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Short communication

An expeditious synthesis of 3-amino 2*H*-pyrazoles promoted by methanesulphonic acid under solvent and solvent free conditions☆

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Abstract

An efficient and clean synthesis of 3-amino 2*H*-pyrazoles has been described by reaction of β-keto nitrile with hydrazine in the presence of methanesulphonic acid under solvent and solvent free conditions.
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Keywords: β-Keto nitrile; Hydrazine; 3-Amino 2*H*-pyrazoles; Methanesulphonic acid; Solvent and solvent free conditions

The synthesis of pyrazoles, in particular 3-amino 2*H*-pyrazoles is of very interest as they possess antihypertensive [1], antibacterial [2], anti-inflammatory muscle relaxant [3,4], and inhibitors of cyclin-dependent kinases (CDK) such as CDK2/cycling A–E [5]. They are also potent and selective aurora kinase inhibitors [6,7]. The 3-amino 2*H*-pyrazoles also have industrial appliance for the inhibition of corrosion on metals like Zn, Cu, Al and Brass [8]. Several methods have been reported in literature for the preparation of 3-amino 2*H*-pyrazoles [1–11]. However, most of these procedures suffers from serious limitations such as longer reaction time (8–72 h) with low yield, use of toxic organic solvents as reaction medium, special apparatus and harsh conditions. In the case of synthesis of 3-amino 2*H*-pyrazoles, we thought that there is scope for further innovation towards short reaction times, mild reaction conditions and better yields. We report here an efficient and facile method for the synthesis of 3-amino 2*H*-pyrazoles by the reaction of β-keto nitriles and hydrazines in the presence of methanesulphonic acid under solvent and solvent free conditions.

In recent years, organic reactions carried out in the absence of solvent have been attracting attention of chemists due to ease of processing and eco-friendly in nature. The methanesulphonic acid has proven to be useful for various transformations [12], also it should be noted that methanesulphonic acid is cheap, commercially available in its anhydrous forms, environmentally benign, easy to handle and readily biodegradable [13]. It is considered to be a natural product and is part of the natural cycle [14].

As we are interested to prepare large number of pyrazoles, we followed literature procedure by reacting benzoylacetonitrile, i.e. β-keto nitrile [15,16] with 4-hydrazino benzoic acid refluxing in absolute ethanol for 10–12 h (10–48 h varies from substrate to substrate) to yield corresponding 3-amino 2*H*-pyrazole in (<70%) yield. However, when we carried out this reaction by adding catalytic amounts of methanesulphonic acid (10 mol%) to the reaction mixture, we found that the reaction is completed in 45 min with nearly 100% conversion. At this stage we used different acid catalysts such as $FeCl_3$, $Bi(OTf)_3$, $ZrCl_4$, $La(NO_3)_3$, and *p*-TSA. We found that methanesulphonic acid and *p*-TSA are to be most effective catalysts in terms of reaction time as well as yield (>95) (Table 1), while other catalysts formed the products with varying yields (0–30%). Also it has been observed that ethanol is the best solvent for carrying this reaction using methanesulphonic acid (10 mol%) as an acid catalyst (Table 2). Further, increasing the amount of methanesulphonic acid (10 mol% to 1 equiv.) did not affect the rate of the reaction as well as yield.

We further investigated the reaction conditions to improve the reaction time. It has been found that, β-keto nitrile **1** (1 mmol) and hydrazine **2** (1 mmol) react very rapidly (<10 min) to give 3-amino 2*H*-pyrazoles using 1 equiv. of methanesulphonic acid under solvent free conditions at 80 °C (Scheme 1) (Table 3, method B). The experimental procedure for this reaction is

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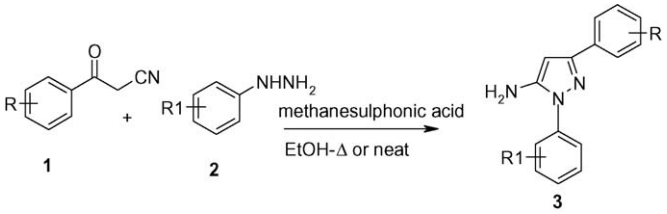
Table 1
Screening of different catalysts on the reaction of benzoylacetonitrile and 4-hydrazino benzoic acid at refluxing temperature in ethyl alcohol

Entry	Catalyst	Time	Yield (%)
1	Methanesulphonic acid	45 min	95
2	*p*-TSA	45 min	95
3	$ZrCl_4$	2 h	30
4	$La(NO_3)_3$	2 h	Trace
5	$FeCl_3$	2 h	Trace
6	$Bi(OTf)_3$	2 h	Trace

Table 2
Solvent effect on the reaction of benzoylacetonitrile and 4-hydrazino benzoic acid catalyzed by methanesulphonic acid at refluxing temperature

Entry	Solvent	Time	Yield (%)
1	EtOH	45 min	95
2	CH_3CN	45 min	93
3	MeOH	2 h	40
4	C_6H_6	2 h	Trace
5	$CHCl_3$	2 h	Trace
6	DCM	2 h	Trace



Scheme 1.

remarkably simple and requires no solvent or inert atmosphere. In many cases it has been noticed, if β-keto nitrile **1** and hydrazine **2** refluxed in ethanol with out adding methanesulphonic acid, the reaction was incomplete and uncyclized product **4** was isolated along with trace amounts of pyrazole (Scheme 2). It has been observed that in the preparation of pyrazoles **3i** and **3n** (Table 3, entries i and n), acids were obtained in method A and esters were obtained in method B, respectively.

In summary, highly efficient and facile methods for the synthesis of 3-amino 2*H*-pyrazole have been developed by the reaction of hydrazines with β-keto nitriles catalyzed by methanesulphonic acid in ethanol (method A) and in solvent free conditions (method B).

1. Experimental

1.1. Typical experimental procedure (method A)

To solution of β-keto nitrile (10 mmol), and hydrazine (10 mmol) in ethanol (50 mL) was added methanesulphonic acid (10 mol%) and stirred at refluxing temperature for the appropriate time (Table 3, method A). After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure to give crude product. To this crude concentrate, ethyl acetate/hexane (1:1) (10 mL) was added and the suspension was stirred for 5 min. The resulting precipitate was filtered. The crude 3-amino 2*H*-pyrazole was purified by crystallization from EtOH or by silica gel chromatography.

1.2. Typical experimental procedure (method B)

To a mixture of β-keto nitrile (10 mmol), and hydrazine (10 mmol) was added methanesulphonic acid (10 mmol) and stirred at 80 °C for appropriate time (Table 3, method B). After completion of the reaction as monitored on TLC, water was added and extracted into ethyl acetate. The organic layer was dried over anhydrous sodium sulphate, concentrated under reduced pressure to give crude 3-amino 2*H*-pyrazole. The crude product was crystallized either from ethanol or purified by silica gel column chromatography.

3a: IR (KBr, cm^{-1}): 3418, 1618, 1509, 1009, 762, 707 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 1.25$ (s, 9H), 5.85 (s, 1H). EIMS: *m/z*, 139 (M^+).

3b: IR (KBr, cm^{-1}): 3420, 1620, 1520, 750 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 2.26$ (s, 3H), 4.75 (br s, 2H), 7.40 (s, 5H). EIMS: *m/z*, 173 (M^+).

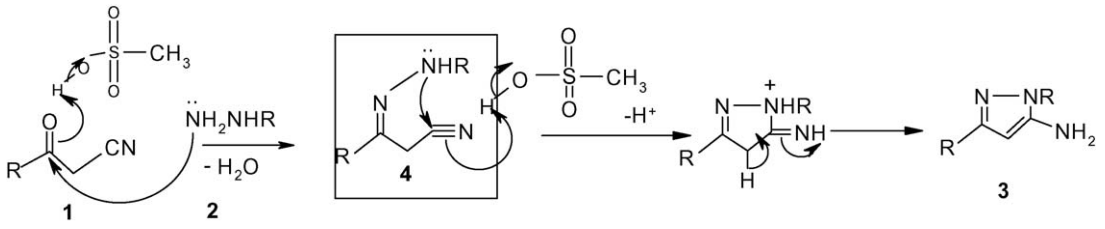
3c: IR (KBr, cm^{-1}): 3415, 1618, 1124, 613 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 4.25$ (br s, 2H), 5.75 (s, 1H), 7.30–7.50 (m, 5H). EIMS: *m/z*, 159 (M^+).

3d: IR (KBr, cm^{-1}): 3448, 1636 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 5.95$ (s, 1H), 7.45 (d, 2H, $J = 8.25$ Hz), 7.75 (d, 2H, $J = 8.25$ Hz). EIMS: *m/z*, 193/195 ($M^+/M^+ + 2$).

3e: IR (KBr, cm^{-1}): 3413, 1618, 1511, 1108, 613 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 2.65$ (s, 3H), 5.72 (s, 1H), 7.25 (d, 2H, $J = 8.2$ Hz), 7.35 (d, 2H, $J = 8.2$ Hz). EIMS: *m/z*, 173 (M^+).

3f: IR (KBr, cm^{-1}): 3415, 1694, 1615, 1179, 616 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 5.68$ (s, 1H), 6.41 (s, 1H), 6.59 (s, 1H), 7.4 (s, 1H). EIMS: *m/z*, 149 (M^+).

3g: IR (KBr, cm^{-1}): 3414, 1616, 1091 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 6.60$ (s, 1H), 7.40 (m, 5H), 7.8



Scheme 2. Proposed mechanism.

Table 3
Synthesis of 3-amino 2*H*-pyrazole catalyzed by methanesulphonic acid under solvent and solvent free conditions[a]

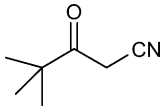
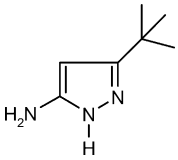
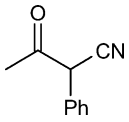
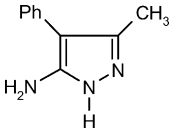
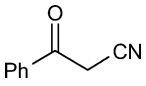
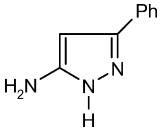
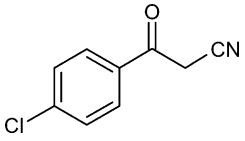
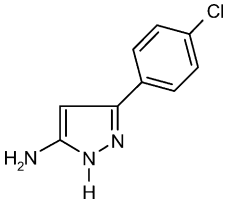
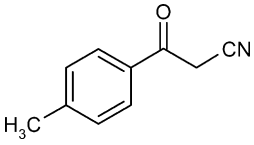
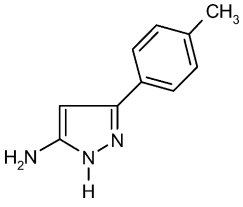
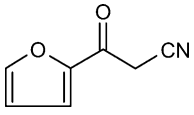
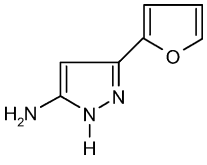
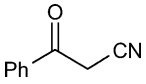
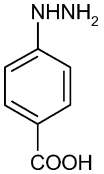
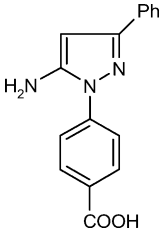
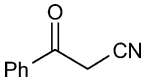
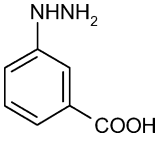
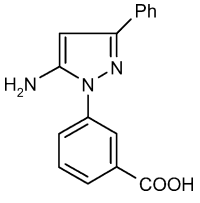
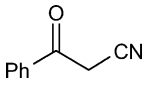
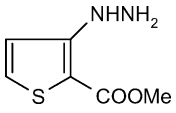
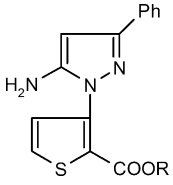
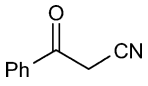
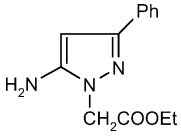
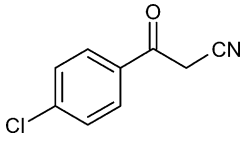
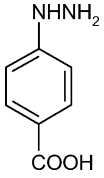
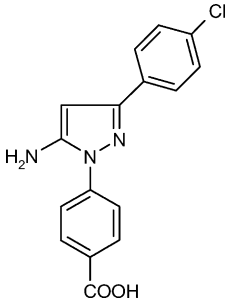
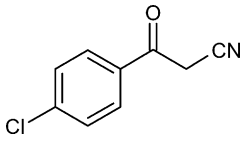
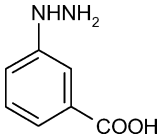
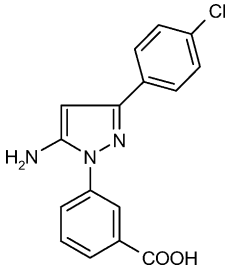
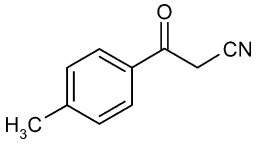
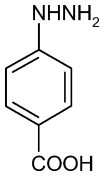
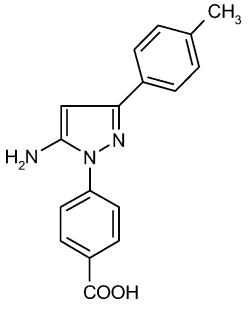
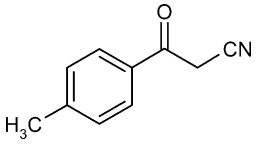
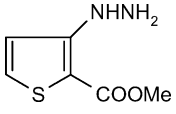
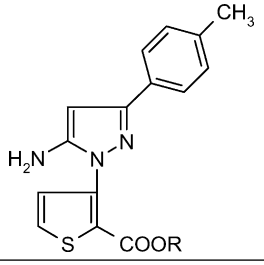
Entry	β-Keto nitrile	Hydrazine	Product	Method A		Method B	
				Time (min)	Yield (%)	Time (min)	Yield (%)
a		$NH_2NH_2H_2O$		45	95	05	95
b		$NH_2NH_2H_2O$		30	96	05	90
c		$NH_2NH_2H_2O$		30	95	05	92
d		$NH_2NH_2H_2O$		30	95	05	98
e		$NH_2NH_2H_2O$		30	95	05	96
f		$NH_2NH_2H_2O$		30	95	05	95
g				30	98	05	98
h				45	90	08	95

Table 3 (*Continued*)

Entry	β-Keto nitrile	Hydrazine	Product	Method A		Method B	
				Time (min)	Yield (%)	Time (min)	Yield (%)
i				30	97 R=H	05	98 R=Me
j		NH_2NHCH_2COOEt		30	95	05	96
k				30	97	05	98
l				30	95	05	92
m				30	96	05	98
n				30	98 R=H	05	98 R=Me

[a] Isolated yields after column chromatography/crystallization and all products gave satisfactory spectral and analytical data.

(d, 2H, $J = 8.5$ Hz), 8.40 (d, 2H, $J = 8.5$ Hz). EIMS: *m/z*, 279 (M^+).

3h: IR (KBr, cm^{-1}): 3414, 1617, 1383, 618 cm^{-1}. ^1H NMR (200 MHz, DMSI + $CDCl_3$): $\delta = 5.90$ (s, 1H), 7.15 (m, 5H), 7.35 (d, 1H, $J = 8.15$ Hz), 7.60 (t, 1H, $J = 3.15$ Hz), 7.85 (d, 1H, $J = 8.25$ Hz), 7.9 (d, 1H, $J = 8.15$ Hz), 8.30 (s, 1H). EIMS: *m/z*, 279 (M^+).

3i (R=H): IR (KBr, cm^{-1}): 3415, 1618, 1285, 761 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 6.25$ (s, 1H), 7.40 (m, 5H), 7.7 (d, 1H, $J = 8.25$ Hz), 8.05 (d, 1H, $J = 8.25$ Hz). EIMS: *m/z*, 285 (M^+).

3j: IR (KBr, cm^{-1}): 3415, 1657, 1615, 1384, 1121, 758 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 1.25$ (t, 3H, $J = 6.5$ Hz), 4.25 (q, 2H, $J = 6.5$ Hz), 4.92 (s, 2H), 5.85 (s, 1H), 7.45–7.50 (m, 5H). EIMS: *m/z*, 245 (M^+).

3k: IR (KBr, cm^{-1}): 3416, 1650, 1384, 1120, 758 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 6.02$ (s, 1H), 7.15 (d, 2H, $J = 8.15$ Hz), 7.35 (d, 2H, $J = 8.23$ Hz), 7.60 (d, 2H, $J = 8.15$ Hz), 8.10 (d, 2H, $J = 8.23$ Hz). EIMS: *m/z*, 313/315 ($M^+/M^+ + 2$).

3l: IR (KBr, cm^{-1}): 3415, 1650, 1090 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 6.81$ (s, 1H), 7.40 (d, 2H, $J = 8.15$ Hz), 7.60 (t, 1H, $J = 3$ Hz), 7.80 (d, 3H, $J = 8.25$ Hz), 8.10 (d, 1H, $J = 8.25$ Hz), 8.30 (s, 1H), 9.93 (s, 1H). EIMS: *m/z*, 313/315 ($M^+/M^+ + 2$).

3m: IR (KBr, cm^{-1}): 3415, 1617, 1384, 764, 619 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 2.37$ (s, 3H), 3.75 (br s, 2H), 7.1 (d, 2H, $J = 8.22$ Hz), 7.40 (d, 2H, $J = 8.15$ Hz), 7.7 (d, 2H, $J = 8.15$ Hz), 8.0 (d, 2H, $J = 8.22$ Hz). EIMS: *m/z*, 293 (M^+).

3n (R=H): IR (KBr, cm^{-1}): 3415, 1618, 1384, 1216, 1047, 816, 619 cm^{-1}. ^1H NMR (200 MHz, DMSO + $CDCl_3$): $\delta = 2.65$ (s, 3H), 6.25 (s, 1H), 7.10 (d, 2H, $J = 8.25$ Hz), 7.60 (d, 2H, $J = 8.25$), 7.70 (d, 1H, $J = 8.15$ Hz), 8.1 (d, 1H, $J = 8.15$ Hz). EIMS: *m/z*, 299 (M^+).

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