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One-pot synthesis of 5-sulfonamidopyrazole from terminal alkynes, sulfonyl azides and hydrozones

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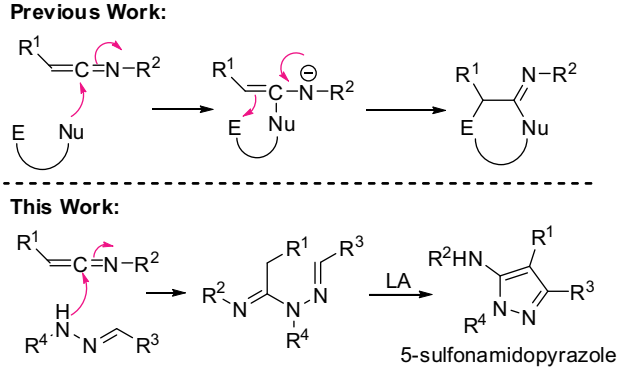
ABSTRACT

5-Sulfonamidopyrazoles were efficiently synthesized from terminal alkynes, sulfonyl azides and hydrozones. The sequential reaction involves a copper-catalyzed three-component reaction, a Lewis acid-catalyzed electrocyclic reaction and a dehydrogenation.

1. Introduction

5-Aminopyrazoles are useful intermediates for the synthesis of pyrazolo[3,4-*b*]pyridines,[1] which are an important class of heterocyclic compounds due to their structural analogy to purine bases[2] and their broad range of bioactivities.[3] These compounds have been extensively investigated over the past 100 years.[4a] Conventional methods, such as condensation of β-ketonitriles, malononitrile and their derivatives with hydrazines in addition to modern methods of resin supported solid-phase synthesis, multicomponent synthesis and ring transformations provide useful synthetic routes to 5-aminopyrazoles.[4] However, efficient synthesis of 5-aminopyrazoles with a broad range of substituents is still necessary.[5]

Ketenimine was firstly described and prepared by Staudinger and Hauser in 1921.[6] Due to the fact that the central carbon of ketenimine is highly electron deficient and active towards various nucleophiles,[7] it has been explored and applied in the construction of various heterocycles. Among several methods leading to the generation of ketenimines, the copper-catalyzed azide–alkyne cycloaddition reaction (CuAAC) attracted much attention because of its reliable mechanism and its mild formation conditions.[8] The in situ generated ketenimine intermediates via this reaction could be trapped by various nucleophiles.[9] Previous works in building heterocycles starting from ketenimines were largely focused on the cascade reaction (Scheme 1). In this way, skeletons of coumarins,[10a,b] quinolines,[10c] pyrrolines,[10d] pyrimidines,[10e] azetidines[10f] and oxetanes[10g] were successfully synthesized. Applying this strategy, we used hydrazones, which could be easily prepared from phenylhydrazines and benzaldehydes, to trap the in situ generated ketenimines and obtained cyclization products in a cascade process. Unfortunately, instead of obtaining the expected 5-sulfonimido-tetrahydropyrazole, we only observed the linear addition product, which could be extended to 5-sulfonamidopyrazole in the presence of a Lewis acid and an oxidant (Scheme 1). Herein, we would like to report the details of this work.



Scheme 1. Heterocycle syntheses via ketenimine intermediate.

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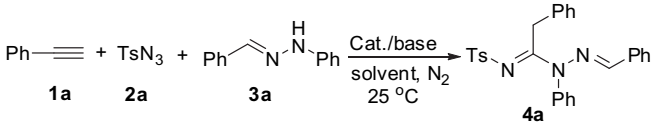
2. Results and discussion

Primarily, when we stirred the mixture of phenylacetylene (**1a**), *p*-toluenesulfonyl azide (**2a**), (*E*)-1-benzylidene-2-phenyl hydrazine (**3a**), CuI and Et_3N at 25 °C for 12 h, we obtained a three-component product **4a** in 88% yield. Its structure was established by single crystal analysis.[11]

Optimization of reaction conditions for the formation of **4a** was then conducted (Table 1). Dichloroethane (DCE) and dichloromethane (DCM) were found to be the suitable solvent for this transformation in comparison with others, such as toluene, acetonitrile and tetrahydrofuran (Table 1, entries 1–6). Triethylamine was the best base in comparison with pyridine and potassium carbonate (Table 1, entries 6–8). Altering the copper source to CuBr, the yield actually decreased (Table 1, entries 6 and 9). Thus, the best reaction condition for the formation of **4a** was established (Table 1, entry 6).

Table 1
Optimization of the reaction condition of the formation of **4a**[a]



1a 2a 3a 4a

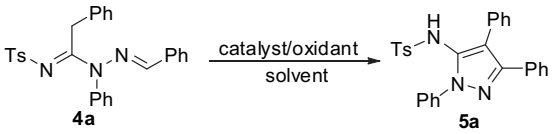
Entry	Solvent	Base	Catalyst	Time (h)	Yield[b] (%)
1	DCE	Et_3N	CuI	12	88
2	PhMe	Et_3N	CuI	12	42
3	CH_3CN	Et_3N	CuI	12	49
4	THF	Et_3N	CuI	12	21
5[c]	DCE	Et_3N	CuI	12	89
6[c]	DCM	Et_3N	CuI	12	89
7[c]	DCM	Py	CuI	12	21
8[c]	DCM	K_2CO_3	CuI	14	86
9[c]	DCM	Et_3N	CuBr	12	66

[a] Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), **3a** (0.5 mmol), solvent (8 mL), Et_3N (1.5 mmol), CuI (0.1 mmol).
[b] Isolated yield.
[c] Reaction conditions: **1a** (0.75 mmol), **2a** (0.75 mmol), **3a** (0.5 mmol), solvent (8 mL), Et_3N (1 mmol), CuI (0. 075 mmol).

We then investigated the possibility for the cyclization of **4a** using a Lewis acid (LA) as catalyst. Initially, we tried $Cu(OTf)_2$ to catalyze the cyclization of **4a** in the presence of di-*tert*-butyl peroxide (DTBP). As we expected, **5a** was isolated in 56% yield. Skeleton of **5a** was established by the comparative crystal analysis of **5h**.[12] We then screened the reaction conditions for the cyclization of **4a** (Table 2). Altering the catalyst from $Cu(OTf)_2$ to AgOTf, and finally to $Zn(OTf)_2$, yield was steadily increased (Table 2, entries 1–3). However, both $Zn(OAc)_2$ and $ZnCl_2$ did not catalyze the cyclization and the starting material (**4a**) was recovered, individually (Table 2, entries 4 and 5). Toluene was found to be the most suitable solvent for this cyclization in comparison with others, such as acetonitrile, dichloroethane and tetrahydrofuran (Table 2, entries 3 and 6–8). Other oxidants, such as dicumyl peroxide (DCP) and oxygen, worked for the reaction, but gave relatively lower yields (Table 2, entries 9 and 10). When *tert*-butyl hydroperoxide (TBHP) or oxone (potassium peroxymonosulfate sulfate) was used as oxidant, only trace amount of **5a** was detected by TLC. Most of starting material was recovered in these cases (Table 2, entries 11 and 12), similar to the case when the reactor was opened to air condition (Table 2, entry 13). Refluxing the reaction mixture for 48 h was essential in order to complete the cyclization (Table 2, entries 3, 14–17). Thus, entry 3 in Table 2 was selected as the most suitable reaction conditions for the formation of **5a**.

With the optimized conditions for these two separated reactions, we tried to efficiently obtain **5a** in a one-pot, sequential procedure. Using DCM for the first step and toluene for the second step, we obtained **5a** in 64% yield (Table 3, entry 1). We then tested the

Table 2
Optimization of the reaction condition for the cyclization of **4a**[a]



4a 5a

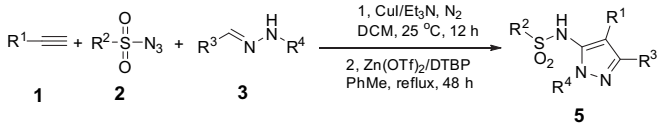
Entry	Catalyst	Solvent	Oxidant	Temp (°C)	Time (h)	Yield[b] (%)
1	$Cu(OTf)_2$	PhMe	DTBP	Reflux	48	56
2	AgOTf	PhMe	DTBP	Reflux	48	62
3	$Zn(OTf)_2$	PhMe	DTBP	Reflux	48	66
4	$Zn(OAc)_2$	PhMe	DTBP	Reflux	48	n.r.
5	$ZnCl_2$	PhMe	DTBP	Reflux	48	n.r.
6	$Zn(OTf)_2$	CH_3CN	DTBP	Reflux	48	15
7	$Zn(OTf)_2$	DCE	DTBP	Reflux	48	32
8	$Zn(OTf)_2$	THF	DTBP	Reflux	48	13
9	$Zn(OTf)_2$	PhMe	DCP	80	72	36
10	$Zn(OTf)_2$	PhMe	O_2	Reflux	120	31
11	$Zn(OTf)_2$	PhMe	TBHP	80	48	Trace
12	$Zn(OTf)_2$	PhMe	Oxone	80	48	Trace
13	$Zn(OTf)_2$	PhMe	Air	Reflux	120	Trace
14	$Zn(OTf)_2$	PhMe	DTBP	80	72	39
15	$Zn(OTf)_2$	PhMe	DTBP	50	72	n.r.
16	$Zn(OTf)_2$	PhMe	DTBP	Reflux	36	61
17	$Zn(OTf)_2$	PhMe	DTBP	Reflux	72	67

[a] Reaction conditions: **4a** (0.5 mmol), catalyst (0.05 mmol), oxidant (2 mmol), solvent (12 mL).
[b] Isolated yield.

substrate diversity for the synthesis of 5-aminopyrazoles **5**. Substrates **1**, **2** and **3** with versatile substituents could tolerate this one-pot procedure (Table 3). Hydrazones **3a**–**f**, derived from phenyl hydrazine and substituted benzaldehydes, performed the reaction smoothly (Table 3, entries 1–6), no matter the substituent on the benzaldehydes was a strong electron donating group (**3b**) or a strong electron withdrawing group (**3f**). Hydrazone **3g**, derived from 2-formyl pyridine, did not form any product even in the first step (Table 3, entry 7). For hydrazones **3h** and **3i**, we also did not obtained the desired products (Table 3, entries 8 and 9), but the first step products **4b** and **4c** (Scheme 2) were isolated in 87% and 49% yields, respectively. Refluxing **4b** or **4c** in the presence of $Zn(OTf)_2$, no isolable pyrazole was obtained although **4b** or **4c** was completely disappeared. Hydrazones **3j** and **3k**, derived from *p*-methylphenyl hydrazine or *p*-chlorophenyl hydrazine, worked for the reaction (Table 3, entries 10 and 11). Aromatic sulfonyl azides **2a**–**d** were suitable for the reaction, while aliphatic sulfonyl azide **2e** gave a decreased yield (Table 3, entries 1 and 12–15). Substituent effect on the phenylacetylenes **1a**–**f** was apparent, typically in case of 4-methoxybenzeneacetylene **1c**, which gave a decreased yield (Table 3, entries 1 and 16–22). 2-Ethynylthiophene (**1g**) furnished **5t** in yield of 41% (Table 3, entry 23). However, aliphatic alkyne, such as 1-hexyne (**1h**), only afforded the linear product **4d** in 73% yield (Table 3, entry 24; Scheme 2). Further efforts to cyclize **4d** in the presence of Lewis acid failed.

Based on these results, we postulated a possible mechanism for this sequential reaction (Scheme 3). In the first step, ketenimine **A** is generated in situ from **1a** and **2a** via a CuAAC mechanism.[9,10] Then, amino nitrogen of hydrazone **3a** nucleophilically attacks the central carbon of ketenimine **A** to generate **B**, which tautomerizes to more stable **4a**. Both imines in **4a** are in *E* configurations that could be seen in its crystal structure. Its isomer *Z*,*E*-**4a** was not found, which might be because of the steric hindrance raised from phenyl and tosyl as indicated in Scheme 3. In the second step, the imine in **B** is activated by Lewis acid,[13] and then a Lewis acid-catalyzed electrocyclic reaction occurs. Electron flows from enamine to iminium to form **D**.[14] Subsequently, **D** encounters a stepwise β-H elimination and metal–hydrogen exchange to form dihydropyrazole **F**. Assisted by the oxidant, dehydrogenation occurs spontaneously and leads to the final

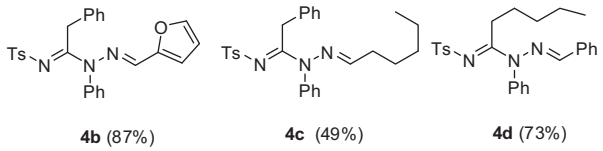
Table 3
Substrate diversity of synthesis of pyrazoles **5**[a]



1 **2** **3** **5**

Entry	**1** (R^1)	**2** (R^2)	**3** (R^3/R^4)	**5**	Yield[b] (%)
1	**1a** (Ph)	**2a** (4-MeC_6H_4)	**3a** (Ph/Ph)	**5a**	64
2	**1a**	**2a**	**3b** (4-MeOC_6H_4/Ph)	**5b**	73
3	**1a**	**2a**	**3c** (4-MeC_6H_4/Ph)	**5c**	63
4	**1a**	**2a**	**3d** (4-BrC_6H_4/Ph)	**5d**	58
5	**1a**	**2a**	**3e** (2-ClC_6H_4/Ph)	**5e**	60
6	**1a**	**2a**	**3f** (4-$NO_2C_6H_4$/Ph)	**5f**	77
7	**1a**	**2a**	**3g** (2-Py/Ph)	—	0
8	**1a**	**2a**	**3h** (2-Furyl/Ph)	—	0
9	**1a**	**2a**	**3i** (*n*-C_5H_{11}/Ph)	—	0
10	**1a**	**2a**	**3j** (Ph/4-MeC_6H_4)	**5g**	52
11	**1a**	**2a**	**3k** (Ph/4-ClC_6H_4)	**5h**	61
12	**1a**	**2b** (Ph)	**3a**	**5i**	57
13	**1a**	**2c** (4-BrC_6H_4)	**3a**	**5j**	57
14	**1a**	**2d** (4-MeOC_6H_4)	**3a**	**5k**	67
15	**1a**	**2e** (Me)	**3a**	**5l**	36
16	**1b** (4-MeC_6H_4)	**2a**	**3a**	**5m**	52
17	**1c** (4-MeOC_6H_4)	**2a**	**3a**	**5n**	42
18	**1d** (2-BrC_6H_4)	**2a**	**3a**	**5o**	51
19	**1d**	**2a**	**3c**	**5p**	52
20	**1d**	**2a**	**3k**	**5q**	54
21	**1e** (3-BrC_6H_4)	**2a**	**3a**	**5r**	53
22	**1f** (4-BrC_6H_4)	**2a**	**3a**	**5s**	52
23	**1g** (2-thienyl)	**2a**	**3a**	**5t**	41
24	**1h** (*n*-C_4H_9)	**2a**	**3a**	—	0

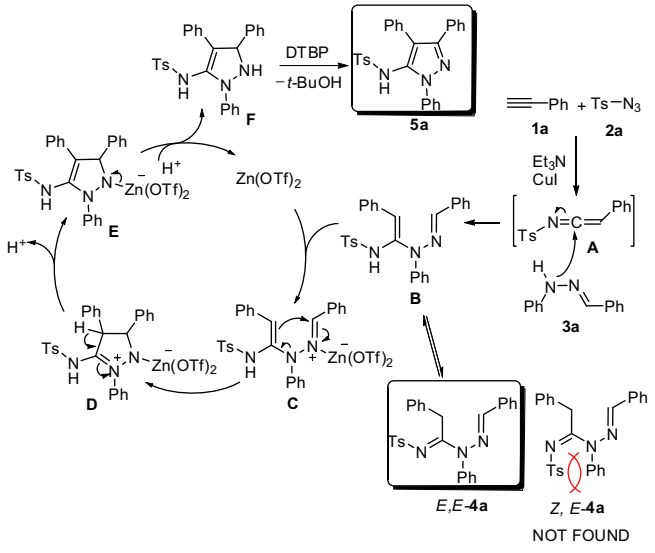
[a] Reaction conditions: (1) **1a** (0.75 mmol), **2a** (0.75 mmol), **3a** (0.5 mmol), DCM (8 mL), Et_3N (1 mmol), CuI (0.075 mmol), 25 °C, 12 h, then DCM and Et_3N was removed under reduced pressure. (2) $Zn(OTf)_2$ (0.05 mmol), DTBP (2 mmol) and toluene (12 mL), reflux, 48 h.
[b] Isolated yield.



4b (87%) **4c** (49%) **4d** (73%)

Scheme 2. Structures of compounds **4b**–**d**.

product **5a**. In this reaction, the activation of imine and the existence of oxidant are essential. $Zn(OTf)_2$ could lower the activation energy and promoted the electron flow possible,[13,15] while DTBP could assist the dehydrogenation to occur and push the reaction forward.



Scheme 3. Proposed mechanism for the formation of **4a** and **5a**.

3. Conclusions

In conclusion, we developed an efficient, one-pot synthesis of 5-sulfonamidopyrazoles from terminal alkynes, sulfonyl azides and hydrazones. This sequential reaction includes a copper-catalyzed three-component reaction, a Lewis acid-catalyzed electrocyclic reaction and a dehydrogenation. Further investigations on ketenimine chemistry and the synthetic applications of this method are ongoing in our laboratory.

4. Experimental section

4.1. General

Melting points were measured with micro melting point apparatus. Infrared spectra were obtained on an FTIR spectrometer. ^1H NMR spectra were recorded on 500 or 400 MHz spectrometer in $CDCl_3$ solution and the chemical shifts were reported relative to internal standard TMS (0 ppm). The following abbreviations are used to describe peak patterns where appropriate: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. Coupling constants are reported in Hertz (Hz). ^{13}C NMR were recorded on 125 or 100 MHz and referenced to the internal solvent signals (central peak is 77.27 ppm). HRMS were obtained using EI ionization.

CH_2Cl_2 was distilled over CaH_2 and toluene was distilled over Na.

4.2. General procedure for the synthesis of 4

To a mixture of CuI (0.075 mmol), sulfonyl azide **2** (0.75 mmol), hydrazone **3** (0.5 mmol) and alkyne **1** (0.75 mmol) in CH_2Cl_2 (8 mL) was added Et_3N (1 mmol) under an N_2 atmosphere. The mixture

was stirred at 25 °C for 12 h and then evaporated on vacuum. The residue was subjected to silica gel column chromatography with petroleum ether/ethyl acetate as eluent. The products were recrystallized from ethyl acetate/hexane.

*4.2.1. (E)-N-(1-((E)-2-Benzylidene-1-phenylhydrazinyl)-2-phenylethylidene)-4-methylbenzenesulfonamide (**4a**).* White solid, mp 170–171 °C; IR (film): *ν* 3060, 3021, 1599, 1552, 1489, 1424, 1278, 1144, 1084, 942, 814, 724, 692, 555 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.52–7.43 (m, 9H), 7.32–7.27 (m, 5H), 7.24–7.17 (m, 2H), 7.09–7.06 (m, 4H), 4.97 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 168.3, 145.5, 142.2, 140.7, 136.4, 135.9, 133.7, 130.7, 130.4, 129.7, 129.1, 129.0, 128.92, 128.87, 128.8, 127.8, 126.8, 126.2, 37.2, 21.6; HRMS (EI) calcd for $C_{28}H_{25}N_3O_2S$, 467.1667; found, 467.1662.

*4.2.2. (E)-N-(1-((E)-2-(Furan-2-ylmethylene)-1-phenylhydrazinyl)-2-phenylethylidene)-4-methylbenzenesulfonamide (**4b**).* Yellow solid, mp 135–136 °C; IR (film): *ν* 3060, 3027, 1599, 1549, 1495, 1427, 1281, 1141, 1084, 817, 680 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.63 (d, *J*=7.0 Hz, 2H), 7.51–7.44 (m, 6H), 7.29 (t, *J*=7.5 Hz, 2H), 7.20 (t, *J*=7.0 Hz, 1H), 7.09–7.03 (m, 5H), 6.57 (d, *J*=3.0 Hz, 1H), 6.43 (m, 1H), 4.91 (s, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 168.3, 149.7, 144.9, 142.2, 140.8, 136.1, 135.8, 134.7, 130.4, 129.8, 129.1, 128.8, 128.6, 126.8, 126.3, 113.5, 112.3, 37.1, 21.6; HRMS (EI) calcd for $C_{26}H_{23}N_3O_3S$, 457.1460; found, 457.1461.

*4.2.3. (E)-N-(1-((E)-2-Hexylidene-1-phenylhydrazinyl)-2-phenylethylidene)-4-methylbenzenesulfonamide (**4c**).* Yellow liquid, IR (film): *ν* 3060, 3030, 2953, 2923, 2852, 1554, 1489, 1424, 1278, 1150, 1084, 924, 811, 698, 552 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.47–7.44 (m, 6H), 7.40 (t, *J*=7.5 Hz, 1H), 7.28 (t, *J*=7.5 Hz, 2H), 7.20 (t, *J*=7.0 Hz, 1H), 7.05(d, *J*=8.0 Hz, 2H), 6.98 (d, *J*=7.5 Hz, 2H), 6.61 (t, *J*=5.5 Hz, 1H), 4.83 (s, 2H), 2.31 (s, 3H), 2.17–2.13 (m, 2H), 1.36–1.30 (m, 2H), 1.25–1.21 (m, 2H), 1.16–1.10 (m, 2H), 0.84 (t, *J*=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 168.1, 150.0, 142.0, 141.0, 136.7, 136.0, 130.2, 129.4, 129.3, 129.0, 128.8, 128.5, 126.6, 126.2, 37.1, 32.7, 31.3, 25.8, 22.5, 21.6, 14.1; HRMS (EI) calcd for $C_{27}H_{31}N_3O_2S$, 461.2137; found, 461.2121.

*4.2.4. (E)-N-(1-((E)-2-Benzylidene-1-phenylhydrazinyl)hexylidene)-4-methylbenzenesulfonamide (**4d**).* White solid, mp 88–89 °C; IR (film): *ν* 3057, 3024, 2952, 2926, 2864, 1557, 1421, 1284, 1153, 1081, 695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.57–7.52 (m, 4H), 7.50–7.46 (m, 3H), 7.39–7.37 (m, 3H), 7.31 (s, 1H), 7.13–7.08 (m, 4H), 3.52 (d, *J*=7.5 Hz, 2H), 2.32 (s, 3H), 1.97–1.91 (m, 2H), 1.60–1.54 (m, 2H), 1.48–1.41 (m, 2H), 0.95 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 171.7, 145.0, 142.0, 141.0, 136.5, 133.9, 130.7, 130.4, 129.6, 129.0, 127.7, 126.1, 32.4, 31.9, 27.3, 22.5, 21.6, 14.2; HRMS (EI) calcd for $C_{26}H_{29}N_3O_2S$, 445.1824; found, 445.1810.

4.3. General procedure for the synthesis of 5

To a mixture of CuI (0.075 mmol), sulfonyl azide **2** (0.75 mmol), hydrazone **3** (0.5 mmol) and alkyne **1** (0.75 mmol) in CH_2Cl_2 (8 mL) was added Et_3N (1 mmol) under an N_2 atmosphere. The mixture was stirred at 25 °C for 12 h and then evaporated on vacuum. The residue was dissolved in toluene (12 mL) and $Zn(OTf)_2$ (0.05 mmol) and DTBP (2 mmol) were added. The mixture was stirred at reflux temperature for 48 h and then evaporated on vacuum. The residue was subjected to silica gel column chromatography with petroleum ether/ethyl acetate as eluent.

*4.3.1. 1,3,4-Triphenyl-N-tosyl-1H-pyrazol-5-amine (**5a**).* White solid, mp 203–204 °C; IR (film): *ν* 3244, 3063, 1599, 1492, 1360, 1162, 760, 724, 698, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.65 (d, *J*=7.5 Hz, 2H), 7.44–7.41 (m, 4H), 7.36 (t, *J*=7.5 Hz, 1H), 7.24–7.14 (m, 8H), 6.96 (d, *J*=7.0 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 6.74 (s, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.5, 143.9, 139.2, 136.2, 132.9, 131.5, 131.3, 129.9, 129.6, 129.2, 128.7, 128.4, 128.2, 128.1, 128.0, 127.3, 127.2, 125.1, 118.8, 21.7; HRMS (EI) calcd for $C_{28}H_{23}N_3O_2S$, 465.1511; found, 465.1513.

*4.3.2. 3-(4-Methoxyphenyl)-1,4-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5b**).* White solid, mp 193–194 °C; IR (film): *ν* 3253, 3066, 1596, 1498, 1435, 1250, 1166, 732, 666, 568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.61 (d, *J*=8.0 Hz, 2H), 7.40–7.31 (m, 5H), 7.18–7.08 (m, 6H), 6.96 (d, *J*=7.2 Hz, 2H), 6.82 (d, *J*=8.4 Hz, 2H), 6.76 (d, *J*=8.8 Hz, 2H), 3.74 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 159.5, 149.3, 143.7, 139.2, 136.2, 131.4, 131.3, 129.9, 129.5, 129.4, 129.1, 128.5, 127.8, 127.1, 125.4, 125.0, 118.6, 113.8, 55.4, 21.7; HRMS (EI) calcd for $C_{29}H_{25}N_3O_3S$, 495.1617; found, 495.1631.

*4.3.3. 1,4-Diphenyl-3-p-tolyl-N-tosyl-1H-pyrazol-5-amine (**5c**).* White solid, mp 217–218 °C; IR (film): *ν* 3253, 3063, 3030, 1596, 1498, 1156, 906, 727, 662, 567 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.62 (d, *J*=8.0 Hz, 2H), 7.38 (t, *J*=7.2 Hz, 2H), 7.33–7.30 (m, 3H), 7.18–7.10 (m, 5H), 7.04–7.02 (m, 3H), 6.98–6.94 (m, 2H), 6.82 (d, *J*=8.4 Hz, 2H), 2.28 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 149.6, 143.7, 139.2, 137.8, 136.2, 131.4, 131.3, 130.0, 129.9, 129.5, 129.1, 128.5, 128.0, 127.8, 127.1, 125.0, 118.9, 21.7, 21.5; HRMS (EI) calcd for $C_{29}H_{25}N_3O_2S$, 479.1667; found, 479.1668.

*4.3.4. 3-(4-Bromophenyl)-1,4-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5d**).* White solid, mp 221–222 °C; IR (film): *ν* 3254, 3063, 1596, 1497, 1441, 1361, 1328, 1165, 662, 573 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.62 (d, *J*=7.5 Hz, 2H), 7.41 (t, *J*=7.5 Hz, 2H), 7.36–7.35 (m, 3H), 7.29 (d, *J*=8.5 Hz, 2H), 7.23–7.14 (m, 5H), 6.95 (d, *J*=7.0 Hz, 2H), 6.90 (s, 1H), 6.85 (d, *J*=8.0 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 148.4, 143.9, 139.1, 136.2, 131.8, 131.7, 131.6, 131.0, 129.9, 129.7, 129.6, 129.2, 128.8, 128.1, 127.5, 127.2, 125.1, 122.3, 119.0, 21.7; HRMS (EI) calcd for $C_{28}H_{22}BrN_3O_2S$, 543.0616; found, 543.0610.

*4.3.5. 3-(2-Chlorophenyl)-1,4-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5e**).* White solid, mp 238–239 °C; IR (film): *ν* 3241, 3063, 1599, 1495, 1435, 1358, 1328, 1162, 903, 751, 727, 662 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.66 (d, *J*=8.0 Hz, 2H), 7.43–7.32 (m, 5H), 7.26–7.18 (m, 5H), 7.09 (t, *J*=7.5 Hz, 1H), 7.03 (t, *J*=7.5 Hz, 2H), 6.84–6.80 (m, 4H), 2.26 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 148.6, 143.9, 139.0, 135.7, 134.3, 132.4, 131.1, 130.4, 129.91, 129.89, 129.5, 129.2, 128.7, 128.4, 128.0, 127.2, 126.80, 126.77, 124.9, 120.4, 21.7; HRMS (EI) calcd for $C_{28}H_{22}ClN_3O_2S$, 499.1121; found, 499.1105.

*4.3.6. 3-(4-Nitrophenyl)-1,4-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5f**).* Yellow solid, mp 192–193 °C; IR (film): *ν* 3256, 3063, 1596, 1516, 1495, 1346, 1165, 858, 724, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 8.07 (d, *J*=8.8 Hz, 2H), 7.64–7.59 (m, 4H), 7.44–7.36 (m, 3H), 7.26 (t, *J*=7.2 Hz, 1H), 7.20–7.14 (m, 5H), 6.98 (d, *J*=7.2 Hz, 2H), 6.86 (d, *J*=8.0 Hz, 2H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 147.3, 147.1, 144.0, 139.4, 138.8, 136.1, 132.2, 130.5, 129.9, 129.6, 129.3, 128.9, 128.5, 128.4, 127.8, 127.1, 125.1, 123.7, 120.0, 21.7; HRMS (EI) calcd for $C_{28}H_{22}N_4O_4S$, 510.1362; found, 510.1357.

*4.3.7. 3,4-Diphenyl-1-p-tolyl-N-tosyl-1H-pyrazol-5-amine (**5g**).* White solid, mp 187–188 °C; IR (film): *ν* 3254, 3060, 1514, 1366, 1333, 1166, 910, 733, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.49 (d, *J*=8.0 Hz, 2H), 7.43–7.41 (m, 2H), 7.25–7.17 (m, 8H), 7.14 (t, *J*=7.0 Hz, 2H), 6.97 (d, *J*=7.0 Hz, 2H), 6.88 (s, 1H), 6.84 (d, *J*=8.0 Hz, 2H), 2.39 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.3, 143.7, 137.9, 136.7, 136.4, 132.9, 131.4, 129.9, 129.7, 129.5, 128.6,

128.4, 128.2, 128.0, 127.2, 125.0, 118.7, 21.7, 21.4; HRMS (EI) calcd for $C_{29}H_{25}N_3O_2S$, 479.1667; found, 479.1674.

*4.3.8. 1-(4-Chlorophenyl)-3,4-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5h**).* White solid, mp 202–203 °C; IR (film): *ν* 3244, 3057, 1492, 1361, 1325, 1159, 1090, 909, 730, 698, 659 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.56 (d, *J*=8.5 Hz, 2H), 7.41–7.40 (m, 2H), 7.32 (d, *J*=8.5 Hz, 2H), 7.25–7.14 (m, 8H), 7.11(s, 1H), 6.97 (d, *J*=7.0 Hz, 2H), 6.87 (d, *J*=8.0 Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.9, 144.1, 137.7, 136.1, 133.7, 132.6, 131.5, 131.0, 129.9, 129.6, 129.2, 128.7, 128.5, 128.3, 128.1, 127.4, 127.1, 126.1, 119.4, 21.8; HRMS (EI) calcd for $C_{28}H_{22}ClN_3O_2S$, 499.1121; found, 499.1119.

*4.3.9. N-(1,3,4-Triphenyl-1H-pyrazol-5-yl)benzenesulfonamide (**5i**).* White solid, mp 201–202 °C; IR (film): *ν* 3250, 3063, 1495, 1358, 1328, 1162, 1087, 912, 751, 683, 587 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.61 (d, *J*=7.5 Hz, 2H), 7.44–7.42 (m, 2H), 7.39 (d, *J*=8.0 Hz, 2H), 7.34–7.12 (m, 10H), 7.07 (t, *J*=8.0 Hz, 2H), 7.01–6.97 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.6, 139.3, 139.1, 133.0, 132.8, 131.4, 131.2, 129.9, 129.2, 128.9, 128.8, 128.4, 128.13, 128.08, 127.5, 127.1, 125.1, 119.1; HRMS (EI) calcd for $C_{27}H_{21}N_3O_2S$, 451.1354; found, 451.1353.

*4.3.10. 4-Bromo-N-(1,3,4-triphenyl-1H-pyrazol-5-yl)benzenesulfonamide (**5j**).* White solid, mp 201–202 °C; IR (film): *ν* 3250, 3063, 1575, 1495, 1337, 1165, 1067, 903, 736, 698, 608 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.62 (d, *J*=8.0 Hz, 2H), 7.44–7.41 (m, 4H), 7.37 (t, *J*=7.5 Hz, 1H), 7.25–7.23 (m, 4H), 7.18 (t, *J*=7.5 Hz, 2H), 7.16–7.10 (m, 4H), 7.01 (s, 1H), 6.96 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.7, 139.0, 138.1, 132.7, 132.2, 131.1, 130.9, 129.8, 129.3, 128.8, 128.54, 128.48, 128.24, 128.17, 127.5, 125.1, 119.2; HRMS (EI) calcd for $C_{27}H_{20}BrN_3O_2S$, 529.0460; found, 529.0458.

*4.3.11. 4-Methoxy-N-(1,3,4-triphenyl-1H-pyrazol-5-yl)benzenesulfonamide (**5k**).* White solid, mp 205–206 °C; IR (film): *ν* 3250, 3057, 1596, 1495, 1260, 1156, 754, 730, 699, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.65 (d, *J*=7.5 Hz, 2H), 7.43–7.40 (m, 4H), 7.34 (t, *J*=7.5 Hz, 1H), 7.25–7.14 (m, 8H), 6.98 (d, *J*=6.5 Hz, 2H), 6.94 (s, 1H), 6.50 (d, *J*=8.0 Hz, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 163.1, 149.5, 139.3, 132.9, 131.6, 131.4, 130.6, 129.9, 129.3, 129.2, 128.7, 128.4, 128.2, 128.1, 128.0, 127.3, 125.0, 118.9, 114.1, 55.7; HRMS (EI) calcd for $C_{28}H_{23}N_3O_3S$, 481.1460; found, 481.1454.

*4.3.12. N-(1,3,4-Triphenyl-1H-pyrazol-5-yl)methanesulfonamide (**5l**).* White solid, mp 94–95 °C; IR (film): *ν* 3238, 3060, 1596, 1498, 1361, 1328, 1150, 968, 903, 730, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.65 (d, *J*=7.5 Hz, 2H), 7.50–7.44 (m, 4H), 7.39–7.33 (m, 6H), 7.27–7.26 (m, 3H), 6.85 (s, 1H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.6, 138.6, 132.7, 131.8, 131.7, 130.3, 129.4, 129.2, 128.6, 128.5, 128.3, 128.2, 128.1, 125.6, 119.0, 41.9; HRMS (EI) calcd for $C_{22}H_{19}N_3O_2S$, 389.1198; found, 389.1197.

*4.3.13. 1,3-Diphenyl-4-p-tolyl-N-tosyl-1H-pyrazol-5-amine (**5m**).* White solid, mp 202–203 °C; IR (film): *ν* 3247, 3063, 1593, 1498, 1447, 1361, 1165, 1090, 909, 730, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.64 (d, *J*=7.5 Hz, 2H), 7.46–7.44 (m, 2H), 7.40 (t, *J*=7.5 Hz, 2H), 7.34 (t, *J*=7.5 Hz, 1H), 7.25–7.23 (m, 3H), 7.18 (d, *J*=8.0 Hz, 2H), 6.94–6.92 (m, 3H), 6.85–6.84 (m, 4H), 2.33 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.5, 143.7, 139.2, 136.9, 136.4, 133.0, 131.4, 129.7, 129.4, 129.3, 129.2, 128.4, 128.2, 128.1, 128.0, 127.9, 127.2, 125.0, 118.9, 21.7, 21.5; HRMS (EI) calcd for $C_{29}H_{25}N_3O_2S$, 479.1667; found, 479.1663.

*4.3.14. 4-(4-Methoxyphenyl)-1,3-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5n**).* White solid, mp 204–205 °C; IR (film): *ν* 3250, 3063, 1593, 1498, 1358, 1248, 1165, 733, 683, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.61 (d, *J*=7.2 Hz, 2H), 7.45–7.10 (m, 11H), 6.89–6.83 (m, 4H), 6.65 (d, *J*=8.4 Hz, 2H), 3.77 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 158.9, 149.5, 143.7, 139.2, 136.5, 133.0, 131.4, 131.0, 129.4, 129.1, 128.4, 128.1, 128.0, 127.8, 127.1, 125.0, 123.5, 118.8, 114.0, 55.3, 21.7; HRMS (EI) calcd for $C_{29}H_{25}N_3O_3S$, 495.1617; found, 495.1615.

*4.3.15. 4-(2-Bromophenyl)-1,3-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5o**).* White solid, mp 214–215 °C; IR (film): *ν* 3256, 3063, 1593, 1498, 1168, 909, 727, 668, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.70–7.68 (m, 2H), 7.52–7.50 (m, 1H), 7.45 (t, *J*=8.0 Hz, 2H), 7.39–7.33 (m, 3H), 7.26–7.21 (m, 5H), 7.11–7.07 (m, 1H), 7.00–6.97 (m, 1H), 6.87 (d, *J*=8.0 Hz, 2H), 6.74–6.72 (m, 1H), 6.64 (s, 1H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.6, 143.8, 139.0, 136.3, 133.4, 132.9, 132.6, 132.4, 131.7, 129.6, 129.24, 129.19, 128.5, 128.2, 128.1, 127.7, 127.6, 127.0, 125.2, 123.8, 117.7, 21.7; HRMS (EI) calcd for $C_{28}H_{22}BrN_3O_2S$, 543.0616; found, 543.0618.

*4.3.16. N-(4-(2-Bromophenyl)-1-phenyl-3-(p-tolyl)-1H-pyrazol-5-yl)-4-methylbenzenesulfonamide (**5p**).* White solid, mp 245–246 °C; IR (film): *ν* 3253, 3062, 2915, 1597, 1496, 1362, 1330, 1166, 1090, 907, 824, 753, 730, 671 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.69–7.67 (m, 2H), 7.52–7.50 (m, 1H), 7.44 (t, *J*=7.5 Hz, 2H), 7.36 (t, *J*=7.5 Hz, 1H), 7.26–7.22 (m, 4H), 7.10–7.07 (m, 1H), 7.02–6.97 (m, 3H), 6.86 (d, *J*=8.0 Hz, 2H), 6.75–6.73 (m, 1H), 6.59 (s, 1H), 2.28 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.6, 143.8, 139.1, 138.0, 136.4, 133.5, 132.8, 132.6, 131.7, 129.8, 129.6, 129.2, 128.0, 127.6, 127.5, 127.1, 125.2, 123.8, 117.6, 21.7, 21.5; HRMS (EI) calcd for $C_{29}H_{24}BrN_3O_2S$, 557.0773; found, 557.0787.

*4.3.17. N-(4-(2-Bromophenyl)-1-(4-chlorophenyl)-3-phenyl-1H-pyrazol-5-yl)-4-methylbenzenesulfonamide (**5q**).* White solid, mp 221–222 °C; IR (film): *ν* 3258, 3056, 1496, 1362, 1333, 1166, 1090, 965, 906, 830, 733, 665 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.66–7.63 (m, 2H), 7.54–7.52 (m, 1H), 7.39–7.37 (m, 2H), 7.34–7.32 (m, 2H), 7.26–7.21 (m, 5H), 7.13–7.09 (m, 1H), 7.01–6.98 (m, 1H), 6.90 (d, *J*=8.0 Hz, 2H), 6.75–6.73 (m, 1H), 6.66 (s, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.9, 144.1, 137.6, 136.3, 133.9, 133.4, 132.9, 132.4, 132.2, 131.9, 129.7, 129.4, 129.3, 128.5, 128.3, 127.7, 127.6, 127.0, 126.2, 123.7, 118.1, 21.7; HRMS (EI) calcd for $C_{28}H_{21}BrClN_3O_2S$, 577.0226; found, 577.0217.

*4.3.18. 4-(3-Bromophenyl)-1,3-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5r**).* White solid, mp 200–201 °C; IR (film): *ν* 3250, 3060, 1590, 1498, 1361, 1328, 1162, 1090, 909, 763, 686 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): *δ* 7.66 (d, *J*=7.5 Hz, 2H), 7.46–7.36 (m, 5H), 7.29–7.25 (m, 4H), 7.21 (d, *J*=8.0 Hz, 2H), 7.06–7.05 (m, 2H) 6.99 (t, *J*=7.5 Hz, 1H), 6.94–6.89 (m, 3H), 2.32 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): *δ* 149.6, 144.1, 138.9, 136.2, 133.5, 132.5, 132.4, 131.6, 130.2, 130.1, 129.6, 129.3, 128.7, 128.5, 128.4, 128.23, 128.20, 127.0, 125.2, 122.6, 117.4, 21.9; HRMS (EI) calcd for $C_{28}H_{22}BrN_3O_2S$, 543.0616; found, 543.0609.

*4.3.19. 4-(4-Bromophenyl)-1,3-diphenyl-N-tosyl-1H-pyrazol-5-amine (**5s**).* White solid, mp 214–215 °C; IR (film): *ν* 3253, 3063, 1495, 1364, 1328, 1165, 906, 730, 695, 665, 573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 7.63 (d, *J*=9.5 Hz, 2H), 7.44–7.36 (m, 6H), 7.24–7.16 (m, 7H), 6.87 (d, *J*=10.0 Hz, 2H), 6.81 (d, *J*=10.5 Hz, 2H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 149.5, 144.2, 136.4, 132.5, 131.6, 131.4, 131.3, 130.2, 129.5, 129.2, 128.5, 128.3, 128.2, 127.0, 125.2, 121.5, 118.0, 21.8; HRMS (EI) calcd for $C_{28}H_{22}BrN_3O_2S$, 543.0616; found, 543.0621.

*4.3.20. 1,3-Diphenyl-4-(thiophen-2-yl)-N-tosyl-1H-pyrazol-5-amine (**5t**).* Yellow solid, mp 92–93 °C; IR (film): *ν* 3250, 3066, 1593, 1492, 1447, 1367, 1328, 1156, 906, 730, 698, 668 cm^{-1}; ^1H NMR (500 MHz,

$CDCl_3$): δ 7.55 (d, J=7.5 Hz, 2H), 7.53–7.51 (m, 2H), 7.36 (d, J=7.5 Hz, 2H), 7.32–7.25 (m, 6H), 7.20 (d, J=5.0 Hz, 1H), 6.92 (d, J=8.0 Hz, 2H), 6.89 (s, 1H), 6.86–6.85 (m, 1H), 6.64 (d, J=3.5 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1, 143.9, 139.0, 136.4, 132.5, 132.1, 131.7, 129.6, 129.2, 128.5, 128.3, 128.1, 128.0, 127.5, 127.2, 126.5, 125.0, 112.3, 21.7; HRMS (EI) calcd for $C_{26}H_{21}N_3O_2S_2$, 471.1075; found, 471.1070.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.067.

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