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PTSA-catalyzed Mannich-type–cyclization–oxidation tandem reactions: one-pot synthesis of 1,3,5-substituted pyrazoles from aldehydes, hydrazines and alkynes†

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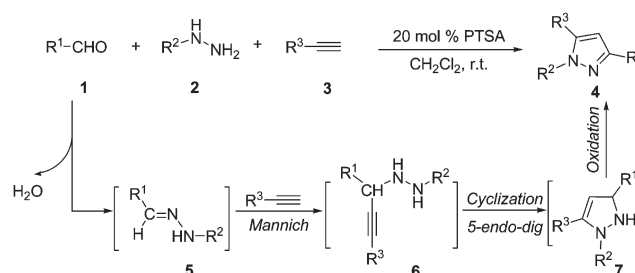
A convenient one-pot Mannich-type–cyclization–oxidation tandem process has been developed for the synthesis of 1,3,5-trisubstituted pyrazoles derivatives from aldehydes, hydrazines and alkynes using *p*-toluenesulfonic acid monohydrate (PTSA) as a multifunctional catalyst. This method provides a flexible and rapid route to 1,3,5-trisubstituted pyrazoles.

The introduction of new methods for the efficient assembly of functionalized intermediates from simple precursors is necessitated due to the ever-increasing complexity of the organic target molecules. An appealing strategy toward this end is the development of novel tandem reactions, whereby sequential transformations can be performed without isolation or purification of intermediates in a single-pot.¹ An especially promising area of research is finding and utilizing a single catalyst that promotes more than one transformation in a selective manner.²

Attracting interest for the past several decades, the field of pyrazole synthesis is continuously and rapidly developing. Conventional approaches for the synthesis of pyrazoles involve either the construction of two C–N bonds by the condensation of hydrazines with 1,3-dicarbonyl compounds or their 1,3-dielectrophilic equivalents or the generation of one C–N bond and one C–C bond by the intermolecular 1,3-dipolar cycloaddition of diazoalkanes and nitrilimines with alkenes and alkynes.³ Each of these methods has its own scope and efficiency limitations. Therefore, the development of a tandem process for the one-pot synthesis of substituted pyrazoles directly from simple and readily available substrates is of significance. Herein, we wish to report a highly efficient Mannich-type–cyclization–oxidation tandem reaction for the synthesis of 1,3,5-trisubstituted pyrazoles directly from aldehydes, hydrazines and alkynes using PTSA as a catalyst.^{4,5} The process outlined in Scheme 1. PTSA acts as a

multifunctional catalyst and effectively catalyzes the three reaction processes in a single reaction vessel.

To identify the optimal conditions for the tandem process, a series of catalysts and solvents were screened (Table 1). Initially,



Scheme 1 Synthesis of 1,3,5-trisubstituted pyrazoles from alkynes, aldehydes and hydrazines.

Table 1 Optimization of the formation of 1,3,5-trisubstituted pyrazoles^a

$\text{Ph-CHO} + \text{Ph-NH-NH}_2 + \text{Ph-C}\equiv\text{CH} \xrightarrow[\text{Solvent, r.t.}]{\text{Catalyst}} \text{Ph-pyrazole-Ph} \quad \mathbf{4aaa}$			
Entry	Catalyst	Solvent	Yield ^b (%)
1	PTSA (10 mol%)	CH ₃ COOH	60
2	PTSA (20 mol%)	CH ₃ COOH	83
3	PTSA (50 mol%)	CH ₃ COOH	86
4	TFA (20 mol%)	CH ₃ COOH	30
5	TfOH (20 mol%)	CH ₃ COOH	70
6	Oxalic acid (20 mol%)	CH ₃ COOH	10
7	InCl ₃ (20 mol%)	CH ₃ COOH	0
8	Cu(OTf) ₂ (20 mol%)	CH ₃ COOH	0
9	PTSA (20 mol%)	HCOOH	40
10 ^c	PTSA (20 mol%)	CH ₂ Cl ₂	86
11 ^d	PTSA (20 mol%)	CH ₃ NO ₂	65
12	PTSA (20 mol%)	H ₂ O	0

^a Reaction conditions: benzaldehyde **1a** (0.5 mmol), phenylhydrazine **2a** (0.5 mmol), phenylacetylene **3a** (0.6 mmol), and catalyst in solvent (2 ml), at room temperature for 24 h. ^b Isolated yield of pure product based on **1a**. ^c The reaction time was shortened to 8 h. ^d The reaction time was prolonged to 2 days.

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benzaldehyde **1a** (0.5 mmol), phenylhydrazine **2a** (0.5 mmol), and phenylacetylene **3a** (0.6 mmol) in the presence of 10 mol% PTSA in CH₃COOH at room temperature for 24 h gave the substituted pyrazole **4aaa** in 60% yield (Table 1, entry 1). The yield of **4aaa** was increased to 83% when the amount of PTSA was increased to 20 mol% (Table 1, entry 2). However, no further improvement in the yield of **4aaa** could be achieved, when the amount of PTSA was increased up to 50 mol% (Table 1, entry 3). Trifluoromethanesulfonic acid (TfOH) also smoothly promoted the tandem reactions, albeit the yield of **4aaa** decreased to 70% (Table 1, entry 5). Unfortunately, the tandem reactions were obviously restrained when using trifluoroacetic acid (TFA) or oxalic acid as a catalyst (Table 1, entries 4 and 6). Lewis acid catalysts, such as Cu(OTf)₂ and InCl₃ did not promote the reaction (Table 1, entries 7 and 8). The choice of the solvent also played a crucial role. Further optimization led to the discovery that dichloromethane (DCM) also facilitated the transformation, reducing the reaction time from 24 h to 8 h (Table 1, entry 10 vs. entry 2). In addition, the tandem process was obviously restrained when performed in HCOOH or CH₃NO₂ (Table 1, entries 9 and 11). In a solvent such as H₂O, most of the starting materials were recovered (Table 1, entry 12). Hence, it was concluded that the optimal conditions for the Mannich-type-cycloisomerization-oxidation tandem reactions involved 20 mol% PTSA in dichloromethane (DCM) at room temperature for 8 h. Furthermore, the Mannich-type-cycloisomerization-oxidation tandem reaction proceeded smoothly without exclusion of moisture or air from the reaction mixture.

With the identification of the optimal conditions in hand, the scope of the substrates was investigated, and the typical results are shown in Table 2. To our delight, various alkynes **3** bearing alkyl or aryl substituents participated well in the reaction, providing the Mannich-type-cyclization-oxidation products in good

yields. 1-Phenyl-2-trimethylsilylacetylene (R³ = Ph; R⁴ = TMS) **3b** reacted with benzaldehyde **1a** and phenylhydrazine **2a** in the presence of 20 mol% PTSA in CH₂Cl₂ affording the pyrazole **4aaa** in 45% yield, only when the reaction time was prolonged to 2 days (Table 2, entry 2). It should be noted that the trimethylsilyl group could not be tolerated under the acidic condition and had fallen off during workup. Whereas, with phenylacetylene (R³ = Ph; R⁴ = H) **3a**, the yield of product **4aaa** dramatically increased to 86% (Table 2, entry 1). Aromatic alkynes **3** having either an electron-donating or electron-withdrawing group on the benzene ring gave the corresponding pyrazoles in good yields (Table 2, entries 3–7). Amongst the alkynes **3b–3g** which were examined, alkyne **3c** (R³ = 4-MeOC₆H₄) gave the most desirable result, providing 1,3-diphenyl-5-(4-methoxyphenyl)-pyrazole **4aac** in 88% yield (Table 2, entry 3). Substrates **3d** and **3e** possessing an electron-withdrawing groups (R³ = 4-F-C₆H₄ and R³ = 4-Br-C₆H₄) on the benzene ring, smoothly furnished to the desired products **4aad** and **4aae** in 75% and 78% yield, respectively (Table 2, entries 4 and 5). Obviously, the electron-rich alkynes provided the desired products in slightly higher yields than the electron-poor alkynes along with the shorter reaction time. The reaction of 4-methyl phenylacetylene **3f** (R³ = 4-MeC₆H₄), benzaldehyde **1a** and phenylhydrazine **2a** also gave the corresponding pyrazole **4aaf** in 83% yield under the optimized conditions (Table 2, entry 6). Aromatic alkynes **3g** with a substituent at the *ortho*-position (R³ = 2-MeOC₆H₄), when treated with benzaldehyde **1a** and phenylhydrazine **2a**, also gave the corresponding pyrazole **4aag** in high yield (Table 2, entry 7). These results suggest that the position of the substituent on the benzene ring has a minor effect on the Mannich-type-cyclization-oxidation tandem reactions (Table 2, entry 7 vs. entry 3). Terminal aliphatic alkynes such as 1-hexyne **3h**, when allowed to react with benzaldehyde **1a** and phenylhydrazine **2a** led to the

Table 2 Synthesis of 1,3,5-trisubstituted pyrazoles from aldehydes, hydrazines and alkynes^a

$\text{R}^1\text{-CHO} + \text{R}^2\text{-NH-NH}_2 + \text{R}^3\text{-C}\equiv\text{C-R}^4 \xrightarrow[\text{CH}_2\text{Cl}_2, \text{ r.t. 8 h}]{20 \text{ mol \% PTSA}} \text{Pyrazole } \mathbf{4}$				
Entry	Aldehyde	Hydrazine	Alkyne	Yield ^b (%)
1	1a : R ¹ = Ph	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	86
2 ^c	1a : R ¹ = Ph	2a : R ² = Ph	3b : R ³ = Ph; R ⁴ = TMS	45
3 ^d	1a : R ¹ = Ph	2a : R ² = Ph	3c : R ³ = 4-MeOC ₆ H ₄ ; R ⁴ = H	88
4	1a : R ¹ = Ph	2a : R ² = Ph	3d : R ³ = 4-FC ₆ H ₄ ; R ⁴ = H	75
5	1a : R ¹ = Ph	2a : R ² = Ph	3e : R ³ = 4-BrC ₆ H ₄ ; R ⁴ = H	78
6	1a : R ¹ = Ph	2a : R ² = Ph	3f : R ³ = 4-MePh; R ⁴ = H	83
7 ^d	1a : R ¹ = Ph	2a : R ² = Ph	3g : R ³ = 2-MeOC ₆ H ₄ ; R ⁴ = H	82
8	1a : R ¹ = Ph	2a : R ² = Ph	3h : R ³ = <i>n</i> -Bu; R ⁴ = H	73
9 ^d	1b : R ¹ = 4-MeOC ₆ H ₄	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	85
10	1c : R ¹ = 4-MeC ₆ H ₄	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	84
11	1d : R ¹ = 4-ClC ₆ H ₄	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	78
12 ^e	1e : R ¹ = Thienyl	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	71
13	1f : R ¹ = 4-NO ₂ C ₆ H ₄	2a : R ² = Ph	3a : R ³ = Ph; R ⁴ = H	72
14	1f : R ¹ = 4-NO ₂ C ₆ H ₄	2a : R ² = Ph	3c : R ³ = 4-MeOC ₆ H ₄ ; R ⁴ = H	75
15 ^d	1a : R ¹ = Ph	2b : R ² = 4-MeOC ₆ H ₄	3d : R ³ = 4-FC ₆ H ₄ ; R ⁴ = H	78
16	1a : R ¹ = Ph	2c : R ² = 4-NO ₂ C ₆ H ₄	3a : R ³ = Ph; R ⁴ = H	63
17	1a : R ¹ = Ph	2a : R ² = Ph	3i : R ³ = Ph; R ⁴ = Ph	0

^a Reaction conditions: aldehyde **1** (0.5 mmol), hydrazine **2** (0.5 mmol), alkyne **3** (0.6 mmol), PTSA (20 mol% to **1**), CH₂Cl₂ (2 ml), at room temperature for 8 h. ^b Isolated yield of pure product based on **1**. ^c The reaction time was prolonged to 2 days. ^d The reaction was carried at 0 °C.

^e PTSA (10 mol% to **1**).

desired product **4aah** in 73% yield (Table 2, entry 8). Unfortunately, the internal alkyne **3i**, when allowed to react with benzaldehyde **1a** and phenylhydrazine **2a** failed to give the desired product (Table 2, entry 17).

Beside the above alkynes, a variety of aldehydes **1a–1f** and hydrazine **2a–2c** were studied and underwent smooth transformation affording the desired products in good yields (Table 2, entries 9–16). Among the examined aldehydes **1a–1f**, aldehydes **1b** ($R^1 = 4\text{-MeOC}_6\text{H}_4$) and **1c** ($R^1 = 4\text{-MeC}_6\text{H}_4$) gave the desired products in higher yields (Table 2, entries 9 and 10). For the reactions with other aldehydes, such as 4-chlorobenzaldehyde and 4-nitrobenzaldehyde, the corresponding pyrazoles **4** were obtained in a bit lower yields (Table 2, entries 11, 13 and 14). Additionally, aldehydes bearing a heterocyclic aromatic substituent such as 2-thiophenaldehyde ($R^1 = 2\text{-thienyl}$) treated with phenylhydrazine **2a** and phenylacetylene **3a** in the presence of 10 mol% PTSA giving the desired product **4eaa** in 71% yield (Table 2, entry 12). Moreover, substrate **2b** possessing an electron-donating group ($R^2 = 4\text{-MeOC}_6\text{H}_4$) on the benzene ring gave the desired product **4abd** in 78% yield; whereas, **2c** possessing an electron-withdrawing group ($R^2 = 4\text{-NO}_2\text{C}_6\text{H}_4$) on the benzene ring gave the desired product **4aca** in 63% yield (Table 2, entries 15 and 16). It should be noted that functional groups such as fluoro, chloro, bromo, nitro, and methoxy, are tolerated under the reaction conditions. The reaction proceeded smoothly under mild conditions and air was tolerated.

In summary, we have developed an effective Mannich-type-cyclization–oxidation tandem reaction for the synthesis of 1,3,5-substituted pyrazoles directly from readily available aldehydes, hydrazines and alkynes, using PTSA as a multifunctional catalyst. A wide range of alkynes, bearing not only aryl groups but also alkyl groups, effectively participated in the reactions. Also, a number of functionalities, such as fluoro, chloro, bromo, nitro, and methoxy, are tolerated under the reaction conditions. This reaction system can be carried out under mild conditions which give a rapid access to a variety of pyrazoles.

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