, 150.52, 145.52, 138.03, 130.13, 130.01, 128.16, 125.40, 121.33, 120.23, 119.73, 116.82, 112.61, EIMS (m/z) 276(M).$^+$

5-amino-3-(4-cynophenyl)-1-phenyl-1*H*-pyrazole-4-carbonitrile (4m). Yellow solid, Melting Powder, 158–160 °C. IR (KBr) ν_{max}, 3434,3316, 3275, 2353, 2229, 1583, 1472, 1265, 1155, 1127, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.72 (s, 1H), 7.85 (s, 1H), 7.77–7.81 (m, 4H),7.24 (t, J = 7.2 Hz, 2H) 7.13 (d, J = 7.6 Hz, 2H), 6.82 (t, J = 7.2 Hz, 1H), ^{13}C NMR (100 MHz, $CDCl_3$) δ = 152.34, 146.19, 137.83, 135.75, 129.70, 128.15, 127.09, 126.74, 120.56, 117.92,115.61, 113.25, 112.82, EIMS (m/z) 285(M^+).

5-amino-1-(4-chlorophenyl)-3-phenyl-1*H*-pyrazole-4-carbonitrile (4n). Pink solid, Melting point, 133–135 °C. IR (KBr) ν_{max}, 3420, 3322, 3095, 2365, 1598, 1487, 1267, 1134, 1096, cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.66 (d, J = 7.6 Hz, 2H), 7.56 (s, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.33–7.36 (m, 1H), 7.25 (d, J = 8.4 Hz, 2H), 7.06 (d, J = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ 155.92, 143.67, 138.37, 135.41, 132.28, 129.52, 129.09, 129.02, 126.60, 125.08, 114.22, 112.05, EIMS (m/z) 294 (M^+), 296 (M + 2)$^+$.

Acknowledgements

We sincerely thank SAIF, Punjab University, Chandigarh, for providing micro-analyses and spectra. The authors also thank UGC, New Delhi, for the award of Junior Research Fellowship.

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