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Palladium-catalyzed amino group arylation of 1,3-disubstituted 1*H*-pyrazol-5-amine based on Buchwald–Hartwig reaction

Mateusz Kucharek[1]*, Andrzej Danel[2]

[1] *Department of Biotechnology and General Technology of Food, Faculty of Food Technology, University of Agriculture in Krakow, 122 Balicka St., Krakow 30-149, Poland; e-mail: mateusz.kucharek@urk.edu.pl*

[2] *Faculty of Materials Engineering and Physics, Cracow University of Technology, 1 Podchorążych St., Krakow 30-048, Poland; e-mail: rrdanela@cyf-kr.edu.pl*

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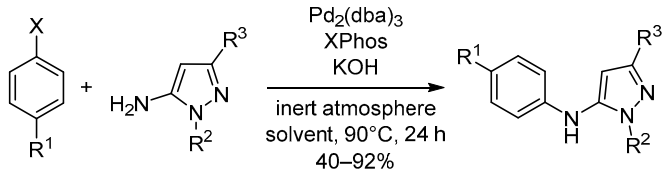


X = Br, I; R^1 = H, NO_2, Me, Ph, *o*-Tol, *t*-Bu, OMe, OPh, NMe_2, NPh_2
R^2, R^3 = Ph, Me

An efficient Pd-catalyzed C–N bond formation for the synthesis of different pyrazole derivatives using XPhos as a ligand and KOH as a base is presented. The developed procedure can be successfully applied for the synthesis of 5-*N*-aryl-1,3-disubstituted 1*H*-pyrazol-5-amines. Contrary to previously described procedures, this one proceeds in one step utilizing commercially available aminopyrazoles and aryl halides. Thus, a series of 5-*N*-aryl-1,3-disubstituted 1*H*-pyrazol-5-amines were obtained with satisfactory yields under optimized reaction conditions.

Keywords: 5-*N*-arylaminopyrazoles, palladium catalyst, arylation, cross coupling.

Nitrogen-containing heterocycles probably are the largest and most studied family of organic compounds. Among them, pyrazole derivatives, e.g., 5-*N*-arylaminopyrazoles, have attracted our interest due to their application as key constituents in the synthesis of luminophores to obtain organic light emitting diodes (OLEDs). One of the known method for the synthesis of 5-*N*-arylaminopyrazoles includes a reaction of β-oxothioanilides with arylhydrazines developed by Pocar and coworkers.[1] Lately, Dodd and Martinez published another methodology for the synthesis of substituted 5-aryl/alkylaminopyrazoles where β-keto-anilides reacted with phenyl/benzylhydrazine in the presence of Lawesson's reagent.[2] Bernhammer and Huynh used 1,3-diphenylpyrazol-5-one, aniline hydrochlorides, and phosphorus pentoxide under microwave irradiation to obtain 1,3-diphenyl-5-phenylaminopyrazoles.[3]

Recently, many synthetic procedures employing Cu- and Pd-mediated C–N bond formation have been published.[4–7] Thus, the reaction of *o*-iodobenzoic acid and 3-amino-5-methyl-2-phenylpyrazole in the presence of Cu catalyst and K_2CO_3 resulted in the formation of (pyrazol-5-yl)-aminobenzoic acid, which was subsequently transformed into 4-hydroxy-1*H*-pyrazolo[3,4-*b*]quinoline – a starting material for potential antimalarial compounds.[8] Moreover, the synthesis of 1,3-diphenyl-5-(*N*-phenylamino)pyrazole using 5-amino-1,3-diphenylpyrazole and aryl halides as starting materials in the presence of 1,10-phenanthroline and catalytic amount of CuI was published.[9] Buchwald and others have developed a series of catalysts used for efficient arylation of some aminoheterocycles such as 2-amino-benzimidazoles, aminopyridines, aminodiazines, amino-triazines, etc.[10–15] It should be mentioned that the same catalysts can be used for the arylation of aminopyrazoles, although this type of reaction was relatively little studied. Patel and coworkers synthesized a series of 3-amino-pyrazole derivatives in the search of potential brain penetrant inhibitors using $Pd_2(dba)_3$–Xantphos system with the product yields varied within 7–66%.[16] Buchwald and Ueda applied the same protocol for arylation of some 3-aminopyrazole and 3-aminoindazole derivatives.[10] The

reaction was carried out in the presence of $Pd_2(dba)_3$–*t*-BuBrettPhos system. The yields of the obtained derivatives ranged from 80 to 92%. Some pyrazole derivatives as modulators of the 5-HT2A serotonin receptors were synthesized employing $Pd_2(dba)_3$–BINAP catalyzed coupling of 3-amino-2,5-dimetylpyrazole with various substituted aryl bromides or arylboronic acids.[17]

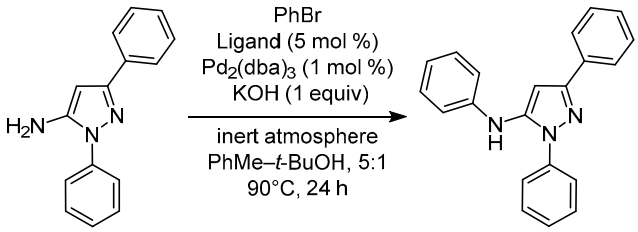
The purpose of our research is the synthesis of 5-*N*-arylaminopyrazoles as valuable precursors of 1*H*-pyrazolo[3,4-*b*]quinolines – potential OLED luminophores or fluorescence sensors.[18–20] However, there are not many examples of the synthesis of this type of compounds in the literature. Recently the methodology for the synthesis of 5-(*o*-nitrophenyl)amino-1,3-disubstituted pyrazole derivatives as precursors of 1*H*-pyrazolo[3,4-*b*]quinoxalines was described.[21] Thus, commercially available 5-aminopyrazoles under $Pd_2(dba)_3$–BINAP catalysis undergo arylation reaction with 5-substituted 2-iodonitrobenzenes.[21] Several other examples of the arylation of 5-aminopyrazoles found in the literature were based on the procedures developed by Buchwald. Such an example is the synthesis of 1,3-dimethyl-5-(3-nitrophenyl)aminopyrazole which was obtained by the reaction of 3-chloronitrobenzene with 5-amino-1,3-dimethylpyrazole in the presence of Pd(0) and biarylphosphine ligand (BrettPhos) in 97% yield.[22] Mitchell and coworkers presented an effective synthesis of 5-*N*-arylaminopyrazole derivative as a potential inhibitor of the Janus kinase A2. The reaction was carried out in the presence of $Pd_2(dba)_3$–Xantphos system with the yield of 79%.[23]

In the present study, we investigated arylation reaction of various 1,3-disubstituted 5-aminopyrazoles with available *para*-substituted aryl halides catalyzed by $Pd_2(dba)_3$ and phosphine ligand XPhos. The *ortho*- and *meta*-substituted aryl halide derivatives will be tested during our further investigations.

As the first step of our investigation, the conditions described before[17] were modified and applied to the model reaction of bromobenzene and 1,3-diphenyl-1*H*-pyrazol-5-amine. Initially, different organic phosphine ligands in presence of $Pd_2(dba)_3$ and KOH as a base were tested in order to optimize the conditions of the process. The results are summarized in Table 1. In the presence of BINAP as a ligand, product **1a** was obtained with 49% yield (Table 1, entry 1), moreover some byproducts caused difficulties during purification. The model reaction was also proceeded under modified conditions of Buchwald and coworkers.[24] Thus, in presence of $P(Tol)_3$ and DavePhos the formation of the desired product **1a** was not observed (Table 1, entries 2, 3, respectively). Similarly, in the presence of CyJohnPhos ligand only traces of product **1a** were observed by TLC (Table 1, entry 4). Higher conversion was obtained in the reactions with JohnPhos and XPhos, resulting in 71 and 79% yield of compound **1a**, respectively (Table 1, entries 5 and 6). Based on preliminary results, JohnPhos and XPhos were selected for the further optimization of the Pd-catalyzed reaction.

With two effective ligands in hand, XPhos and JohnPhos, chloro- and iodobenzenes were tested under the

Table 1. Screening of ligands for the synthesis of compound **1a**



1a

Entry	Ligand	Yield of compound **1a**, %
1	BINAP	49
2	$P(Tol)_3$	Not observed
3	DavePhos	Not observed
4	CyJohnPhos	Traces
5	**JohnPhos**	**71**
6	**XPhos**	**79**

model reaction conditions: 1,3-diphenyl-1*H*-pyrazol-5-amine (1 equiv), aryl halide (1.1 equiv), $Pd_2(dba)_3$ (1 mol %), and KOH (1 equiv) (Table 2). Product **1a** was formed in reaction with iodobenzene in the presence of XPhos with 79% yield (Table 2, entry 3), however in the presence of JohnPhos product **1a** was not obtained (Table 2, entry 5). Coupling reaction conditions were ineffective in the presence of chlorobenzene for both ligands (Table 2, entries 2, 4). Based on the obtained results, XPhos was selected as a more versatile ligand for this transformation.

Later on, the influence of the base on the coupling reaction was investigated. Model reaction was carried out under the standard conditions in the presence of different inorganic bases, and product **1a** was isolated by column chromatography on silica gel. Base screening results are presented in Table 3. In the reaction with KOH and K_2CO_3, product **1a** formed with satisfactory yields of 79 and 77%, respectively (Table 3, entries 1, 2). In the case of K_3PO_4 (Table 3, entry 3) the product was obtained with 68% yield. It is worth to mention that in the reaction using *t*-BuOK

Table 2. Screening of aryl halides for the synthesis of compound **1a**

Entry	Ligand	Aryl halide	Yield of compound **1a**, %
1	**XPhos**	**PhBr**	**79**
2	XPhos	PhCl	Traces
3	**XPhos**	**PhI**	**79**
4	JohnPhos	PhCl	Not observed
5	JohnPhos	PhI	Traces

Table 3. Screening of inorganic bases for the synthesis of compound **1a**

Entry	Base	Mp of compound **1a**, °C	Yield of compound **1a**, %
1	KOH	155	79
2	K_2CO_3	154–155	**77**
3	K_3PO_4	152–153	68
4	*t*-BuOK		Traces, not isolated

(Table 3, entry 4) product **1a** was identified by TLC, but purification by column chromatography was unsuccessful.

Finally, the influence of ligand, catalyst, and base amount on the yield of compound **1a** was investigated (Table 4). The reduction of the ligand amount from 5 mol % to 3 and to 1 mol % resulted in decrease of the formation of compound **1a** to 59 and 50%, respectively (Table 4, entries 2, 3). Application of 5 mol % of $Pd_2(dba)_3$ instead of 1 mol % did not influence the reaction yield (Table 4, entry 4) comparing to the entry 3, where both catalyst and ligand were used in amount of 1 mol % (Table 4). However, the increase of catalyst amount up to 5 mol % resulted in the formation of side products, which sophisticated the isolation of pure product **1a** (Table 4, entry 5). The same effect was observed changing base amount from 1 to 3 and to 5 equivalents (Table 4, entries 6, 7).

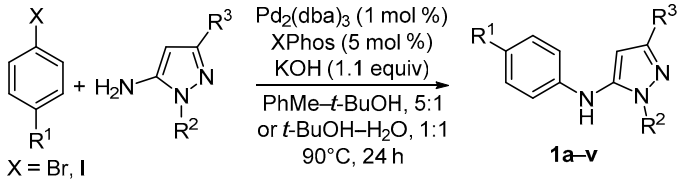
Taking into account experimental results, optimized reaction conditions for the synthesis of substituted aminopyrazoles were applied: XPhos (5 mol %), $Pd_2(dba)_3$ (1 mol %), KOH (1 equiv). Other reaction factors including temperature, solvent, and reaction time were selected according to the previously described procedure.[24] Based on the optimized reaction conditions, the synthesis of a series of pyrazole derivatives **1a**–**v** to prove the potency of developed synthetic methodology was realized (Table 5).

Table 4. Optimization of the ligand, catalyst, and base amount for the synthesis of compound **1a**

Entry	$Pd_2(dba)_3$, mol %	XPhos, mol %	KOH, equiv	Yield of compound **1a**, %
1	**1**	**5**	**1**	**79**
2	1	3	1	59
3	**1**	**1**	**1**	50
4	5	5	1	50
5	5	1	1	Identified with TLC, not isolated
6	1	5	3	Identified with TLC, not isolated
7	1	5	5	Identified with TLC, not isolated

In most cases, the product was obtained with satisfactory yields from 53 to over 90%. The lowest yield (40%) was obtained in the case of compound **1d** which might be explained by instability and possible decomposition of product during purification process. Moreover, products with *p*-OMe substituent **1c**,**l**,**p** were found to be unstable on storage.

Table 5. Yields of 1,3-disubstituted *N*-aryl-1*H*-pyrazol-5-amines **1a**–**v**



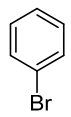
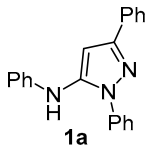
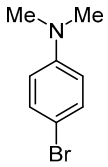
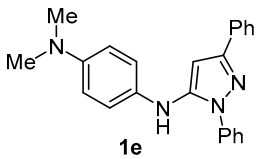
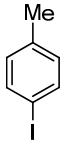
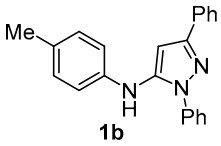
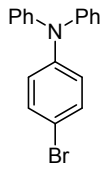
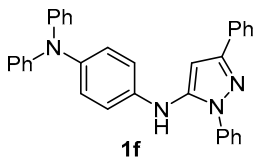
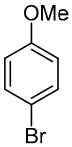
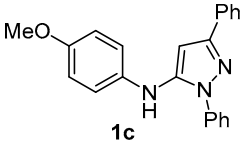
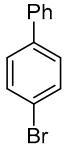
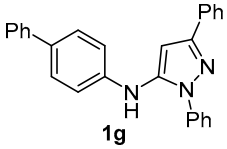
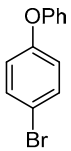
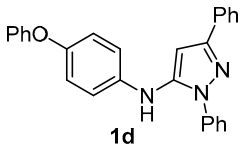
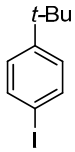
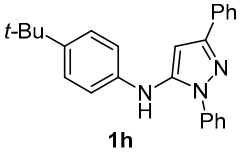
Aryl halide	Product	Yield, %	Aryl halide	Product	Yield, %
	 **1a**	79		 **1e**	53
	 **1b**	64		 **1f**	62
	 **1c**	78		 **1g**	74
	 **1d**	40		 **1h**	60

Table 5 (continued)

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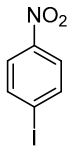
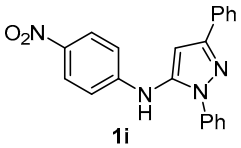
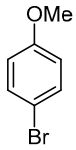
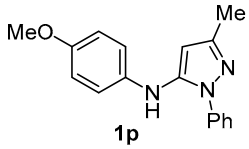
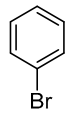
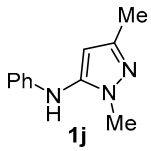
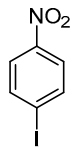
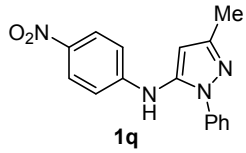
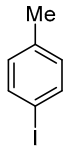
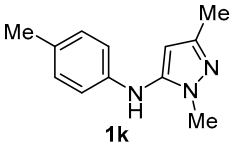
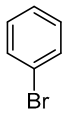
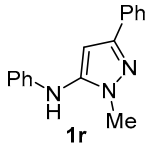
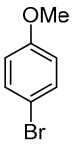
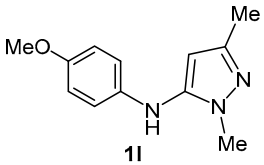
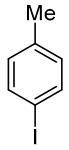
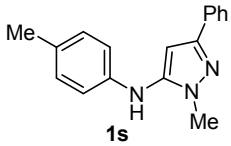
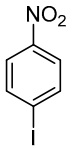
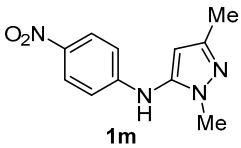
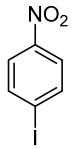
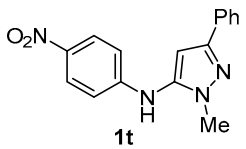
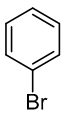
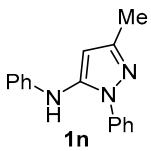
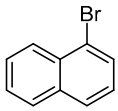
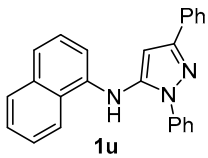
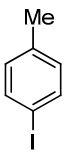
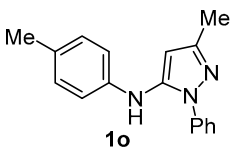
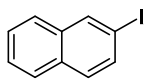
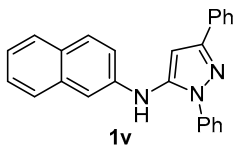
	 **1i**	77		 **1p**	88
	 **1j**	58		 **1q**	87
	 **1k**	61		 **1r**	67
	 **1l**	84		 **1s**	72
	 **1m**	77		 **1t**	84
	 **1n**	60		 **1u**	53
	 **1o**	56		 **1v**	92

In case of $R^1 = NO_2$, optimized conditions were slightly modified and the use of more polar solvent mixture such as *t*-BuOH–H_2O, 1:1 allowed to obtain product **1i** with 77% yield instead of 30% in PhMe/*t*-BuOH mixture. The solvent system *t*-BuOH–H_2O, 1:1 was also used in the synthesis of all derivatives **1i**,**q**,**t** containing NO_2 group.

In conclusion, an efficient arylation method of disubstituted 1*H*-pyrazol-5-amines was developed using a protocol based on the Buchwald–Hartwig methodology. The *para*-substituted aryl halides and 1,3-disubstituted 1*H*-pyrazol-5-amines were used as the substrates to obtain a series of 5-*N*-substituted 1*H*-pyrazol-5-amines with satisfactory yields. The complex of XPhos and $Pd_2(dba)_3$ exhibited high activity as the catalytic system in this transformation. The developed one-step procedure requires less time, energy and produces higher yields than previously reported methods.

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 MHz spectrometer (400 and 100 MHz, respectively) in $CDCl_3$ for compounds **1a**,**j**–**t** and on a Bruker Avance III 600 MHz spectrometer (600 and 150 MHz, respectively) in $CDCl_3$ for compounds **1b**–**i**,**u**,**v**, using residual $CDCl_3$ signals or TMS as internal standard. Elemental analyses were performed using a CHNS Vario MICRO Cube analyzer combined with an electronic microbalance. Melting points were determined on a MEL-TEMP II

apparatus. TLC was accomplished on 0.2 mm precoated plates of silica gel on TLC Al foils with fluorescence indicator 254 nm purchased in Sigma Aldrich. Visualization was made with a UV lamp Spectroline model ENF-260C/FE (254 nm). Column chromatography was carried out using 70–230 mesh ASTM silica gel purchased in Merck KGaA.

Chemicals racemic 2,2'-bis(diphenylphosphino)-1,1'-binaphthalene (97%), (2-biphenyl)di-*tert*-butylphosphine (97%), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (97%), and 2-(dicyclohexylphosphino)biphenyl (97%) were purchased from Sigma-Aldrich and used without additional purification. Tri(*o*-tolyl)phosphine (97%) was purchased from Merck-Schuchardt OHG and 2-dicyclohexylphosphino-2'-(*N*,*N*-dimethylamino)biphenyl (98%) from Alfa Aesar.

Synthesis of 1,3-disubstituted *N*-aryl-1*H*-pyrazol-5-amines 1a–v (General method). 1,3-Disubstituted 1*H*-pyrazol-5-amine (1 mmol) was dissolved in degassed PhMe–*t*-BuOH, 5:1 mixture (5 ml) (*t*-BuOH–H_2O, 1:1 for compounds **1i**,**m**,**q**,**t**) in Schlenck tube under Ar atmosphere. Aryl halide (1.1 mmol) was added to the reaction mixture followed by the addition of XPhos (5 mol %), $Pd_2(dba)_3$ (1 mol %), and KOH (1 mmol). The reaction mixture was heated at 90°C for 24 h, cooled to room temperature, then solids were filtrated off and the filtrate was evaporated. The residue was purified by column chromatography on silica gel (Al_2O_3 for compound **1v**), eluent PhMe (for compounds **1a**–**d**,**f**–**i**,**k**,**m**,**n**,**r**,**s**,**u**,**v**), CH_2Cl_2 (for compound **1e**), or gradient mixture of PhMe–EtOAc (for compounds **1j**,**l**,**o**–**q**,**t**). Products **1a**,**b**,**f**,**g**,**k**,**o**,**r**,**u** were additionally recrystallized from petroleum ether – EtOAc mixture.

***N*,1,3-Triphenyl-1*H*-pyrazol-5-amine (1a)**. Yield 245 mg (79%), oil was crystallized upon standing in a freezer to afford a light-yellow crystals, mp 152–155°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.91–7.86 (2H, m, H Ar); 7.68–7.62 (2H, m, H Ar); 7.49 (2H, t, *J* = 7.8, H Ar); 7.41 (3H, dd, *J* = 16.0, *J* = 8.0, H Ar); 7.36–7.32 (2H, m, H Ar); 7.29 (2H, dd, *J* = 8.3, *J* = 7.6, H Ar); 7.01 (1H, d, *J* = 7.7, H Ar); 6.96 (1H, t, *J* = 7.4, H Ar); 6.53 (1H, s, H Ar); 5.56 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 151.5; 142.9; 142.1; 138.4; 133.2; 129.5; 129.4; 128.5; 128.0; 127.7; 125.6; 124.4; 121.0; 115.9; 93.6. Found, %: C 81.06; H 5.54; N 13.40. $C_{21}H_{17}N_3$. Calculated, %: C 81.00; H 5.50; N 13.50.

***N*-(4-Methylphenyl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1b)**. Yield 208 mg (64%), white powder, mp 78–79°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.89–7.82 (2H, m, H Ar); 7.66–7.62 (2H, m, H Ar); 7.47 (2H, t, *J* = 7.9, H Ar); 7.40 (2H, t, *J* = 7.6, H Ar); 7.36 (1H, t, *J* = 7.5, H Ar); 7.31 (1H, t, *J* = 7.4, H Ar); 7.09 (2H, d, *J* = 8.1, H Ar); 6.92 (2H, d, *J* = 8.4, H Ar); 6.44 (1H, s, H Ar); 5.48 (1H, s, NH); 2.30 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 151.5; 142.9; 140.3; 138.5; 133.3; 130.8; 130.0; 129.5; 128.6; 127.9; 127.6; 125.6; 124.5; 116.5; 92.6; 20.6. Found, %: C 81.28; H 5.94; N 12.78. $C_{22}H_{19}N_3$. Calculated, %: C 81.20; H 5.89; N 12.91.

***N*-(4-Methoxyphenyl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1c)**. Yield 267 mg (78%), yellow waxy solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.86–7.83 (2H, m, H Ar); 7.68–7.62 (2H, m, H Ar); 7.49 (2H, t, *J* = 7.9, H Ar); 7.41–7.35 (3H, m, H Ar); 7.33–7.29 (1H, m, H Ar); 7.01 (2H, d, *J* = 8.9, H Ar); 6.86 (2H, d, *J* = 8.9, H Ar); 6.32 (1H, s, H Ar); 5.44 (1H, s, NH); 3.79 (3H, s, CH_3).^{13}C NMR spectrum, δ, ppm: 154.9; 151.5; 144.1; 138.5; 135.9; 133.3; 129.5; 128.5; 127.9; 127.7; 125.6; 124.5; 119.1; 114.8; 91.0; 55.6. Found, %: C 77.25; H 5.44; N 12.53. $C_{22}H_{19}N_3O$. Calculated, %: C 77.40; H 5.61; N 12.31.

***N*-(4-Phenoxyphenyl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1d)**. Yield 162 mg (40%), light-red waxy solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.91–7.85 (2H, m, H Ar); 7.69–7.64 (2H, m, H Ar); 7.50 (2H, t, *J* = 7.9, H Ar); 7.44–7.37 (3H, m, H Ar); 7.35–7.32 (3H, m, H Ar); 7.08 (1H, tt, *J* = 7.5, *J* = 1.0, H Ar); 7.04–6.97 (6H, m, H Ar); 6.46 (1H, s, H Ar); 5.57 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 158.1; 151.6; 151.1; 142.9; 138.7; 138.5; 133.3; 129.7; 129.5; 128.6; 128.1; 127.8; 125.6; 124.5; 122.7; 120.7; 117.9 (2C); 92.5. Found, %: C 80.45; H 5.29; N 10.45. $C_{27}H_{21}N_3O$. Calculated, %: C 80.37; H 5.25; N 10.41.

***N*'-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-*N*,*N*-dimethylbenzene-1,4-diamine (1e)**. Yield 215 mg (53%), yellow powder, mp 99–103°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.87–7.81 (2H, m, H Ar); 7.71–7.62 (2H, m, H Ar); 7.53–7.48 (2H, m, H Ar); 7.41–7.35 (3H, m, H Ar); 7.33–7.28 (1H, m, H Ar); 7.03 (2H, d, *J* = 8.5, H Ar); 6.77 (2H, d, *J* = 8.0, H Ar); 6.26 (1H, s, H Ar); 5.43 (1H, s, NH); 2.93 (6H, s, $2CH_3$). ^{13}C NMR spectrum, δ, ppm: 151.5; 145.1; 138.6; 133.5; 132.8; 129.5; 128.5; 127.8; 127.5; 125.6; 124.5; 120.1; 114.2; 89.8; 41.3. Found, %: C 77.98; H 6.28; N 15.74. $C_{23}H_{22}N_4$. Calculated, %: C 77.94; H 6.26; N 15.81.

***N*'-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-*N*,*N*-diphenylbenzene-1,4-diamine (1f)**. Yield 294 mg (62%), yellow powder, mp 157–158°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.91–7.84 (2H, m, H Ar); 7.69–7.64 (2H, m, H Ar); 7.55–7.47 (2H, m, H Ar); 7.45–7.37 (3H, m, H Ar); 7.36–7.30 (1H, m, H Ar); 7.28–7.21 (4H, m, H Ar); 7.12–7.04 (6H, m, H Ar); 7.02–6.92 (4H, m, H Ar); 6.49 (1H, s, H Ar); 5.57 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 151.5; 148.0; 142.7; 141.5; 138.5; 138.4; 133.3; 129.5; 129.1; 128.6; 128.0; 127.7; 126.7; 125.6; 124.5; 123.2; 122.1; 117.5; 92.2. Found, %: C 82.91; H 5.52; N 11.57. $C_{33}H_{26}N_4$. Calculated, %: C 82.82; H 5.48; N 11.71.

***N*-[(1,1'-Biphenyl)-4-yl]-1,3-diphenyl-1*H*-pyrazol-5-amine (1g)**. Yield 286 mg (74%), white solid, mp 177°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.92–7.89 (2H, m, H Ar); 7.69–7.65 (2H, m, H Ar); 7.59–7.57 (2H, m, H Ar); 7.56–7.53 (2H, m, H Ar); 7.52–7.48 (2H, m, H Ar); 7.46–7.41 (4H, m, H Ar); 7.39 (1H, t, *J* = 7.5, H Ar); 7.37–7.30 (2H, m, H Ar); 7.10–7.05 (2H, m, H Ar); 6.58 (1H, s, H Ar); 5.64 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 151.5; 142.3; 141.9; 140.6; 138.4; 134.0; 133.2; 129.5; 128.8; 128.6; 128.2; 128.0; 127.8; 126.7; 126.6; 125.6; 124.5; 116.2; 93.9. Found, %: C 83.75; H 5.48; N 10.77. $C_{27}H_{21}N_3$. Calculated, %: C 83.69; H 5.46; N 10.84.

***N*-(4-*tert*-Butylphenyl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1h)**. Yield 222 mg (60%), white solid, mp 142–143°C. ^{1}H NMR spectrum, δ, ppm: 7.95–7.80 (2H, m, H Ar); 7.73–7.59 (2H, m, H Ar); 7.54–7.45 (2H, m, H Ar); 7.44–7.36 (3H, m, H Ar); 7.35–7.31 (3H, m, H Ar); 7.01–6.97 (2H, m, H Ar); 6.50 (1H, s, H Ar); 5.53 (1H, s, NH); 1.33 (9H,

s, $C(CH_3)_3$). ^{13}C NMR spectrum, δ, ppm: 151.5; 144.2; 142.8; 140.1; 138.5; 133.3; 129.5; 128.5; 127.9; 127.7; 126.3; 125.6; 124.5; 116.1; 92.4; 34.2; 31.4. Found, %: C 81.77; H 6.89; N 11.34. $C_{25}H_{25}N_3$. Calculated, %: C 81.71; H 6.86; N 11.43.

***N*-(4-Nitrophenyl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1i)**. Yield 274 mg (77%), yellow powder, mp 83°C (decomp.). ^1H NMR spectrum, δ, ppm: 8.16–8.10 (2H, m, H Ar); 7.90–7.84 (2H, m, H Ar); 7.58–7.50 (2H, m, H Ar); 7.48–7.41 (4H, m, H Ar); 7.40–7.34 (2H, m, H Ar); 6.93–6.86 (2H, m, H Ar); 6.64 (1H, s, H Ar); 6.14 (1H, s, H Ar). ^{13}C NMR spectrum, δ, ppm: 151.7; 149.2; 140.7; 138.7; 138.0; 132.7; 129.5; 129.0; 128.7; 128.4; 128.2; 128.1; 126.2; 125.6; 125.3; 124.2; 113.7; 97.9. Found, %: C 70.79; H 4.51; N 15.74. $C_{21}H_{16}N_4O_2$. Calculated, %: C 70.77; H 4.53; N 15.72.

1,3-Dimethyl-*N*-phenyl-1*H*-pyrazol-5-amine (1j). Yield 109 mg (58%), light-yellow powder, mp 153–155°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.25–7.19 (2H, m, H Ar); 6.87 (1H, t, *J* = 7.4, H Ar); 6.72 (2H, d, *J* = 7.6, H Ar); 5.83 (1H, s, H Ar); 5.31 (1H, s, NH); 3.64 (3H, s, NCH_3); 2.25 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 147.5; 144.7; 140.8; 129.4; 120.1; 114.6; 98.5; 34.6; 14.1. Found, %: C 70.50; H 7.03; N 22.47. $C_{11}H_{13}N_3$. Calculated, %: C 70.56; H 7.00; N 22.44.

1,3-Dimethyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine (1k). Yield 122 mg (61%), light yellow-brown powder, mp 116–117°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.03 (2H, d, *J* = 8.2, H Ar); 6.65 (2H, d, *J* = 8.4, H Ar); 5.79 (1H, s, H Ar); 5.19 (1H, s, NH); 3.63 (3H, s, NCH_3); 2.27 (3H, s, CH_3); 2.24 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 147.4; 142.1; 141.4; 129.9; 129.6; 114.9; 97.8; 34.5; 20.4; 14.1. Found, %: C 71.83; H 7.56; N 20.61. $C_{12}H_{15}N_3$. Calculated, %: C 71.61; H 7.51; N 20.88.

***N*-(4-Methoxyphenyl)-1,3-dimethyl-1*H*-pyrazol-5-amine (1l)**. Yield 182 mg (84%), white powder, mp 187–190°C. ^1H NMR spectrum, δ, ppm: 6.87–6.66 (4H, m, H Ar); 5.73 (1H, s, H Ar); 5.50 (1H, s, NH); 3.76 (3H, s, OCH_3); 3.61 (3H, s, NCH_3); 2.23 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 153.9; 147.4; 142.7; 138.0; 116.9; 114.8; 96.3; 55.6; 34.4; 14.0. Found, %: C 66.22; H 6.90; N 19.46. $C_{12}H_{15}N_3O$. Calculated, %: C 66.34; H 6.96; N 19.34

1,3-Dimethyl-*N*-(4-nitrophenyl)-1*H*-pyrazol-5-amine (1m). Yield 178 mg (77%), dark-brown waxy solid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.12 (2H, d, *J* = 9.1, H Ar); 6.70 (2H, d, *J* = 9.2, H Ar); 6.01 (1H, s, H Ar); 5.94 (1H, s, NH); 3.65 (3H, s, NCH_3); 2.27 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 150.6; 148.0; 140.4; 137.7; 126.2; 113.1; 100.7; 34.8; 14.0. Found, %: C 56.97; H 5.24; N 24.16. $C_{11}H_{12}N_4O_2$. Calculated, %: C 56.89; H 5.21; N 24.12.

3-Methyl-*N*,1-diphenyl-1*H*-pyrazol-5-amine (1n). Yield 149 mg (60%), white powder, mp 122–123°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.58–7.54 (2H, m, H Ar); 7.46 (2H, t, *J* = 7.8, H Ar); 7.38–7.32 (1H, m, H Ar); 7.31–7.25 (2H, m, H Ar); 6.99–6.91 (3H, m, H Ar); 6.03 (1H, s, H Ar); 5.54 (1H, s, NH); 2.35 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 149.3; 142.9; 141.3; 138.4; 129.4; 129.3; 127.3; 124.2; 120.8; 115.7; 96.1; 14.1. Found, %: C 77.17; H 6.10; N 16.72. $C_{16}H_{15}N_3$. Calculated, %: C 77.08; H 6.06, N 16.85.

3-Methyl-1-phenyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine (1o). Yield 148 mg (56%), light-brown powder, mp 106–107°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.58–7.50 (2H, m, H Ar); 7.44 (2H, t, *J* = 7.8, H Ar); 7.35–7.29 (1H, m, H Ar); 7.07 (2H, d, *J* = 8.2, H Ar); 6.90–6.83 (2H, m, H Ar); 5.94 (1H, s, H Ar); 5.45 (1H, s, NH); 2.31 (3H, s, CH_3); 2.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 149.3; 142.1; 140.3; 138.5; 130.5; 129.9; 129.4; 127.2; 124.2; 116.3; 95.1; 20.5; 14.1. Found, %: C 77.62; H 6.57; N 15.82. $C_{17}H_{17}N_3$. Calculated, %: C 77.54; H 6.51; N 15.96.

***N*-(4-Methoxyphenyl)-3-methyl-1-phenyl-1*H*-pyrazol-5-amine (1p)**. Yield 246 mg (88%), yellow waxy solid. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.59–7.53 (2H, m, H Ar); 7.45 (2H, t, *J* = 7.9, H Ar); 7.37–7.30 (1H, m, H Ar); 6.99–6.92 (2H, m, H Ar); 6.87–6.80 (2H, m, H Ar); 5.82 (1H, s, H Ar); 5.40 (1H, s, NH); 3.78 (3H, s, OCH_3); 2.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 154.7; 149.3; 143.3; 138.5; 136.0; 129.4; 127.2; 124.2; 118.7; 114.7; 93.6; 55.6; 14.1. Found, %: C 73.16; H 6.15; N 14.89. $C_{17}H_{17}N_3O$. Calculated, %: C 73.10; H 6.13; N 15.04.

3-Methyl-*N*-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-5-amine (1q). Yield 217 mg (87%), light-brown powder, mp 173–176°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 8.11 (2H, d, *J* = 9.1, H Ar); 7.49–7.36 (5H, m, H Ar); 6.85 (2H, d, *J* = 9.2, H Ar); 6.16 (1H, s, H Ar); 6.13 (1H, s, NH); 2.34 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 149.6; 149.3; 140.6; 138.0; 137.9; 129.4; 127.8; 126.1; 124.0; 113.6; 100.2; 14.1. Found, %: C 65.45; H 4.84; N 18.78. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.30; H 4.79; N 19.04

1-Methyl-*N*,3-diphenyl-1*H*-pyrazol-5-amine (1r). Yield 167 mg (67%), white powder, mp 148–150°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.81 (2H, d, *J* = 7.1, H Ar); 7.42 (2H, t, *J* = 7.5, H Ar); 7.36–7.22 (3H, m, H Ar); 6.93 (1H, t, *J* = 7.4, H Ar); 6.80 (2H, d, *J* = 7.6 H Ar); 6.39 (1H, s, H Ar); 5.37 (1H, s, NH); 3.79 (3H, s, NCH_3).^{13}C NMR spectrum, δ, ppm: 150.1; 144.5; 141.5; 133.6; 129.5; 128.6; 127.6; 125.0; 120.4; 114.7; 96.4; 35.1. Found, %: C 77.14; H 6.09; N 16.76. $C_{16}H_{15}N_3$. Calculated, %: C 77.08; H 6.06; N 16.85.

1-Methyl-3-phenyl-*N*-(*p*-tolyl)-1*H*-pyrazol-5-amine (1s). Yield 190 mg (72%), light-yellow powder, mp 186–187°C. ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.78 (2H, d, *J* = 7.1, H Ar); 7.39 (2H, t, *J* = 7.5, H Ar); 7.33–7.27 (1H, m, H Ar); 7.07 (2H, d, *J* = 8.2, H Ar); 6.71 (2H, d, *J* = 8.4, H Ar); 6.33 (1H, s, H Ar); 5.26 (1H, s, NH); 3.76 (3H, s, NCH_3); 2.29 (3H, s, CH_3). ^{13}C NMR spectrum, δ, ppm: 150.0; 142.2; 142.0; 133.6; 130.0; 129.9; 129.0; 128.6; 128.2; 127.6; 125.3; 125.2; 115.2; 95.6; 35.0; 20.5. Found, %: C 77.60; H 6.53; N 15.84. $C_{17}H_{17}N_3$. Calculated, %: C 77.54; H 6.51; N 15.96.

1-Methyl-*N*-(4-nitrophenyl)-3-phenyl-1*H*-pyrazol-5-amine (1t). Yield 246 mg (84%), orange powder, mp 175–179°C. ^1H NMR spectrum, δ, ppm: 8.21–8.10 (2H, m, H Ar); 7.82–7.78 (2H, m, H Ar); 7.46–7.41 (2H, m, H Ar); 7.38–7.33 (1H, m, H Ar); 6.79–6.74 (2H, m, H Ar); 6.48 (1H, s, H Ar); 6.06 (1H, s, NH); 3.79 (3H, s, CH_3).

^{13}C NMR spectrum, δ, ppm: 150.6; 150.5; 140.6; 138.5; 133.0; 128.7; 128.0; 126.2; 125.2; 113.2; 98.6; 35.3. Found, %: C 65.38; H 4.84; N 18.86. $C_{16}H_{14}N_4O_2$. Calculated, %: C 65.30; H 4.79; N 19.04.

***N*-(Naphthalen-1-yl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1u)**. Yield 190 mg (53%), light-pink solid, mp 129–131°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.90–7.87 (3H, m, H Ar); 7.84 (1H, d, *J* = 8.4, H Ar); 7.75–7.72 (2H, m, H Ar); 7.56–7.45 (5H, m, H Ar); 7.43–7.39 (3H, m, H Ar); 7.39–7.32 (2H, m, H Ar); 7.28 (1H, d, *J* = 7.0, H Ar); 6.41 (1H, s, H Ar); 6.09 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 151.6; 143.0; 138.5; 138.4; 134.5; 133.2; 129.6; 128.8; 128.6; 128.0; 127.7; 126.2; 126.1; 125.8; 125.6; 125.2; 124.2; 122.3; 120.5; 112.6; 93.9. Found, %: C 83.12; H 5.36; N 11.52. $C_{25}H_{19}N_3$. Calculated, %: C 83.08; H 5.30; N 11.63.

***N*-(Naphthalen-2-yl)-1,3-diphenyl-1*H*-pyrazol-5-amine (1v)**. Yield 332 mg (92%), dark-yellow waxy solid. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.95–7.89 (2H, m, H Ar); 7.78–7.76 (2H, m, H Ar); 7.70–7.65 (3H, m, H Ar); 7.51–7.41 (5H, m, H Ar); 7.40–7.36 (4H, m, H Ar); 7.16 (1H, dd, *J* = 8.8, *J* = 2.4, H Ar); 6.63 (1H, s, H Ar); 5.71 (1H, s, NH). ^{13}C NMR spectrum, δ, ppm: 151.6; 141.9; 140.7; 138.5; 134.5; 133.2; 129.5 (2C); 129.1; 128.6; 128.1; 127.8; 127.7; 126.8; 126.5; 125.7; 124.4; 123.7; 118.1; 110.2; 94.5. Found, %: C 83.16; H 5.23; N 11.61. $C_{25}H_{19}N_3$. Calculated, %: C 83.08; H 5.30; N 11.63.

Supplementary information file containing ^{1}H and ^{13}C NMR spectra of all synthesized compounds is available at the journal website at http://link.springer.com/journal/10593.

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References

1. Pocar, D.; Bianchetti, G.; Maiorana, S. *Gazz. Chim. Ital*. **1963**, *93*, 100.
2. Dodd, D. S.; Martinez, R. L. *Tetrahedron Lett*. **2004**, *45*, 4265.
3. Bernhammer, J. C.; Huynh, H. V. *Dalton Trans*. **2012**, *41*, 8600.
4. Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev*. **2008**, *108*, 3054.
5. Fischer, C.; Koenig, B. *Beilstein J. Org. Chem*. **2011**, *7*, 59.
6. Bhunia, S.; Pawar, G. G.; Kumar, S. V.; Jiang, Y.; Ma, D. *Angew. Chem., Int. Ed*. **2017**, *56*, 16136.
7. Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev*. **2016**, *116*, 12564.
8. Crenshaw, R. R.; Luke, G. M.; Siminoff, P. *J. Med. Chem.* **1976**, *19*, 262.
9. Chang, E.-C.; Chen, C.-Y.; Wang, L.-Y.; Huang, Y.-Y.; Yeh, M-Y.; Wong, F. F. *Tetrahedron* **2013**, *69*, 570.
10. Ueda, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 10364.
11. Hanthorn, J. J.; Valgimigli, L.; Pratt, D. A. *J. Am. Chem. Soc*. **2012**, *134*, 8306.
12. Rauws, T. R. M.; Biancalani, C.; De Schutter, J. W.; Maes, B. U. W. *Tetrahedron* **2010**, *66*, 6958.
13. Dao, P.; Jarray, R.; Le Coq, J.; Lietha, D.; Loukaci, A.; Lepelletier, Y.; Hadj-Slimane, R.; Garbay, C.; Raynaud, F.; Chen, H. *Bioorg. Med. Chem. Lett*. **2013**, *23*, 4552.
14. Wakabayashi, K.-I.; Imai, K.; Miyachi, H.; Hashimoto, Y.; Tanatani, A. *Bioorg. Med. Chem*. **2008**, *16*, 6799.
15. Hornberger, K. R.; Badiang, J. G.; Salovich, J. M.; Kuntz, K. W.; Emmitte, K. A.; Cheung, M. *Tetrahedron Lett*. **2008**, *49*, 6348.
16. Patel, S.; Harris, S. F.; Gibbons, P.; Deshmukh, G.; Gustafson, A.; Kellar, T.; Lin, H.; Liu, X.; Liu, Y.; Liu, Y.; Ma, C.; Scearce-Levie, K.; Ghosh, A. S.; Shin, Y. G.; Solanoy, H.; Wang, J.; Wang, B.; Yin, J.; Siu, M.; Lewcock, J. W. *J. Med. Chem.* **2015**, *58*, 8182.
17. Strah-Pleynet, S.; Teegarden, B.; Unett, D. J. WO Patent 2006060762.
18. Tao, Y. T.; Balasubramaniam, E.; Danel, A.; Jarosz, B.; Tomasik, P. *Chem. Mater*. **2001**, *13*, 1207.
19. Tomasik, P.; Funaki, J.; Imai, K.; Danel, A. *Pol. J. Chem.* **2003**, *77*, 1141.
20. Rurack, K.; Danel, A.; Rotkiewicz, K.; Grabka, D.; Spieles, M.; Rettig, W. *Org. Lett.* **2002**, *4*, 4647.
21. Danel, A.; Wojtasik, K.; Szlachcic, P.; Gryl, M.; Stadnicka, K. *Tetrahedron* **2017**, *73*, 5072.
22. Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914.
23. Mitchell, D.; Cole, K. P.; Pollock, P. M.; Coppert, D. M.; Burkholder, T. P.; Clayton, J. R. *Org. Process Res. Dev.* **2012**, *16*, 70.
24. Wolfe, J. P.; Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158.