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Synthesis of 5-arylamino-1-arylpyrazoles from 5-aminopyrazoles with arylhalides via CuI catalyzed Ullman coupling reaction

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ABSTRACT

An efficient method for synthesis of 5-arylamino-1-arylpyrazoles was developed by Ullman coupling reaction of 5-aminopyrazoles and arylhalides in the presence of cuprous iodide (CuI) as the catalyst. The corresponding 5-*N*-arylaminopyrazole products were obtained in good yields (≥65%).

1. Introduction

Numerous compounds containing 1-*N*-arylpyrazole moiety have been shown to exhibit antihyperglycemic, analgesic, anti-inflammatory sedative, and hypnotic activities.[1–3] 5-Alkyl/arylamino substituted pyrazoles have been exploited in the design of pharmaceuticals and agrochemical agents exhibiting a range of biological activities.[2,4–6] Several previous literature were reported for the synthesis of 1-aryl-5-*N*,*N*-disubstituted aminopyrazoles by means of the cyclization of hydrazines with β-ketoamides,[5d,6,7] the defined starting precursors containing the hydrazones with an electron withdrawing group,[5b,8] or the pre-generated 2-oxocarbothioamides (β-ketothioamides).[9] However, a few methods could provide the satisfactory reaction conditions for the preparation of the 5-arylamino-1-arylpyrazoles. Herein, we reported an efficient method for the synthesis of 5-arylamino-1-arylpyrazoles derivatives, of which analogues are known selective COX-2 inhibitors,[2,10] via CuI-catalyzed Ullman coupling reaction.

Introduction of nitrogen functionalities on aromatic rings has been one of the main topics in organic synthesis due to compounds containing aromatic C(sp^2)–N bonds possess various important pharmacologically activities.[11] Many metal-catalyzed aryl amination methods were reported by using palladium catalyst and phosphine ligand[11–13] or copper iodide and salicylic amide derivatives or proline.[14–16] However, most of methods were performed in the amination of aryl compounds. That we provided the new development of a novel 5-amino-pyrazoles amination catalyzed by CuI, K_2CO_3, and 1,10-phenanthroline for efficient synthesis of 5-arylamino-1-arylpyrazole derivatives in this study was due to the copper-mediated reactions are significantly superior to the conventional palladium-mediated reactions.[17]

2. Result and discussion

The 5-aminopyrazoles **1**–**13** were prepared as the starting substrates by following our previous published procedure via cyclodehydration and dehydrogenation in the neat condition.[18] In this newly developed method, we chose 3-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine (**1**)[18] as the model for the selection of best condition for the CuI-catalyzed Ullman coupling reaction (see Scheme 1). To search for the optimum conditions and establish a reproducible procedure, we firstly investigated the ligand effect. Compound **1** was allowed to react with phenyl iodide (PhI), K_2CO_3, and the various ligands including L-proline, DMEDA, pyrozole-2-COOH, *N*-methylglycine, and 1,10-phenanthroline in the presence

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[1] The contribution equal to first author.

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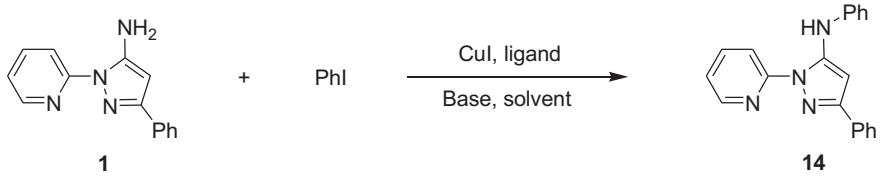


Scheme 1.

of the catalytic amount of CuI (0.10 equiv) at 70 °C for 1.0 h in DMF. Following the experimental results, we found that the use of 0.10 equiv of 1,10-phenanthroline as the ligand in DMF provided the best result to give the corresponding product **14** in 84% yield (see entries 1–5 of Table 1). Consequently, we explored the cross-coupling reaction by modifying the polarity of aprotic polar solvents, such as DMF, DMSO, and DMAC. Based on the result, the 0.10 equiv of 1,10-phenanthroline in DMF solution can be considered as the best suitable ligand and solvent system (see entry 5–7 of Table 1).

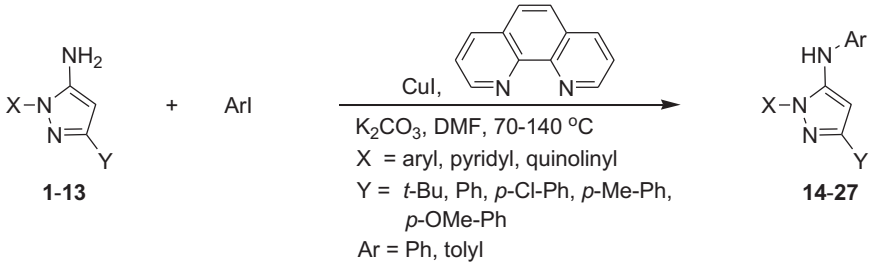
Table 1
The result of optimization studies

Entry	Ligand	Solvent	Base	Yields[a,b] (%) of compound **14**
1	L-Proline	DMF	K_2CO_3	62
2	DMEDA	DMF	K_2CO_3	77
3	Pyrozole-2-COOH	DMF	K_2CO_3	74
4	*N*-Methylglycine	DMF	K_2CO_3	16
5	1,10-Phenanthroline	DMF	K_2CO_3	84
6	1,10-Phenanthroline	DMSO	K_2CO_3	52
7	1,10-Phenanthroline	DMAC	K_2CO_3	34
8	1,10-Phenanthroline	DMF	Li_2CO_3	34
9	1,10-Phenanthroline	DMF	Na_2CO_3	39
10	1,10-Phenanthroline	DMF	Cs_2CO_3	43
11	1,10-Phenanthroline	DMF	*t*-BuOK	60
12	1,10-Phenanthroline	DMF	NaOMe	55
13	1,10-Phenanthroline	DMF	$NaHCO_3$	54
14	1,10-Phenanthroline	DMF	K_3PO_4	72
15	1,10-Phenanthroline	DMF	—	Non-detectable

[a] Compound **1** (1.0 mmol, 1.0 equiv), PhI (1.0 mmol, 1.0 equiv), and various bases (1.2 mmol, 1.2 equiv) and ligands (0.10 mmol, 0.10 equiv) with catalytic amount CuI (0.10 mmol, 0.10 equiv) in aprotic polar solvents at 70 °C for 1.0 h under nitrogen gas.
[b] The isolated yields were determined by column chromatography on silica gel.

with column chromatography on silica gel, the desired 5-*N*-monoarylamino substituted pyrazole **14** was isolated as solids (entries 5 and 8–12 of Table 1). Among of bases, we found that the use of potassium phosphate (K_3PO_4) and potassium carbonate (K_2CO_3) gave the better results in 72% and 84% yields, respectively (see entries 5 and 14 of Table 1). Yields of the desired 5-arylamino-1-arylpyrazole **14** after 1.0 h were substantially decreased when using potassium, sodium, and lithium carbonate salts (entries 5 and 8–9 of Table 1). However, low yield was also observed with Cs_2CO_3 (entry 10 of Table 1). Conditions using other bases, such as sodium bicarbonate ($NaHCO_3$), potassium *tert*-butoxide (*t*-BuOK), or without bases resulted in only poor result (entries 11 and 13–15 of Table 1). Based on these optimizations, we finally decided to choose the combination of CuI, 1,10-phenanthroline, and K_2CO_3 in DMF as the standard conditions for the metal catalyzed cross-coupling reaction of 5-arylamino-1-arylpyrazoles in the following studies.

In this reaction, the reliable procedure involved the treatment of 5-amino-pyrazole substrates, aryl halide, and K_2CO_3 using 0.10 equiv of catalytic amount CuI and 1,10-phenanthroline ligand in anhydride DMF at 70 or 140 °C for more than 1.0 h (see Scheme 2). For investigation of the reactivity of different phenyl halide substrates, the amination reaction was performed with phenyl chloride, bromide, and iodide, and tolyl iodide. After comparing the results, we found that the use of phenyl and tolyl iodides were obviously better than the use of phenyl bromide and chloride (entries 1–4 of Table 2). For phenyl chloride, reaction was incomplete even after 7.0 h at 140 °C (entry 1 of Table 2). These results were consistent with the literature amination order.[18] Application of same cross-coupling reaction conditions to 3-*p*-methylphenyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine **2**, 3-*p*-methoxylphenyl -1-(pyridin-2-yl)-1*H*-pyrazol-5-amine **3**, and 3-*tert*-butyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine **4** with various of aryl iodine, including PhI, tolyl iodine, and *p*-methoxylphenyl iodine also gave the corresponding products **16**–**18** in good yields (80–93%, entries 5–7 of Table 2).



Scheme 2.

We knew that the appropriate choice of base might be important for the cross-coupling reaction. Thus, we treated an anhydrous DMF solution of 3-phenyl-1-(pyridin-2-yl)-1*H*-pyrazol-5-amine (**1**) and PhI with catalytic amount of CuI and 1,10-phenanthroline in the presence of 1.2 equiv of different bases, including lithium, sodium, cesium and potassium carbonate (Li_2CO_3, Na_2CO_3, Cs_2CO_3 and K_2CO_3), potassium *tert*-butoxide (*t*-BuOK), sodium methoxide (NaOMe), sodium bicarbonate ($NaHCO_3$) and potassium phosphate (K_3PO_4) at 70 °C for 1.0 h. After normal work-up and purification

The synthetic strategy was applicable to 3-*p*-totyl-1-(quinolin-2-yl)-1*H*-pyrazol-5-amine **5** with phenyl chloride, bromide, and iodide to afford the desired amination products **18** in 23%, 77%, and 96% yields, respectively (see entries 8–10 of Table 2). Although phenyl bromide and chloride were also successfully coupled by using the CuI/L catalyst system, higher temperatures (>100 °C) and long reaction times were required. For further demonstration of the reactivity of phenyl halides, 3-(4-methoxyphenyl)-1-(quinolin-2-yl)-1*H*-pyrazol-5-amine **6**, 3-*tert*-butyl-1-(quinolin-2-yl)-1*H*-

Table 2
The result of CuI catalyzed Ullman coupling reaction of 5-aminopyrazoles with arylhalides

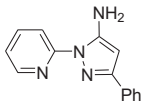
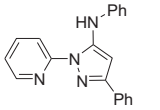
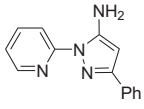
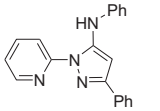
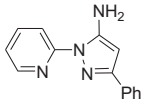
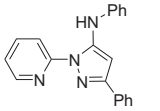
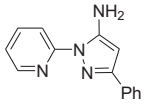
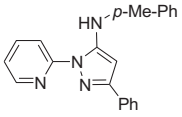
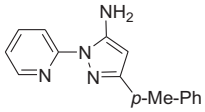
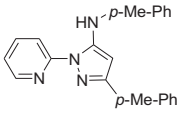
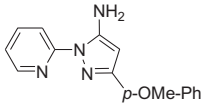
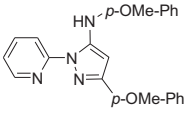
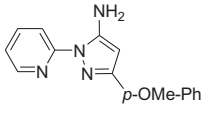
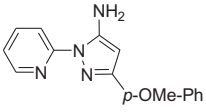
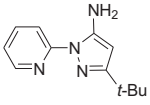
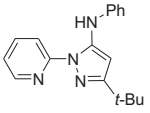
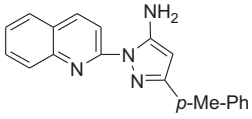
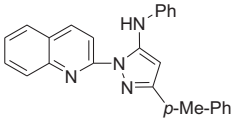
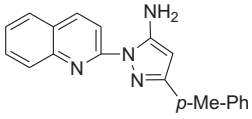
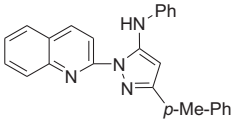
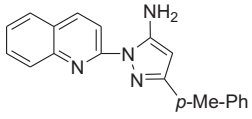
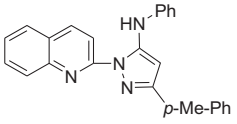
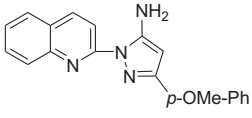
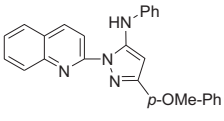
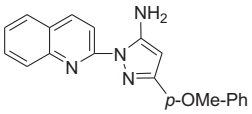
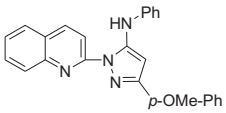
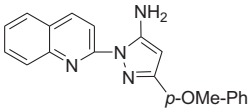
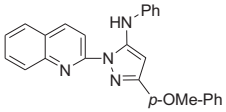
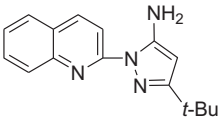
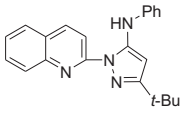
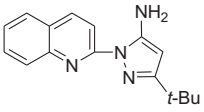
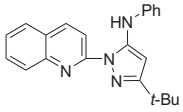
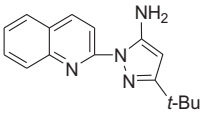
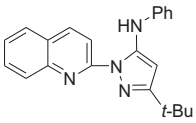
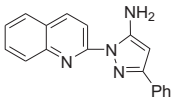
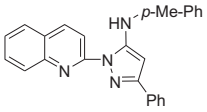
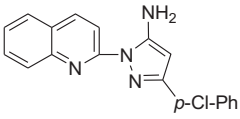
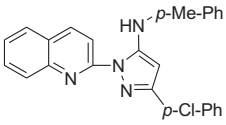
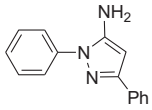
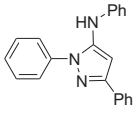
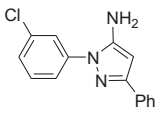
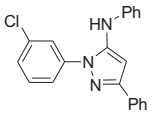
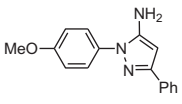
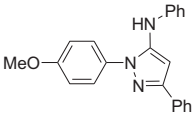
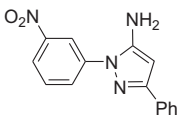
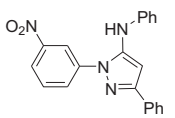
Entry	5-Aminopyrazoles		ArX	Reaction time & temperature		Products		Yields[a,b] (%)
				h	°C			
1		**1**	PhCl	48	140		**14**	—
2		**1**	PhBr	7	70		**14**	75
3		**1**	PhI	4	70		**14**	91
4		**1**	Tolyl–I	3	70		**15**	84
5		**2**	Tolyl–I	2	70		**16**	93
6		**3**	*p*-OMe–Ph–I	1	70		**17**	80
7		**3**	*p*-NO_2–Ph–I	>3	70	—[c]	—	—[c]
8		**3**	*p*-NO_2–Ph–Br	>7	70	—[c]	—	—[c]
9		**4**	PhI	3	70		**18**	86
10		**5**	PhCl	12	140		**19**	23
11		**5**	PhBr	5	70		**19**	77
12		**5**	PhI	3	70		**19**	96
13		**6**	PhCl	22	140		**20**	21

Table 2 (*continued*)

Entry	5-Aminopyrazoles		ArX	Reaction time & temperature		Products		Yields[a,b] (%)
				h	°C			
14		**6**	PhBr	3	70		**20**	68
15		**6**	PhI	3	70		**20**	94
16		**7**	PhCl	48	140		**21**	17
17		**7**	PhBr	24	70		**21**	73
18		**7**	PhI	22	70		**21**	95
19		**8**	Tolyl–I	3	70		**22**	90
20		**9**	Tolyl–I	3	70		**23**	86
21		**10**	PhI	30	70		**24**	78
22		**11**	PhI	36	70		**25**	72
23		**12**	PhI	2	70		**26**	88
24		**13**	Tolyl–I	36	70		**27**	65

[a] 5-Amino-pyrazole substrates **1**–**13** (1.0 mmol, 1.0 equiv), arylhalides (PhCl, PhBr, PhI, *p*-MeO-PhI, or tolyl iodide, 1.0 mmol, 1.0 equiv), and K_2CO_3 (1.2 mmol, 1.2 equiv) with catalytic amount CuI (0.10 mmol, 0.10 equiv) and 1,10-phenanthroline (0.10 mmol, 0.10 equiv) in DMF at 70 or 140 °C within 1–48 h under nitrogen gas.

[b] The isolated yields were performed by column chromatography on silica gel.

[c] Non-detectable.

pyrazol-5-amine **7** were allowed to react with phenyl halides (PhCl, PhBr, and PhI) under the same reaction conditions. Following the experimental results, the similar reactive tendency of phenyl halides (PhI>PhBr>>PhCl) were detected in the newly developed Ullman coupling amination (see the entries 11–16 of Table 2). When employing 3-phenyl-1-(quinolin-2-yl)-1*H*-pyrazol-5-amine **8** and 3-*p*-chlorophenyl-1-(quinolin-2-yl)-1*H*-pyrazol-5-amine **9** as the reactant to treat with tolyl iodine, a good to excellent yields were also achieved (90% and 86%, entry 17–18 of Table 2).

On the other hand, we extended the new developed coupling amination to 1-aryl-3-phenyl-5-amino-1*H*-pyrazoles **10**–**13**, bearing various *N*-1 substituents including Ph, *m*-Cl–Ph, *m*-NO_2Ph, and *p*-OMePh. The corresponding 5-arylamino-1-aryl-3-phenyl-pyrazole products **24**–**27** were obtained in good yields (65–88%, entries 19–22 in Table 2). All 5-mono-*N*-substituted aminopyrazole Products **14**–**27** were fully characterized by spectroscopic methods and consistent with the literature data. Served as an example, compound **14** presented a peak at δ 6.41 ppm for ^{1}H–C= in C-4 position of pyrazole ring in ^{1}H NMR. In ^{13}C NMR spectrum, compound **14** possessed characterization absorptions at δ 87.30 ppm for sp^2 carbon ^{13}C–H and at δ 146.80 ppm for imine carbon N=^{13}C in pyrazole ring. The IR absorptions of **14** showed peaks at 3215 cm^{-1} for the stretching of the –NH group.

3. Conclusion

In conclusion, we have successfully developed a new cross-coupling method for the synthesis of 5-arylamino-1-arylpyrazoles using 1,10-phenanthroline as the ligand and CuI as catalyst. This methodology can applicable to the wide range of *N*-1 substituted aryl, pyridin-2-yl, isoquinolinyl or C-3 substituted aryl and *tert*-butyl of 5-amino-pyrazole substrates to give the corresponding 5-arylamino-1-arylpyrazole products in good yields.

4. Experimental section

4.1. General procedure for the CuI catalyzed cross-coupling reaction of primary 5-amino-pyrazoles

A 5-amino-pyrazole substrates (1.0 mmol, 1.0 equiv), arylhalides (PhCl, PhBr, PhI, *p*-MeO–PhI, or tolyl iodide, 1.0 mmol, 1.0 equiv), and K_2CO_3 (1.2 mmol, 1.2 equiv) with catalytic amount CuI (0.1 mmol, 0.1 equiv) and 1,10-phenanthroline (0.1 mmol, 0.1 equiv) in DMF at 70 or 140 °C within 1–48 h under nitrogen gas. After 5-amino-pyrazoles were completely consumed, the reaction mixture was work-up, extracted with CH_2Cl_2 (20 mL×2), and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give the corresponding 5-arylamino-1-arylpyrazole products in 17–96%.

*4.1.1. 5-Anilino-3-phenyl-1-(2-pyridyl)-1H-pyrazole (**14**).* Yellow powder; mp 98–99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.41 (s, 1H, Py), 7.01 (t, 1H, *J*=7.1 Hz, ArH), 7.13 (t, 1H, *J*=6.4 Hz, ArH), 7.28–7.45 (m, 7H, ArH), 7.81–7.92 (m, 3H, ArH), 8.19 (d, 1H, *J*=8.4 Hz, ArH), 8.38 (d, 1H, *J*=4.3 Hz, ArH), 10.59 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 87.30, 114.24, 118.20, 119.71, 121.76, 125.91, 128.31, 128.52, 129.38, 133.11, 138.83, 141.27, 146.03, 146.80, 152.25, 154.96; IR (diffuse reflectance) 3215 (m), 2927 (m), 2862 (w), 1682 (m), 1651 (s), 1557 (s), 1538 (m), 1505 (m), 1455 (m), 1252 (m), 1140 (m), 1075 (m) cm^{-1}; MS (ESI) *m*/*z*: 313 $(M+H)^+$. HRMS (ESI) calcd for $C_{20}H_{17}N_4$ $(M+H)^+$ 313.1453, found 313.1454.

*4.1.2. 3-Phenyl-1-(2-pyridyl)-5-p-toluidine-1H-pyrazole (**15**).* Yellow powder; mp 77–78 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H, CH_3), 6.32 (s, 1H, Py), 7.10–7.22 (m, 5H, ArH), 7.34–7.44 (m, 3H, ArH), 7.80–7.86 (m, 1H, ArH), 7.90 (d, 2H, *J*=7.4 Hz, ArH), 8.18 (d, 1H, *J*=8.3 Hz, ArH), 8.37 (d, 1H, *J*=4.5 Hz, ArH), 10.43 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.72, 86.75, 114.15, 117.65, 118.77, 119.59, 125.89, 128.25, 128.49, 129.87, 131.50, 133.18, 138.76, 146.03, 147.47, 152.27, 154.99; IR (diffuse reflectance) 3282 (m), 3056 (w), 2924 (m), 2855 (m), 1683 (m), 1651 (s), 1557 (m), 1505 (s), 1455 (s), 1361 (m), 1262 (m), 1044 (m), 955 (m) cm^{-1}; MS (ESI) *m*/*z*: 327 $(M+H)^+$. HRMS (ESI) calcd for $C_{21}H_{19}N_4$ $(M+H)^+$ 327.1610, found 327.1609.

*4.1.3. 1-(2-Pyridyl)-5-p-toluidine-3-p-tolyl-1H-pyrazole (**16**).* Yellow powder; mp 86–87 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 6.29 (s, 1H, Py), 7.09–7.23 (m, 7H, ArH), 7.76–7.85 (m, 3H, ArH), 8.16 (d, 1H, *J*=8.3 Hz, ArH), 8.36 (dd, 1H, *J*=4.8, 1.1 Hz, ArH), 10.42 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.72, 21.32, 86.64, 114.12, 118.73, 119.48, 125.79, 129.19, 129.86, 130.37, 131.41, 138.09, 138.72, 138.80, 146.01, 147.38, 152.34, 155.01; IR (diffuse reflectance) 3253 (m), 2923 (m), 2852 (m), 1594 (s), 1557 (s), 1539 (m), 1468 (m), 1442 (m), 1362 (m), 1248 (m), 948 (m) cm^{-1}; MS (ESI) *m*/*z*: 341 $(M+H)^+$. HRMS (ESI) calcd for $C_{22}H_{21}N_4$ $(M+H)^+$ 341.1766, found 341.1764.

*4.1.4. 5-Anisidino-3-(4-methoxyphenyl)-1-(2-pyridyl)-1H-pyrazole (**17**).* Yellow powder; mp 110–111 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.12 (s, 1H, Py), 6.89–7.26 (m, 7H, ArH), 7.79–7.81 (m, 3H, ArH), 8.14 (d, 1H, *J*=8.3 Hz, ArH), 8.34 (d, 1H, *J*=3.4 Hz, ArH), 10.22 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.27, 55.57, 85.64, 113.86, 113.91, 114.63, 119.34, 121.30, 125.95, 127.15, 134.65, 138.69, 146.03, 148.43, 152.10, 154.99, 155.28, 159.77; IR (diffuse reflectance) 3243 (m), 2923 (m), 2852 (m), 1593 (s), 1556 (s), 1531 (s), 1470 (s), 1441 (s), 1361 (m), 1295 (m), 1246 (s), 1173 (m), 1033 (m), 948 (m) cm^{-1}; MS (ESI) *m*/*z*: 373 $(M+H)^+$. HRMS (ESI) calcd for $C_{22}H_{21}N_4O_2$ $(M+H)^+$ 373.1665, found 373.1667.

*4.1.5. 5-Anilino-3-tert-butyl-1-(2-pyridyl)-1H-pyrazole (**18**).* ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 9H, 3× CH_3), 5.95 (s, 1H, Py), 6.96 (t, 1H, *J*=7.3 Hz, ArH), 7.06 (t, 1H, *J*=6.2 Hz, ArH), 7.21 (d, 2H, *J*=8.2 Hz, ArH), 7.29–7.34 (m, 2H, ArH), 7.77 (td, 1H, *J*=8.1, 1.4 Hz, ArH), 8.04 (d, 1H, *J*=8.4 Hz, ArH), 8.32 (d, 1H, *J*=4.9 Hz, ArH), 10.50 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.04, 32.51, 86.89, 114.13, 117.81, 119.12, 121.28, 129.27, 138.62, 141.51, 145.81, 145.93, 155.10, 163.42; IR (diffuse reflectance) 3247 (m), 2949 (m), 2923 (m), 2854 (m), 1592 (s), 1556 (s), 1470 (s), 1441 (s), 1365 (m), 1255 (m), 1132 (m), 1086 (m), 981 (m) cm^{-1}; MS (ESI) *m*/*z*: 293 $(M+H)^+$. HRMS (ESI) calcd for $C_{18}H_{21}N_4$ $(M+H)^+$ 293.1766, found 293.1767.

*4.1.6. 5-Anilino-1-(2-quinolinyl)-3-p-tolyl-1H-pyrazole (**19**).* Yellow powder; mp 160–161 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.40 (s, 3H, CH_3), 6.44 (s, 1H, Py), 7.03–7.06 (m, 1H, ArH), 7.27–7.51 (m, 7H, ArH), 7.69–7.85 (m, 4H, ArH), 7.95 (d, 1H, *J*=8.5 Hz, ArH), 8.24 (d, 1H, *J*=9.0 Hz, ArH), 8.40 (d, 1H, *J*=8.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.35, 87.21, 114.08, 117.84, 121.66, 125.65, 125.73, 125.88, 127.34, 127.74, 129.25, 129.47, 130.20, 130.26, 138.30, 138.80, 141.24, 145.00, 147.09, 152.57, 154.00; IR (diffuse reflectance) 3210 (m), 3057 (m), 2922 (m), 2855 (m), 1602 (s), 1589 (s), 1556 (s), 1504 (s), 1455 (m), 1430 (s), 1371 (s), 1252 (m), 1119 (m), 1042 (m), 947 (m) cm^{-1}; MS (ESI) *m*/*z*: 377 $(M+H)^+$. HRMS (ESI) calcd for $C_{25}H_{21}N_4$ $(M+H)^+$ 377.1766, found 377.1763.

*4.1.7. 5-Anilino-3-(4-methoxyphenyl)-1-(2-quinolinyl)-1H-pyrazole (**20**).* Yellow powder; mp 183–184 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.86 (s, 3H, OCH_3), 6.40 (s, 1H, Py), 6.96–7.05 (m, 3H, ArH), 7.33–7.51 (m, 5H, ArH), 7.69–7.96 (m, 5H, ArH), 8.24 (d, 1H, *J*=9.0 Hz, ArH), 8.38 (d, 1H, *J*=9.2 Hz, ArH), 11.40 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.30, 87.00, 113.95, 114.04, 117.86, 121.66,

125.62, 125.70, 125.77, 127.28, 127.32, 127.74, 129.47, 130.26, 138.79, 141.24, 145.01, 147.11, 152.34, 153.99, 159.93; IR (diffuse reflectance) 3195 (w), 3072 (m), 2920 (m), 2847 (m), 1591 (s), 1556 (s), 1504 (s), 1455 (m), 1428 (s), 1366 (m), 1245 (s), 1174 (m), 1025 (m), 944 (m) cm^{-1}; MS (ESI) *m*/*z*: 393 $(M+H)^+$. HRMS (ESI) calcd for $C_{25}H_{21}N_4O$ $(M+H)^+$ 393.1715, found 393.1716.

*4.1.8. 5-Anilino-3-tert-butyl-1-(2-quinolinyl)-1H-pyrazole (**21**).* Yellow powder; mp 119–120 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (s, 9H, 3× CH_3), 6.03 (s, 1H, Py), 7.00 (t, 1H, *J*=7.0 Hz, ArH), 7.27–7.49 (m, 5H, ArH), 7.67–7.72 (m, 1H, ArH), 7.78 (d, 1H, *J*=8.0 Hz, ArH), 7.92 (d, 1H, *J*=8.4 Hz, ArH), 8.19 (d, 1H, *J*=9.1 Hz, ArH), 8.29 (d, 1H, *J*=9.1 Hz, ArH), 11.32 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 30.04, 32.62, 86.98, 114.18, 117.56, 121.29, 125.39, 125.54, 127.29, 127.70, 129.40, 130.11, 138.58, 141.47, 145.07, 146.28, 154.16, 163.69; IR (diffuse reflectance) 3456 (m), 3223 (m), 3063 (w), 2959 (m), 2862 (m), 1586 (s), 1556 (s), 1504 (s), 1430 (s), 1371 (s), 1225 (m), 1134 (m), 1044 (m), 981 (m) cm^{-1}; MS (ESI) *m*/*z*: 343 $(M+H)^+$. HRMS (ESI) calcd for $C_{22}H_{23}N_4$ $(M+H)^+$ 343.1923, found 343.1922.

*4.1.9. 3-Phenyl-1-(2-quinolinyl)-5-p-toluidine-1H-pyrazole (**22**).* Yellow powder; mp 174–175 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H, CH_3), 6.39 (s, 1H, Py), 7.18–7.52 (m, 8H, ArH), 7.72 (td, 1H, *J*=7.5, 1.0 Hz, ArH), 7.81 (d, 1H, *J*=7.9 Hz, ArH), 7.93–7.95 (m, 3H, ArH), 8.25 (d, 1H, *J*=9.0 Hz, ArH), 8.40 (d, 1H, *J*=9.0 Hz, ArH), 11.22 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.74, 86.78, 114.04, 118.41, 125.65, 125.75, 125.98, 127.38, 127.73, 128.39, 128.53, 129.97, 130.25, 131.45, 133.09, 138.69, 138.79, 145.04, 147.81, 152.53, 154.01; IR (diffuse reflectance) 3210 (m), 3057 (m), 2922 (m), 2855 (w), 1621 (m), 1592 (s), 1556 (s), 1504 (s), 1430 (m), 1367 (m), 1249 (m), 1042 (m), 946 (m) cm^{-1}; MS (ESI) *m*/*z*: 377 $(M+H)^+$. HRMS (ESI) calcd for $C_{25}H_{21}N_4$ $(M+H)^+$ 377.1766, found 377.1768.

*4.1.10. 3-(4-Chlorophenyl)-1-(2-quinolinyl)-5-p-toluidine-1H-pyrazole (**23**).* Yellow powder; mp 180–181 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.36 (s, 3H, CH_3), 6.31 (s, 1H, Py), 7.18–7.22 (m, 4H, ArH), 7.38 (d, 2H, *J*=8.3 Hz, ArH), 7.48 (t, 1H, *J*=7.5 Hz, ArH), 7.70 (t, 1H, *J*=7.8 Hz, ArH), 7.77–7.93 (m, 4H, ArH), 8.22 (d, 1H, *J*=9.0 Hz, ArH), 8.34 (d, 1H, *J*=9.0 Hz, ArH), 11.21 (br, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.75, 86.50, 113.88, 118.46, 125.72, 125.75, 127.20, 127.37, 127.72, 128.67, 129.98, 130.28, 131.58, 131.62, 134.08, 138.55, 138.81, 144.97, 147.94, 151.31, 153.87; IR (diffuse reflectance) 3217 (m), 3065 (m), 2921 (m), 2855 (w), 1602 (s), 1591 (s), 1556 (s), 1504 (s), 1465 (m), 1431 (s), 1367 (s), 1249 (m), 1090 (m), 1043 (m), 1013 (m), 946 (m) cm^{-1}; MS (ESI) *m*/*z*: 413 $(M+3)^+$, 411 $(M+H)^+$. HRMS (ESI) calcd for $C_{25}H_{20}ClN_4$ $(M+H)^+$ 411.1376, found 411.1380.

*4.1.11. 5-Anilino-1,3-diphenyl-1H-pyrazole (**24**).* Yellow powder; mp 152–153 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.55 (br, 1H, NH), 6.52 (s, 1H, Py), 6.99 (d, 2H, *J*=7.8 Hz, ArH), 7.18–7.50 (m, 9H, ArH), 7.63 (d, 2H, *J*=7.7 Hz, ArH), 7.86 (d, 2H, *J*=7.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 93.72, 115.91, 120.94, 124.38, 125.61, 127.67, 127.93, 128.50, 129.34, 129.44, 133.18, 138.33, 142.17, 142.98, 151.47; IR (diffuse reflectance) 3233 (m), 3004 (m), 2935 (m), 1596 (s), 1494 (m), 1452 (m), 1361 (m), 1301 (m), 1255 (w), 1165 (m) cm^{-1}; MS (ESI) *m*/*z*: 312 $(M+H)^+$. HRMS (ESI) calcd for $C_{21}H_{18}N_3$ $(M+H)^+$ 312.1501, found 312.1503.

*4.1.12. 5-Anilino-1-(3-chlorophenyl)-3-phenyl-1H-pyrazole (**25**).* Yellow powder; mp 128–129 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.49 (br, 1H, NH), 6.51 (s, 1H, Py), 6.97 (d, 2H, *J*=8.4 Hz, ArH), 7.28–7.43 (m, 7H, ArH), 7.56 (d, 1H, *J*=7.7 Hz, ArH), 7.73 (s, 1H, ArH), 7.85 (d, 2H, *J*=7.4 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 94.54, 116.10, 121.32, 121.86, 124.39, 125.60, 127.54, 128.18, 128.59, 129.55, 130.28, 132.92, 135.09, 139.60, 142.37, 142.79, 151.92; IR (diffuse reflectance) 3390 (m), 3065 (w), 2923 (m), 2855 (m), 1593 (s), 1557 (s), 1538 (m), 1362 (m), 1250 (m), 1076 (m), 952 (m) cm^{-1}; MS (ESI) *m*/*z*: 348 $(M+3)^+$, 346 $(M+H)^+$. HRMS (ESI) calcd for $C_{21}H_{17}ClN_3$ $(M+H)^+$ 346.1111, found 346.1109.

*4.1.13. 5-Anilino-1-(4-methoxyphenyl)-3-phenyl-1H-pyrazole (**26**).* Yellow powder; mp 147–148 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.78 (s, 3H, OCH_3), 6.77 (s, 1H, Py), 7.04 (d, 2H, *J*=8.8 Hz, ArH), 7.32–7.45 (m, 6H, ArH), 7.63 (d, 2H, *J*=8.8 Hz, ArH), 7.70 (d, 2H, *J*=7.6 Hz, ArH), 7.90 (d, 2H, *J*=7.1 Hz, ArH), 8.76 (br, 1H, NH); IR (diffuse reflectance) 3434 (m), 2922 (s), 2852 (m), 1651 (m), 1613 (m), 1557 (s), 1539 (s), 1505 (s), 1455 (m), 1273 (m), 1252 (m), 1161 (m), 1024 (m) cm^{-1}; MS (ESI) *m*/*z*: 342 $(M+H)^+$. HRMS (ESI) calcd for $C_{22}H_{20}N_3O$ $(M+H)^+$ 342.1606, found 342.1605.

*4.1.14. 1-(3-Nitrophenyl)-3-phenyl-5-p-toluidine-1H-pyrazole (**27**).* Yellow powder; mp 148–149 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.28 (s, 3H, CH_3), 5.43 (br, 1H, NH), 6.48 (s, 1H, Py), 6.83 (d, 2H, *J*=8.3 Hz, ArH), 7.07 (d, 2H, *J*=8.3 Hz, ArH), 7.34–7.45 (m, 3H, ArH), 7.58 (t, 1H, *J*=8.1 Hz, ArH), 7.84 (d, 2H, *J*=7.5 Hz, ArH), 8.08–8.14 (m, 2H, ArH), 8.63–8.65 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.55, 96.02, 116.51, 118.33, 121.41, 125.63, 128.44, 128.65, 128.77, 130.03, 130.09, 131.20, 132.61, 139.87, 140.43, 143.36, 148.70, 152.45; IR (diffuse reflectance) 3376 (m), 3036 (w), 2923 (m), 2855 (m), 1593 (m), 1556 (s), 1532 (s), 1455 (m), 1350 (s), 1247 (m), 1078 (m), 951 (m) cm^{-1}; MS (ESI) *m*/*z*: 371 $(M+H)^+$. HRMS (ESI) calcd for $C_{22}H_{19}N_4O_2$ $(M+H)^+$ 371.1508, found 371.1510.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.11.022.

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