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Revisit: The Synthesis of *3*-amino pyrazoles promoted by *p*-toluenesulfonic acid as an efficient catalyst under solvent and solvent-free conditions

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ABSTRACT

An efficient and facile synthesis of *3*-amino pyrazoles has been described. The reaction of β-keto nitriles with hydrazines using *p*-toluenesulfonic acid as an efficient catalyst under solvent and solvent-free conditions afford corresponding *3*-amino pyrazoles in excellent yields

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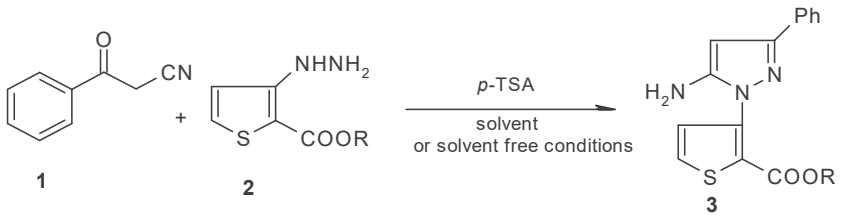
Introduction

Pyrazoles, in particular *3*-amino pyrazoles are an important class of compounds in medicinal chemistry and it has been well documented to posses antihypertensive,[1] antibacterial,[2] anti-inflammatory muscle relaxant[3,4] and inhibitors of cyclin dependent kinases (CDK) such as CDK_2/cycling A-E.[5] They are also potent and selective Aurora kinase inhibitors.[6,7] In addition the *3*-amino pyrazoles also have industrial appliance in inhibition of corrosion on metals such as Zn, Cu, Al and Brass.[8]

Despite their importance from a pharmacological, industrial and synthetic point of view, comparatively few methods for the preparation of *3*-amino pyrazoles have been reported. These includes condensation of hydrazines with β-keto nitriles,[9] β-formyl nitriles,[4] β-methoxy vinyl nitriles,[10] α-nitrilo ethyl acetate[11] and solid phase synthesis of 5-substituted amino pyrazoles.[12] Unfortunately many of these processes suffer from one or other limitations such as incompletion of starting materials, long reaction times, with unsatisfactory yields. Thus there is a need for the development of an alternate route to construct the *3*-amino pyrazoles.

In recent years,*p*-toluenesulfonic acid is used as an efficient catalyst in various organic transformations,[13] also it should be noted that *p*-toluenesulfonic acid is cheap, commercially available and comparatively non-toxic. The organic reactions assisted by microwaves,[14] in particular have been gained special attention. One reason is that the use of microwave activation in organic synthesis can increase the purity of the resulting products, enhance the chemical yield and shorten the reaction times. And also organic reactions carried out in the absence of solvent, has been attracting attention of chemists due to ease of processing to the further step and eco-friendly in nature. In the case of synthesis of *3*-amino pyrazoles, we thought that there is a scope for further innovation towards short reaction times and better yields. Here, we report an efficient and facile method for the synthesis of *3*-amino pyrazoles catalyzed by *p*-toluenesulfonic acid under solvent and solvent-free conditions.



1 2 3

Scheme 1

Results & discussion

Reaction of benzoyl acetonitrile i. e. β-keto nitrile[15] with 4-hydrazinobenzoic acid under reflux conditions in absolute ethanol for 8-10hr resulted in the formation of the corresponding *3*-amino pyrazoles in <90% yield. However, we carried out the reaction in presence of catalytic amounts of *p*-toluenesulfonic acid (0.01 equiv.) and found reaction is completed in 45 min with nearly 100% conversion (Table 1, entry 7). This success has encouraged us to extend the generality of the reaction; various hydrazines with various β-keto nitriles in presence*p*-toluenesulfonic acid proceeded efficiently and smoothly at refluxing temperature and the products are obtained in excellent yields. And the reaction conditions are very favorable, no by-products are observed (Table 1, Method A).

We further investigated the reaction conditions to improve the reaction conditions. It has been found that, β-keto nitrile **1** (1 mmol) and hydrazine **2** (1 mmol) reacts very rapidly (<5min) to give *3*-amino pyrazoles in the presence of *p*-toluenesulfonic acid under microwave irradiation in solvent-free conditions (Table 1, Method B). The experimental procedure for this reaction is remarkably simple and no solvents or inert atmosphere is required. Under above conditions, in many cases it is noticed that in the absence of *p*-toluenesulfonic acid, the reaction is incomplete and uncyclized product was isolated along with pyrazole.

Table 2: Synthesis of *3*-Amino pyrazole catalyzed by *p*-toluenesulfonic acid under solvent and solvent free conditions.

Entry	β-Keto nitrile	Hydrazine	Product	Method A		Method B	
				Time (min)	Yield (%)	Time (min)	Yield (%)
1	Pivoloyl acetonitrile	Hydrazine hydrate	3a	45	98	3	99
2	α-Phenyl acetyl acetonitrile	Hydrazine hydrate	3b	45	97	3	99
3	Benzoyl acetonitrile	Hydrazine hydrate	3c	45	99	3	98
4	*p*-Chloro benzoyl acetonitrile	Hydrazine hydrate	3d	45	98	3	98
5	*p*-methyl benzoyl acetonitrile	Hydrazine hydrate	3e	45	97	3	98
6	Furoyl acetonitrile	Hydrazine hydrate	3f	45	98	3	99
7	Benzoyl acetonitrile	*p*-Hydrazino benzoic acid	3g	45	98	3	98
	Benzoyl	*m*-Hydrazino benzoic					

8	acetonitrile	acid	3h	120	90	5	95
9	Benzoyl acetonitrile	*3*-Hydrazino thiophene 2-(ethyl carboxylate)	3i	45	99	3	98
10	Benzoyl acetonitrile	α-Hydrazino ethyl acetate	3j	60	98	3	98
11	*p*-Chloro benzoyl acetonitrile	*p*-Hydrazino benzoic acid	3k	45	98	3	98
12	*p*-Chloro benzoyl acetonitrile	*m*-Hydrazino benzoic acid	3l	150	95	3	92
13	*p*-methyl benzoyl acetonitrile	*p*-Hydrazino benzoic acid	3m	45	99	3	98
4	*p*-methyl benzoyl acetonitrile	*3*-Hydrazino thiophene 2-(ethyl carboxylate	3n	45	99	3	98
15	Pivoloyl acetonitrile	*p*-Nitro phenyl hydrazine	3o	120	95	4	95
6	α-Phenyl acetyl acetonitrile	*p*-Nitro phenyl hydrazine	3p	120	90	4	96
7	Benzoyl acetonitrile	*p*-Nitro phenyl hydrazine	3q	120	90	4	97
18	*p*-Chloro benzoyl acetonitrile	*p*-Nitro phenyl hydrazine	3r	120	96	4	98
19	*p*-methyl benzoyl acetonitrile	*p*-Nitro phenyl hydrazine	3s	120	90	4	96
20	Furroyl acetonitrile	*p*-Nitro phenyl hydrazine	3t	90	95	4	98

[a]Isolated yields after crystallization/column chromatography and all products gave satisfactory spectral (IR, [1]HNMR and MASS) and analytical data

In summary, the present procedures for the synthesis of *3*-amino pyrazole have been developed by condensation reaction of hydrazines with β-keto nitriles catalyzed by *p*-toluenesulfonic acid under solvent and solvent free conditions. The advantage of present method is high efficient, reduced reaction time and inexpensive catalyst with high yields of products and simple experimental work-up procedure, which makes it, is a useful and important addition to the present existing methodologies.

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Typical Experimental procedure (Method A, Conventional): A mixture of β-keto nitile (10 mmol), hydrazine (10 mmol) and to this *p*-TSA (0.1mmol) was added and refluxed in absolute ethanol for appropriate time (Table 1, Method A). After completion of the reaction, as monitored by TLC, the solvent was evaporated under reduced pressure. The product was extracted into ethyl acetate (3 x 20 mL). The combined organic layer was washed with saturated sodium bicarbonate followed by brine solution, then dried over anhydrous sodium sulphate. The solvent was removed to afford crude product and purified by column chromatography.

Typical Experimental procedure (Method B, Microwave):A mixture of β-keto nitile (10 mmol), hydrazine (10 mmol), *p*-TSA (0.1mmol) was suspended in water (1mL) in a reaction vessel, sealed without degassing and was subjected to microwave irradiation at 450Watt. at 135^{0}C for appropriate time (Table 1, Method B). After completion of the reaction, as monitored by TLC, the reaction mass was cooled and product was extracted into ethyl acetate (3 x 20 mL). The combined organic layer was washed with saturated sodium bicarbonate followed by brine solution, then dried over anhydrous sodium sulphate. The solvent was removed under reduced pressure to afford crude product, it was purified by recrystallized from ethanol/column chromatography to give corresponding pure *3*-amino pyrazoles.

3a:IR (KBr): 3418, 1618, 1509, 1009, 762, 707 cm^{-1};^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 1.25 (s, 9H), 5.85 (s, 1H); EIMS: *m/z*139; Anal. Calcd. for $C_7H_{13}N_3$: C, 60.431; H, 9.352; N, 30.215. *Found:* C, 60.399; H, 9.412, N, 30.186.

3b:IR (KBr): 3420, 1620, 1520, 750 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 2.26 (s, 3H), 4.75 (s, 2H br), 7.40 (s, 5H); EIMS: *m/z* 173; Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.280; H, 6.350; N, 24.277. *Found:* C, 69.340; H, 6.401, N, 24.258.

3c:IR (KBr): 3415, 1618, 1124, 613 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$) δ 4.25 (s, 2H br.), 5.75 (s, 1H), 7.30 (m, 5H); EIMS: *m/z* 157; Anal. Calcd. for $C_9H_9N_3$: C, 67.924; H, 5.660; N, 26.415. *Found:* C, 67.905; H, 5.698, N, 26.396.

3d:IR(neat): 3448, 1636 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 5.5 (s, 1H), 7.25 (d, 2H, *J* = 8.25Hz), 7.35 (d, 2H, *J* = 8.25Hz); EIMS: *m/z* 193, 195; Anal. Calcd. for $C_9H_8ClN_3$: C, 55.958; H, 4.145; Cl, 18.393; N, 21.761. *Found:* C, 55.826; H, 4.164; Cl, 18.308; N, 21.700.

3e:IR (KBr): 3413, 1618, 1511, 1108, 613 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+CDCl3): δ 2.50 (s, 3H), 5.95 (s, 1H), 7.45 (d, 2H, *J* = 8.20Hz), 7.75 (d, 2H, *J* = 8.20Hz); EIMS: *m/z* 173. Anal. Calcd. for $C_{10}H_{11}N_3$: C, 69.364; H, 6.358; N, 24.277. *Found:* C, 69.340; H, 6.401; N, 24.258.

3f: IR (KBr): 3415, 1694, 1615, 1179, 616 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 5.68 (s, 1H), 6.41 (s, 1H), 6.59 (s, 1H), 7.4 (s, 1H); EIMS: *m/z* 149; Anal. Calcd. for $C_7H_7N_3O$: C, 56.375; H, 4.697; N, 28.187; O, 10.738. *Found:* C, 56.369; H, 4.730; N, 28.173; O, 10.736.

3g:IR (KBr): 3414, 1616, 1091 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 6.60 (s, 1H), 7.40 (m, 5H), 7.8 (d, 2H, *J* = 8.50Hz), 8.40 (d, 2H, *J* = 8.50Hz); EIMS: *m/z* 279; Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.817; H, 4.659; N, 15.053; O, 11,469. *Found:* C, 68.806; H, 4.691; N, 15.044; O, 11.456.

3h:IR (KBr): 3414, 1617, 1383, 618 cm^{-1}; ^{1}H NMR (200 MHz, DMSI+$CDCl_3$): δ 5.9 (s, 1H), 7.15 (m, 5H), 7.35 (d, 1H, *J* = 8.15Hz), 7.60 (t, 1H, *J* = 3.15Hz), 7.85 (d, 1H, *J* = 8.25Hz), 7.9 (d, 1H, *J* = 8.15Hz), 8.30 (s, 1H); EIMS: *m/z* 279; Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.817; H, 4.659; N, 15.053; O, 11.469. *Found:* C, 68.806; H, 4.691; N, 15.044; O, 11.456.

3i: IR (KBr): 3415, 1618, 1285, 761 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 1.25 (t, 3H), 3.90 (q, 2H), 6.25 (s, 1H), 7.40 (m, 5H), 7.7 (d, 2H, *J* = 8.25Hz), 8.05 (d, 2H, *J* = 8.25Hz); EIMS: *m/z* 313;

3j: IR (KBr): 3415, 1657, 1615, 1384, 1121, 758 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 1.25 (t, 3H), 4.25 (q, 2H), 4.925 (s, 2H), 5.85 (s, 1H), 7.5 (m, 5H); EIMS: *m/z* 245; Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.673; H, 6.122; N, 17.142; O, 13.067. *Found:* C, 63.658; H, 6.164; N, 17.131; O, 13.045.

3k: IR (KBr): 3416, 1650, 1384, 1120, 758 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$) δ 6.02 (s, 1H), 7.15 (d, 2H, *J* = 8.15Hz), 7.35 (d, 2H, *J* = 8.23Hz), 7.60 (d, 2H, *J* = 8.15Hz), 8.10 (d, 2H, *J* = 8.23Hz); EIMS: *m/z* 303, 305; Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.341; H, 3.833; Cl, 11.341; N, 13.415; O, 10.223. *Found:* C, 61.252; H, 3.855; Cl, 11.299; N, 13.393; O, 10.198.

3l: IR (KBr): 3415, 1650, 1090 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$) δ 6.8 (s, 1H), 7.4 (d, 2H, *J* = 8.15Hz), 7.6 (t, 1H, *J* = 3.00Hz), 7.8 (d, 3H, *J* = 8.25Hz), 8.1 (d, 1H, *J* = 8.25Hz), 8.3 (s, 1H, *J* = 8.15Hz), 9.93 (s, 1H); EIMS: *m/z* 303, 305; Anal. Calcd. for $C_{16}H_{12}ClN_3O_2$: C, 61.341; H, 3.833; Cl, 11.341; N, 13.415; O, 10.223. *Found:* C, 61.252; H, 3.855; Cl, 11.299; N, 13.393; O, 10.198.

3m:IR (KBr): 3415, 1617, 1384, 764, 619 cm^{-1};^{1}H NMR (200MHz, DMSO+CDCl3) δ 2.37 (s, 3H), 3.75 (s, 2H broad), 7.1 (d, 2H, *J* = 8.22Hz), 7.4 (d, 2H, *J* = 8.15Hz), 7.7 (d, 2H, *J* = 8.15Hz), 8.0 (d, 2H, *J* = 8.22Hz); EIMS: *m/z* 291; Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.624; H, 5.119; N, 14.334; O, 10.921. *Found:* C, 69.611; H, 5.154; N, 14.325; O, 10.908.

3n: IR (KBr): 3415, 1618, 1384, 1216, 1047, 816, 619, 476 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$) δ 1.25 (t, 3H), 2.50 (s, 3H), 3.90 (q, 2H), 6.25 (s, 1H), 7.1 (d, 2H, *J* = 8.25Hz), 7.6 (d, 2H, *J* = 8.25Hz), 7.7 (d, 2H, *J* = 8.15Hz),8.1 (d, 2H, *J* = 8.15Hz); EIMS: *m/z* 328; Anal. Calcd. for $C_{17}H_{17}N_3O_2S$: C, 62.385; H, 5.198; N, 12.84; O, 9.785; S, 9.785. *Found:* C, 62.365; H, 5.233; N, 12.834; O, 9.773; S, 9.793.

3o:^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 1.26 (s, 9H), 5.95 (s, 1H), 7.60 (d, 2H, *J* = 8.80Hz), 8.50 (d, 2H, *J* = 8.80Hz); EIMS: *m/z*260.

3p: ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 2.26 (s, 3H), 7.40 (s, 5H), 7.62 (d, 2H, *J* = 8.60Hz), 8.56 (d, 2H, *J* = 8.60Hz); EIMS: *m/z* 294.

3q:^{1}H NMR (200 MHz, DMSO+$CDCl_3$) δ 5.75 (s, 1H), 7.30 (m, 5H), 7.66 (d, 2H, *J* = 8.30Hz), 8.46 (d, 2H, *J* = 8.30Hz); EIMS: *m/z* 280.

3r:^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 5.5 (s, 1H), 7.26 (d, 2H, *J* = 8.25Hz), 7.36 (d, 2H, *J* = 8.25Hz), 7.68 (d, 2H, *J* = 8.20Hz), 8.49 (d, 2H, *J* = 8.20Hz); EIMS: *m/z* 314.

3s:^{1}H NMR (200 MHz, DMSO+CDCl3): δ 2.50 (s, 3H), 6.05 (s, 1H), 7.55 (d, 2H, *J* = 8.26Hz), 7.76 (d, 2H, *J* = 8.55Hz), 7.80 (d, 2H, *J* = 8.26Hz), 8.49 (d, 2H, *J* = 8.55Hz); EIMS: *m/z* 294.

3t: IR (KBr): 3425, 1694, 1615, 1500, 1485, 1425, 1179, 616 cm^{-1}; ^{1}H NMR (200 MHz, DMSO+$CDCl_3$): δ 5.75 (s, 1H), 6.46 (s, 1H), 6.65 (s, 1H), 7.4 (s, 1H), 7.66 (d, 2H, *J* = 8.30Hz), 8.46 (d, 2H, *J* = 8.30Hz); EIMS: *m/z* 270; Anal. Calcd. for $C_{13}H_{10}N_4O_3$: C, 57.77; H, 5.119; N, 20.74; O, 17.77. *Found:* C, 57.78; H, 3.73; N, 20.73; O, 17.76.

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