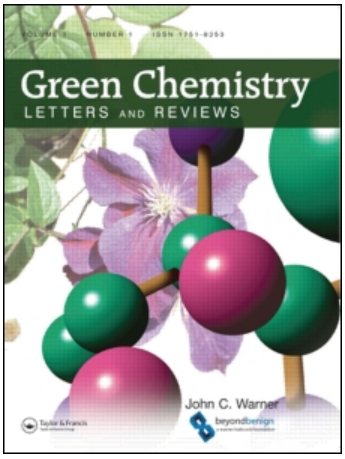

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RESEARCH LETTER

2,4,6-Trichloro[1,3,5]triazine (TCT)-catalyzed one-pot Mannich-type reaction: three component synthesis of β-amino carbonyl compounds

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Three-component Mannich-type reaction of acetophenon, aromatic aldehydes, and aromatic amines is catalyzed by 2,4,6-trichloro[1,3,5]triazine at ambient temperature in EtOH and solvent-free conditions to give various β-amino ketones in high yields.

Keywords: 2,4,6-trichloro[1,3,5]triazine (TCT); Mannich-type reaction; β-amino carbonyl compounds one-pot reaction; green chemistry

Introduction

Mannich reaction has gained popularity in synthetic chemistry over the past decades because it is one of the most important and fundamental reactions in organic chemistry, since it affords synthetically and biologically important β-amino carbonyl compounds (*1–7*). These compounds are useful building blocks for molecules with applications in pharmaceutical and material sciences (*8*). The development of new synthetic methods leading to β-amino carbonyl compounds or their derivatives has attracted much attention.

The preferred route for a Mannich reaction is to use a one-pot three-component strategy that gives a wide range of structural variations. A few one-pot procedures on the use of unmodified aldehydes or ketones have been reported in the literature using a variety of catalysts, including $Zn(OTf)_2$ (*9,10*), $H_3PW_{12}O_4$ (*11*), $ZrOCl_2{\cdot}8H_2O$ (*12*), (*s*)-serine (*13*), $Bi(OTf)_3{\cdot}4H_2O$ (*14*), sodium tetrakis(3,5-trifluoromethyl phenyl)·borate (*15*), polymer supported sulfonic acid (PS-SO_3H) (*16*), $InCl_3$ (*17*), $NbCl_5$ (*18*), silica sulfuric acid (*19*), [$RE(PFO)_3$] (*20*), Cu-nanoparticles (*21*), Tröger's base (*22*), adenine (*23*), $H_3PMo_{12}O_{40}$ (*24*), and CAN (*25*).

Most of these methods suffer from severe drawbacks including the use of large amounts of catalyst and expensive reagents or catalysts. In some instances, long reaction times, use of toxic reagents, and special efforts for catalyst preparation are the main problems.

Hence, a more efficient and practical alternative synthetic method using environmentally friendly conditions or catalysts are warranted. 2,4,6-Trichloro-[1,3,5]triazine (cyanuric chloride or TCT) is a stable, non-volatile, inexpensive, and safe reagent, which has been employed in many organic reactions (*26–31*).

Results and discussion

Herein, we report the synthesis of various β-amino carbonyls by the reaction of aryl aldehydes, aromatic amines, and acetophenone in EtOH using TCT (10% mol) as a catalyst at room temperature (Scheme 1).

To our knowledge, the direct Mannich-type reaction catalyzed by TCT has not previously been reported. In this reaction, the TCT reacted with incipient moisture and released three moles of HCl and cyanuric acid (removable by washing with water) as by-product (Scheme 2). The in situ generated HCl acted as a protic acid and catalyzed the Mannich reaction (*32*).

Our initial experiments focused on the optimization of the amount of TCT by using one equivalent of benzaldehyde, one equivalent of acetophenone, one equivalent of aniline, and variable amounts of TCT. It was observed that 10% mol of TCT effectively catalyzed the reaction and increasing the amount of TCT caused a decrease in the yield, most likely due to the formation of hydrochloric salts of the β-amino carbonyl compounds (*33*).

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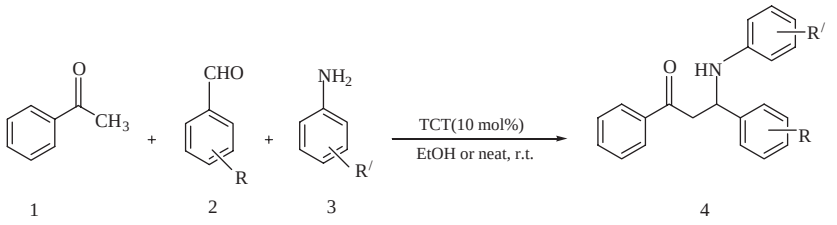


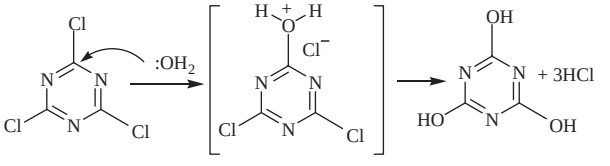
Scheme 1. The Mannich reaction using TCT.

In an effort to obtain improved yields, various solvents and solvent-free conditions were screened in the three-component reaction of benzaldehyde, acetophenone, and aniline at room temperature and results are summarized in Table 1. 1,4-Dioxane and ethanol provided excellent yields and proved to be the solvents of choice. The reaction in toluene afforded very poor yields.

We then examined the scope of the reaction by using various aromatic amines and aryl aldehydes (Table 2). Aldehydes bearing various functional groups, such as $-CH_3$, $-OMe$, $-Cl$, and $-Br$, all reacted to produce the corresponding β-amino ketones (*34,35*). The aldehydes with electron-withdrawing substituents failed to yield any desired product. Aniline rings carrying either electron-donating or electron-withdrawing substituents reacted successfully. Particularly, anilines having electron-withdrawing groups were found to be favorable. The *ortho*-substituted anilines, however, gave very low yield.

The synthesis of β-amino ketones in solvent-free conditions was another goal of this study. In the presence of 10% mol TCT under solvent-free conditions, the expected product was obtained in lower yields than the reactions were achieved in EtOH. In some entries, the isolated yields were comparable. The results are summarized in Table 2.

In summary, a concise, high-yielding three-component Mannich reaction has been described. The significant features of this procedure include: (1) high yields; (2) use of inexpensive and non-hazardous catalyst; (3) facile operations; and (4) non-toxic solvent and by-product.



Scheme 2. The reaction of TCT with H_2O to release HCl.

Experimental

The β-amino ketones were isolated and characterized by melting point, IR, and ^{1}H NMR. ^{1}H NMR spectra were recorded on Bruker Avance-300 MHz spectrometers with 7–10 mM solutions in $CDCl_3$ in the presence of tetramethylsilane as internal standard. IR spectra were recorded using a Perkin–Elmer 843 spectrometer with KBr plates. Melting points were determined on Electro thermal 9100, and are not corrected. All products are known compounds, which were identified by IR and ^{1}H NMR spectral data and their melting points were compared with those reported in literature.

General procedure for the synthesis of β*-amino carbonyl compounds*

Method A

A mixture of benzaldehyde (1.0 mmol), aniline (1.0 mmol), acetophenone (1.0 mmol), and TCT (0.018 g, 0.1 mmol) was stirred in EtOH (3 mL) at room temperature for 1 h (the reaction monitored in TLC). The reaction products were filtered to get crude product. The crude product was washed with H_2O (70°C) to remove cyanuric acid and was purified by recrystallization from EtOH. The yield was 0.29 g (98%), mp 168–170°C (lit. (*20*) mp 170–171°C).

Method B

A mixture of benzaldehyde (1.0 mmol), aniline (1.0 mmol), acetophenone (1.0 mmol), TCT (0.018 g, 0.1

Table 1. TCT-catalyzed three-component Mannich-type reaction of benzaldehyde, aniline, and acetophenone in different solvents.

Entry	Solvent	Yield (%)
1	EtOH	98
2	1,4-dioxane	90
3	THF	85
4	CH_3CN	75
5	CH_2Cl_2	50
6	Toluene	30
7	Neat	90

Table 2. TCT-catalyzed direct Mannich reaction of various aryl aldehydes and aromatic amines.

			Method A[a]	Method B[b]	
Entry	R	*R′*	Yield[c] (%)	Yield[c] (%)	MP (°C)
1	H	H	98	95	170–171 (*34, 35*)
2	4-Me	H	96	80	130–132 (*20*)
3	4-OMe	H	95	90	147–149 (*36*)
4	4-Cl	H	89	50	115–117 (*36*)
5	4-Br	H	88	55	131–132 (*19*)
6	H	3-NO_2	96	90	138–140 (*20*)
7	H	4-NO_2	97	95	177–180 (*36*)
8	4-Me	4-NO_2	95	89	161–163
9	H	4-Br	95	85	179–180
10	4-Me	4-Br	93	65	175–178
11	H	4-Me	95	60	165–167 (*36*)

[a]Reaction conditions: aromatic aldehydes (1.0 mmol), acetophenon (1.0 mmol), aromatic amines (1.0 mmol), TCT (10% mol), EtOH (1 ml), and room temperature 1–7 h.
[b]Reaction conditions: aromatic aldehydes (1.0 mmol), acetophenon (1.0 mmol), aromatic amines (1.0 mmol), wet TCT(10% mol), and room temperature 3–12 h.
[c]Isolated yield: products were confirmed by ^{1}H NMR.

mmol), and H_2O (0.3 mmol) at room temperature for 3 h (the reaction monitored in TLC). The reaction products were washed with H_2O (70°C) to remove cyanuric acid and purified by recrystallization from EtOH. The yield was 0.28 g (95%), mp 170–171°C.

New compound characterization

3-(4-Nitrophenylamino)-1-phenyl-3-p-tolylpropan-1-one

MP = 161–163°C ^{1}H NMR (300 MHz; DMSO; Me_4Si): Δ 7.97–7.90 (m, 3H), 7.76 (d, J = 7.12 Hz, 1H), 7.63 (t, J = 7.25 Hz, 1H), 7.51 (t, 2H), 7.32 (d, J = 8 Hz, 2H), 7.12 (d, J = 7.9, 2H), 6.58 (d, J = 9.22 Hz, 2H), 5.11 (d,t, br, J = 11.7, J = 1.65 Hz, 1H), 4.35 (s, 1H), 3.71 (d,d, J = 17.65, J = 9.2 Hz, 1H), 3.38 (d,d, J = 18.25, J = 6 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): Δ 197.83, 152.17, 138.23, 137.99, 137.63, 136.24, 129.74, 128.77, 128.36, 128.15, 127.73, 126.55, 112.12, 53.94, 45.54, 21.05; IR (KBr): ν_{max}/cm: 3384, 1678, 1599, 1112, 839, 763. Anal. calc. for $C_{22}H_{20}N_2O_3$: C 73.25, H 5.54, N 7.76; Found: C 73.10, H 5.75, N 7.93 (Table 2, entry 8).

3-(4-Bromophenylamino)-1,3-diphenylpropan-1-one

MP = 180–182°C ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): Δ 7.89 (d, J = 7.76 Hz, 2H), 7.59–7.54 (m, 1H), 7.47–7.40 (m, 4H), 7.35–7.19 (m, 3H), 7.16 (dd, J = 7.9, J = 1.95 Hz, 2H), 6.46 (d, J = 8.3 Hz, 2H), 4.97–4.93 (m, 1H), 3.52(d,d, J = 5, J = 16.3 Hz, 1H), 3.26 (d,d, J = 7.3, J = 17.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): Δ 198.4, 133.52, 131.83, 128.91, 128.72, 128.15, 127.58, 126.37, 115.77, 55.15, 46.0; IR (KBr): ν_{max}/cm: 3372, 1667, 1285, 703. Anal. Calc. for $C_{21}H_{18}BrNO$: C 66.31, H 4.73, N 3.68; Found: C 66.01, H 5.05, N 3.58 (Table 2, entry 9).

3-(4-Bromophenylamino)-1-phenyl-3-p-tolylpropan-1-one

MP = 175–178°C ^{1}H NMR (300 MHz; $CDCl_3$; Me_4Si): Δ 7.95 (s, 1H), 7.94 (d, J = 1.28 Hz, 1H), 7.62 (t, J = 7.27 Hz, 1H), 7.5 (t, J = 7.3 Hz, 2H), 7.3 (d, J = 7.9 Hz, 2H), 7.10–7.07 (m, 3H), 6.44–6.40 (m, 3H), 4.9 (d,t, J = 11, J = 4.7 Hz, 1H), 3.59 (d,d, J = 17, J = 8.8 Hz, 1H), 3.26 (d,d, J = 17, J = 4.54 Hz, 1H), 2.22 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): Δ 198.47, 136.11, 134.85, 129.83, 129.80, 126.63, 129.02, 128.91, 128.72, 128.15, 127.84, 120.79, 114.04, 54.42, 46.37, 21.01, 20.36. IR (KBr): ν_{max}/cm: 3333, 1665, 1293, 816. Anal. Calc. for $C_{22}H_{20}BrNO$: C 66.95, H 5.07, N 3.55; Found: C 67.01, H 5.00, N 3.76 (Table 2, entry 10).

Acknowledgements

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