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A simple and efficient synthesis of pyrazoles in water

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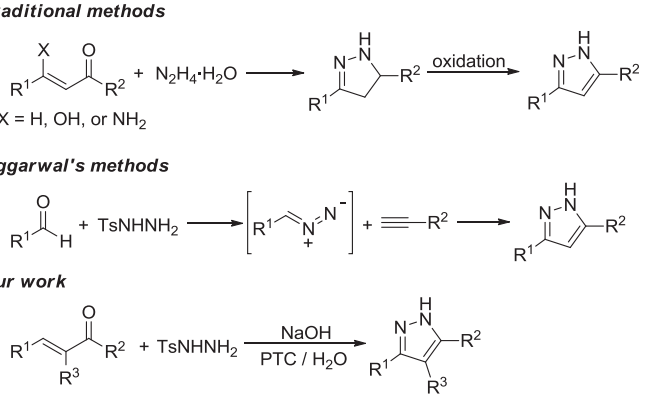
ABSTRACT

A simple, highly efficient, and environmentally friendly method for the synthesis of substituted 1*H*-pyrazoles by one-pot condensation reaction of α,β-unsaturated carbonyl compounds with tosyl hydrazide in water was developed. The reaction system exhibited tolerance with various functional groups, Aromatic moiety with both electron-rich and electron-deficient substituents could give desired products in good to excellent yields.

1. Introduction

Pyrazoles are well known five-membered nitrogen-containing heterocyclic compounds possessing diverse bioactivities, such as analgesic agent, platelet aggregation inhibitors, and nonsteroidal anti-inflammatory agents, thus these compounds are widely used in the development of drug research[1] and agriculture.[2] Consequently, pyrazoles have attracted much attention, and various procedures for their syntheses have been developed.[3]

As reported in the literature, the synthesis methods toward substituted pyrazoles include: (a) Condensation of α,β-unsaturated carbonyl compounds with hydrazines, which is used as a major strategy.[4] However, these reactions often result in a mixture of regioisomeric 4,5-dihydro-1*H*-pyrazoles that need to be further oxidized to corresponding pyrazoles (Scheme 1). (b) 1,3-Dipolar cycloadditions of diazo compounds onto triple bonds,[5] whereas diazo compounds were known to be toxic and potentially explosive. (c) Pyrazoles could be formed through the nucleophilic attack of hydrazines to chromones, flavones, or isoxazoles.[6] However, these special substrate sources have limited application of this method. Of these approaches, hydrazine hydrate is a major nitrogen source for the synthesis of 1*H*-pyrazoles, and a large excess of hydrazine hydrate was required for most of these reactions. In 2003, Aggarwal and co-workers have reported a convenient one-pot procedure for the preparation of pyrazoles by 1,3-dipolar cycloaddition (Scheme 1).[7] In their studies, only 1 equiv of tosyl hydrazide with substrate aldehyde was used as nitrogen source. Nevertheless, only aldehyde substrates were reported, and moderate yields were obtained in this reaction.



Scheme 1. Methods toward the preparation of substituted pyrazoles.

Considering the requirement of green chemistry, the use of water as solvent in place of organic solvent led to remarkable progress in the development of organic synthesis due to the low cost, safety, and environmental benignity.[8] Herein, we report a one-pot condensation reaction of α,β-unsaturated carbonyl compounds with tosyl hydrazide by using water as the sole reaction medium (Scheme 1), and a wide variety of substituted pyrazoles were obtained in good to excellent yields.

2. Results and discussion

For initial optimization of the reaction conditions, the condensation between benzylidenacetone (**1a**) and tosyl hydrazide (**2**) was selected as the model reaction system, and the results are summarized in Table 1. Initially, we found that the desired product

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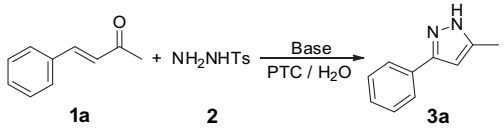
could be obtained in 47% yield with NaOH as base, and no product was detected in the absence of base (entries 1 and 2). Addition of $(n\text{-Bu})_4NBr$ as phase transfer catalyst (PTC) to the reaction system led to dramatically increased yields (entries 3–5). After the screening of PTC amounts on a small scale, 1.5 equiv of $(n\text{-Bu})_4NBr$ was found to be the best amount for the reaction, in which 94% yield was obtained (entry 4). Comparison among PTCs with different anions indicated that $(n\text{-Bu})_4NBr$ is superior to others (entries 4, 6–7). A range of bases including NaOH, KOH, K_3PO_4, *t*-BuOK, and K_2CO_3 were then screened, and NaOH was found to be most suitable (entries 4, 8–11). The reaction was also carried out under nitrogen atmosphere, and same yield was found, indicating that oxygen is not necessary for this reaction (entry 12).

The substrate scope was subsequently investigated under the optimized conditions. Table 2 summarizes the results of condensation reactions between a variety of substituted benzylidenacetone and tosyl hydrazide mediated by NaOH in water. Substituted benzylidenacetone with both electron-rich and electron-deficient substituents could afford the corresponding pyrazoles in good to excellent yields, and most of them were higher than those from literature in different methods.[4-7] It is worth mentioning that *o*-hydroxyphenylpyrazole, which is usually be prepared by treatment of chromone with hydrazines[6] and widely used as ultraviolet stabilizers, analytical reagents, and analgesic agents,[9] could also be formed smoothly in moderate yield (entry 6), indicating good substituent tolerance of the synthetic method.

Table 1
Optomization of the reaction conditions[a]



1a 2 3a

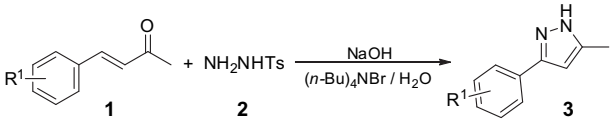
Entry	Base	PTC	Yield[b] (%)
1	—	—	NR
2	NaOH	—	47
3[c]	NaOH	$(n\text{-Bu})_4NBr$	74
4	NaOH	$(n\text{-Bu})_4NBr$	94
5[d]	NaOH	$(n\text{-Bu})_4NBr$	79
6	NaOH	$(n\text{-Bu})_4NCl$	83
7	NaOH	$(n\text{-Bu})_4NI$	76
8	KOH	$(n\text{-Bu})_4NBr$	60
9	K_3PO_4	$(n\text{-Bu})_4NBr$	75
10	*t*-BuOK	$(n\text{-Bu})_4NBr$	39
11	K_2CO_3	$(n\text{-Bu})_4NBr$	35
12[e]	NaOH	$(n\text{-Bu})_4NBr$	92

[a] Reaction conditions: **1a** (0.2 mmol), **2** (0.24 mmol), base (1.5 equiv), PTC (1.5 equiv), H_2O (2 mL), 80 °C, 10 h, under air.
[b] Isolated yields.
[c] $(n\text{-Bu})_4NBr$ (1 equiv).
[d] $(n\text{-Bu})_4NBr$ (2 equiv).
[e] Under N_2.

Subsequently, reactions of some others substituted α,β-unsaturated carbonyl compounds with tosyl hydrazide were investigated. Table 3 summarizes the results. Various substituted cinnamaldehyde could give target pyrazoles through the same reaction with excellent yields (**5a**–**d**). Chalcone was also investigated, and product **5e** was obtained in low yield. We speculated that this result might be ascribed to the difficulty of chalcone to form tosyl hydrazone. Tetrahydroindazole could also be synthesized in good yield by this method (**5g**). Several α,β-unsaturated carbonyl compounds with both electron-rich and electron-deficient heteroarenes can also be successfully applied to this reaction (**5h**–**k**).

To demonstrate the practicality of the present approach, a gram-scale synthesis of the 5-methyl-3-phenyl-1*H*-pyrazole was performed under the optimized conditions. As shown in Scheme 2,

Table 2
Condensation reactions between a variety of substituted benzylidenacetone and tosyl hydrazide[a]

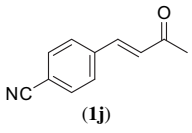
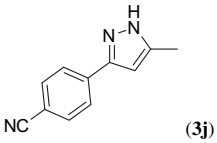
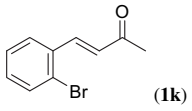
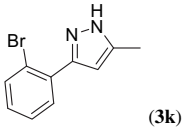
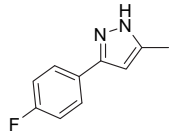
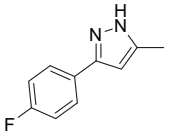


1 2 3

Entry	R^1	Product	Yield[b] (%)
1		(**1a**) (**3a**)	94
2	MeO	(**1b**) (**3b**)	87
3	Me	(**1c**) (**3c**)	88
4	Cl	(**1d**) (**3d**)	82
5	O_2N	(**1e**) (**3e**)	82
6	OH	(**1f**) (**3f**)	69
7	F_3C	(**1g**) (**3g**)	93
8	Br	(**1h**) (**3h**)	96
9	Cl	(**1i**) (**3i**)	94

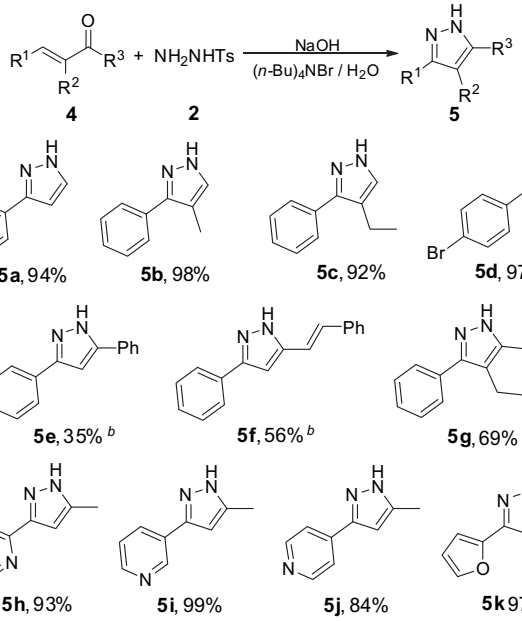
(*continued on next page*)

Table 2 (*continued*)

Entry	R^1	Product	Yield[b] (%)
10	 (**1j**)	 (**3j**)	99
11	 (**1k**)	 (**3k**)	96
12	 (**1l**)	 (**3l**)	99

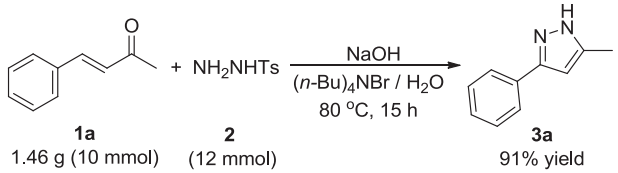
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), NaOH (1.5 equiv), $(n\text{-Bu})_4NBr$ (1.5 equiv), H_2O (2 mL), 80 °C, 10 h, under air.
[b] Isolated yields.

Table 3
Condensation reactions between substituted α,β-unsaturated carbonyl compounds and tosyl hydrazide[a]



[a]Reaction conditions: **1** (0.5 mmol), **2** (0.6 mmol), NaOH (1.5 equiv), $(n\text{-Bu})_4NBr$ (1.5 equiv), H_2O (2 mL), 80 °C, 10 h, under air, all yields given are isolated yields.
[b]NaOH (3 equiv), 20 h.

upon treatment of 10 mmol of starting materials, product **3a** was provided in 91% yield.



Scheme 2. Gram-scale reactions of benzylidenacetone and tosyl hydrazide. Reaction conditions: **1a** (10 mmol), **2** (12 mmol), NaOH (1.5 equiv), $(n\text{-Bu})_4NBr$ (1.5 equiv), H_2O (50 mL), 80 °C, 15 h, under air, isolated yield.

3. Conclusion

In conclusion, we have developed a simple, highly efficient, and environmentally friendly method for the synthesis of substituted 1*H*-pyrazoles in water. The reaction system exhibits tolerance with various functional groups, and gives desired product in good to excellent yields. Moreover, the present reaction process provides a potential for the large-scale synthesis of substituted 1*H*-pyrazoles. Further applications of this methodology are now in progress.

4. Experimental

4.1. General

^1H NMR, ^{13}C NMR spectra were measured on a Bruker AM400 NMR spectrometer (400 MHz or 100 MHz, respectively) with $CDCl_3$ as solvent and recorded in parts per million relative to internal tetramethylsilane standard. Mass spectroscopy data of the product was collected on an Agilent 6890-5973N GCMS-EI instrument. ESI-MS spectral data were recorded on a Finnigan LCQDECA mass spectrometer. Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Solvents were freshly distilled prior to use.

4.2. General procedure for the substituted benzylidenacetone

To a solution of aldehyde **6** (5 mmol) in acetone (12.5 mL) was added amine salt **7** (1 mmol, 201.14 mg). The reaction mixture was stirred at 75 °C in a sealed vial. After stirring at this temperature for 10 h, the reaction mixture was cooled to room temperature, saturated $NaHCO_3$ solution and ethyl acetate was added. After phase separation the aqueous phase was extracted three times with ethyl acetate and the organic layer was dried over sodium sulfate and concentrated in vacuo to give mostly analytical pure products. If necessary the crude product was purified by column chromatography (ethyl acetate/hexane).

4.3. General procedure for the substituted benzylidenacetone

A Schlenk tube with a magnetic stir bar charged with α,β-unsaturated carbonyl compounds (0.5 mmol, 1 equiv), tosyl hydrazide (0.6 mmol, 1.2 equiv), NaOH (1.5 equiv), $(n\text{-Bu})_4NBr$ (1.5 equiv). The reaction vessel was placed in an 80 °C oil bath, and then stirring at this temperature for 10 h. The reaction mixture was then allowed to cool to ambient temperature, and diluted with 20 mL of ethyl acetate, and washed with brine (15 mL), water (15 mL), and then the organic layer was dried over Na_2SO_4. After concentrated in vacuo, the crude product was purified by column chromatography. The identity and purity of the known product was confirmed by ^1H NMR, ^{13}C NMR, and GC-MS.

Compound **3a**: White solid, ^1H NMR (400 MHz, $CDCl_3$) δ=7.71–7.68 (m, 2H), 7.36–7.33 (d, 2H), 7.33–7.38 (m, 1H), 6.31 (s, 1H), 2.23 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$), δ=148.91, 142.14, 131.53, 127.63, 126.74, 124.72, 101.02, 10.61. MS (EI) *m*/*z* (%) 158 (M^+, 100), 128 (8), 77 (4). HRMS (ESI): *m*/*z*=159.0925 $[M+H]^+$.

Compound **5a**: Colorless oil, ^1H NMR (400 MHz, $CDCl_3$) δ=9.23 (s, 1H), 7.79–7.76 (m, 2H), 7.62–7.61 (d, 1H), 7.43–7.39 (m, 2H), 7.36–7.43 (d, 1H), 6.63–6.62 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$), δ=149.10, 133.29, 132.14, 128.81, 128.05, 125.86, 102.65. MS (EI) *m*/*z* (%) 144 (M^+, 100), 115 (12), 90 (6), 77 (6). HRMS (ESI): *m*/*z*=145.0762 $[M+H]^+$.

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Supplementary data

Detailed experimental procedures and compound characterization. Supplementary data related to this article can be found in the online version. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.09.074.

References and notes

1. Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Pyrazoles as Drugs: Facts and Fantasies In. *Targets in Heterocyclic Systems*; Attanasi, O. A., Spinelli, D., Eds.; The Royal Society of Chemistry: Cambridge, U.K., 2002; Vol. 6, pp 52–98.
2. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles Structure, Reactions, Synthesis and Application* (Translated by H. Suschitzky and J. Suschitzky); Georg Thieme: Stuttgart, 1995; 184.
3. (a) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F., Eds.; Pergamon: Oxford, 1996; Vol. 3, pp 1–75; (b) Palacios, F.; Retana, A. M. O.; Pagalday, J. *Tetrahedron* **1999**, *55*, 14451; (c) Oliveira, R.; Sanmartin, R.; Domínguez, E. *J. Org. Chem.* **2000**, *65*, 7010; (d) Recnik, S.; Svete, J.; Stanovnik, B. *Heterocycles* **2002**, *57*, 2091.
4. (a) Huang, Y. R.; Katzenellenbogen, J. A. *Org. Lett.* **2000**, *2*, 2833; (b) Katritzky, A. R.; Wang, M.; Zhang, S.; Voronkov, M. V. *J. Org. Chem.* **2001**, *66*, 6787; (c) Yoshihara, N.; Hasegawa, T.; Hasegawa, S. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 719; (d) Kim, J.; Song, H.; Park, S. B. *Eur. J. Org. Chem.* **2010**, 3815; (e) Chimichi, S.; Boccalini, M.; Matteucci, A. *Tetrahedron* **2008**, *64*, 9275; (f) Schmidt, A.; Habeck, T.; Kindermann, M. K.; Nieger, M. *J. Org. Chem.* **2003**, *68*, 5977; (g) Chun, Y. S.; Lee, K. K.; Ko, Y. O.; Shin, H.; Lee, S. *Chem. Commun.* **2008**, 5098.
5. Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*; John: New York, NY, 1984; Vol. 1.
6. (a) Elmaged, A.; Sammour, A. *J. Org. Chem.* **1960**, *25*, 1458; (b) Lévai, A.; Silva, A. M. S.; Cavaleiro, J. A. S.; Alkorta, I.; Elguero, J.; Jekő, J. *Eur. J. Org. Chem.* **2006**, 2825; (c) Sviridov, S. I.; Vasilév, A. A.; Shorshnev, S. V. *Tetrahedron* **2007**, *63*, 12195.
7. Aggarwal, V. K.; Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381.
8. (a) *Organic Synthesis in Water*; Grieco, P. A., Ed.; Blackie A & P: London, 1998; (b) Siskin, M.; Katritzky, A. R. *Chem. Rev.* **2001**, *101*, 825; (c) Lindstrçm, U. M. *Chem. Rev.* **2002**, *102*, 2751; (d) Kobayahi, S.; Manabe, K. *Acc. Chem. Res.* **2002**, *35*, 209; (e) Akiya, N.; Savage, P. E. *Chem. Rev.* **2002**, *102*, 2725; (f) DeSimone, J. M. *Science* **2002**, *297*, 799; (g) Poliakoff, M.; Fitzpatrick, J. M.; Farren, T. R.; Anastas, P. T. *Science* **2002**, *297*, 807; (h) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095; (i) Minakata, S.; Komatsu, M. *Chem. Rev.* **2008**, *108*, 825; (j) Chanda, A.; Fokin, V. V. *Chem. Rev.* **2009**, *109*, 725.
9. (a) Catalán, J.; Fabero, F.; Claramunt, R. M.; Maria, M. D. S.; Foces-Foces, M. C.; Cano, F. H.; Martinez-Ripoll, M.; Elguero, J.; Sastre, R. *J. Am. Chem. Soc.* **1992**, *114*, 5039; (b) Ahmad, R.; Ahmad, N.; Zia-Ul-Haq, M.; Wahid, A. *J. Chem. Soc. Pak.* **1996**, *18*, 38; (c) Takagi, K.; Tanaka, M.; Murakami, Y.; Morita, H.; Aotsuka, T. *Eur. J. Med. Chem. Chim. Ther.* **1986**, *21*, 65.