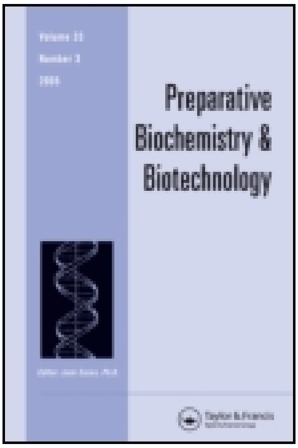

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$SnCl_4 \cdot 5H_2O$-CATALYZED SYNTHESIS OF β-AMINO CARBONYL COMPOUNDS VIA A DIRECT MANNICH-TYPE REACTION

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☐ *An efficient three-component, one-pot synthesis of* β-*amino carbonyl compounds from aromatic ketones, aromatic aldehydes, and aromatic amines using tin tetrachloride at room temperature in ethanol is described. The advantages of the new method are good yields (62–96%), simple workup, and inexpensive catalyst.*

Keywords β-amino carbonyl compounds, Mannich reaction, one-pot synthesis, tin tetrachloride

INTRODUCTION

As is well known, β-amino carbonyl compounds are important synthetic intermediates for various pharmaceuticals, natural products, and biologically attractive compounds.[1,2] Generally, β-amino carbonyl compounds are synthesized from aromatic ketones, aromatic aldehydes, and aromatic amines through the Mannich reaction catalyzed by HCl/EtOH,[3] dodecylbenzenesulfonic acid,[4] Ps-SO_3H,[5] $NbCl_5$,[6] $Re(PFO)_3$,[7] $Re(OPf)_3$,[8] ionic liquid,[9] $H_3PW_{12}O_{40}$,[10] $NaBAr_4^F$,[11] SiO_2-$OAlCl_2$,[12] QAS gemini fluorosurfactant,[13] etc. However, most of these methods suffer from drawbacks such as the use of a corrosive reagent, expensive and large amount of catalyst, harmful reaction media (fluorous solvent), and low yields. Furthermore, *ortho*-substituted aromatic amines generally gave trace or no products because of large steric hindrance effects. Hence, it was of interest to develop a more universal method for the synthesis of these products.

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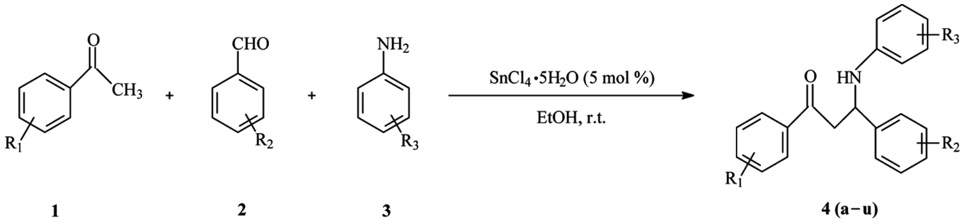

FIGURE 1 $SnCl_4 \cdot 5H_2O$-catalyzed Mannich reaction.

Recently, $SnCl_4$ has emerged as an efficient Lewis acid in promoting various organic transformations, such as aromatization,[14] heterocyclo additions,[15] coupling reactions,[16] rearrangement of epoxides,[17] oxidation,[18] and ring opening reactions.[19] The versatility of this reagent encouraged us to study its utility for the three-component Mannich-type reaction. To our knowledge, direct Mannich-type reactions catalyzed by $SnCl_4 \cdot 5H_2O$ have not been reported. Herein, we report an $SnCl_4 \cdot 5H_2O$-catalyzed three-component, one-pot Mannich-type reaction of aromatic ketones **1**, aromatic aldehydes **2**, and aromatic amines **3**, which led to the efficient synthesis of β-amino ketones **4** under mild conditions (Figure 1).

EXPERIMENTAL

Melting points were determined using RY-1 micro-melting-point apparatus. Infrared spectra were recorded on a Perkin-Elmer Spectrum GX series Fourier transform instrument. ^1H-Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-600 spectrometer in dimethyl sulfoxide (DMSO)-d_6 using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained with an Agilent 1100 series LC/MSD VL ESI instrument. Elemental analyses were carried out on an EA 2400II elemental analyzer (Perkin-Elmer) and agreed well with calculated values.

General Procedures for the Preparation of Products (4)

A mixture of aromatic ketone **1** (11 mmol), aromatic aldehyde **2** (10 mmol), aromatic amine **3** (10 mmol), and $SnCl_4 \cdot 5H_2O$ (0.5 mmol) was stirred in EtOH (5 mL) at room temperature for an appropriate time (Table 3). After completion of the reaction (monitored by TLC), saturated $NaHCO_3$ solution (10 mL) was added, and the precipitated solid was collected by filtration and washed with ethanol. The crude product was purified via recrystallization from ethanol or ethanol/acetone (v/v = 3:2) to give the corresponding pure compound. Then the pure products **4** were identified by comparing their melting point (mp), infrared (IR), ^{1}H-NMR, mass spectroscopy (MS), and elemental analysis with those reported for the authentic samples.

RESULTS AND DISCUSSION

In the initial experiments, we screened different solvents for their effects on the yields in the three-component reaction of acetophenone, benzaldehyde, and aniline at room temperature, and the results are summarized in Table 1. Ethanol provided an excellent yield and proved to be the best, whereas acetonitrile afforded a lower yield. The reactions in tetrahydrofuran (THF), toluene, CH_2Cl_2, Et_2O, cyclohexane, H_2O, and under solvent-free conditions all failed to yield any product.

Next, we groped for the optimal reaction conditions using the same model reaction. The amounts of acetophenone, $SnCl_4 \cdot 5H_2O$, and EtOH are studied in Table 2. It was found that the use of 3 mol% (based on benzaldehyde) catalyst gave a low yield even after a long reaction time (Entry 3). In comparison, 5 mol% catalyst led to a 92% yield of product in 2 hr (Entry 2). Increasing the amount of catalyst could not bring better results. Hence, the best result was obtained after several trials by carrying out the reaction with 1.1:1:1 molar ratio of acetophenone, benzaldehyde, and aniline at ambient temperature in the presence of 5 mol% of $SnCl_4 \cdot 5H_2O$ in 5 mL EtOH for 2 hr (Entry 2).

To generalize our protocol, a serial of *β*-amino ketones were prepared from different aromatic ketones, aromatic aldehydes, and aromatic amines under optimal reaction conditions described earlier. As shown in Table 3, the reactions proceeded smoothly at room temperature in the presence

TABLE 1 $SnCl_4 \cdot 5H_2O$-Catalyzed Mannich Reaction of Acetophenone, Benzaldehyde, and Aniline in Different Solvents[a]

Entry	Solvent	Isolated Yield (%)
1	EtOH	92
2	CH_3CN	69
3	THF	0
4	Toluene	0
5	CH_2Cl_2	0
6	Et_2O	0
7	Cyclohexane	0
8	H_2O	0
9	None	0

[a] Reaction conditions: acetophenone (11 mmol), benzaldehyde (10 mmol), aniline (10 mmol), $SnCl_4 \cdot 5H_2O$ (0.5 mmol), solvent (5 mL), room temperature, 2 hr.

TABLE 2 Screening of Different Reaction Conditions for the Mannich Reactions of Acetophenone, Benzaldehyde, and Aniline[a]

Entry	Acetophenone (mmol)	$SnCl_4 \cdot 5H_2O$ (mol%)	EtOH (mL)	Time (h)	Isolated Yield (%)
1	10	5	5	2	83
2	11	5	5	2	92
3	11	3	5	6	72
4	11	5	3	2	81
5	11	5	8	2	67

[a] Reaction conditions: benzaldehyde (10 mmol), aniline (10 mmol), room temperature.

of $SnCl_4 \cdot 5H_2O$ to afford the desired products in good yields. The substituents of aromatic aldehydes affect the yields of β-amino ketones to an extent. Electron-donating substituents of aromatic aldehydes are disadvantageous to the Mannich reaction, and the yield of 4-methoxybenzaldehyde (**4o**) was lower than those of other aromatic aldehydes. Moreover, no β-amino ketone was obtained when using 4-dimethylaminobenzaldehyde

TABLE 3 $SnCl_4 \cdot 5H_2O$-Catalyzed One-Pot, Three-Component Mannich Reaction of Aromatic Ketones, Aromatic Aldehydes, and Aromatic Amines[a]

						mp (°C)	
Product	R_1	R_2	R_3	Time (h)	Isolated Yield (%)	Found	Reported
4a	H	H	H	2	92	168–170	169–170[20]
4b	H	H	2-Cl	48	68	114–116	115–116[20]
4c	H	H	3-Cl	2	87	130–133	130–131[20]
4d	H	H	4-Cl	48	80	170–172	171–173[21]
4e	H	H	3-COOH	35	68	156–158	159–161[20]
4f	H	H	4-COOH	35	82	193–195	193–195[20]
4g	H	H	3-NO_2	32	85	143–145	140–142[20]
4h	H	H	4-CH_3	5.5	64	162–164	163–166[20]
4i	H	H	4-OCH_3	26.5	62	123–126	127–129[20]
4j	H	4-Cl	H	18	87	108–110	109–111[20]
4k	H	4-NO_2	H	12	90	80–82	80–82[20]
4l	H	4-NO_2	3-Cl	17.5	93	100–102	99–102[20]
4m	H	4-NO_2	4-Cl	48	96	127–130	129–131[21]
4n	H	4-NO_2	4-COOH	0.5	74	190–192	190–192[20]
4o	H	4-OCH_3	H	34	78	135–137	137–139[20]
4p	H	4-$(CH_3)_2N$	H	48	0	—	—
4q	4-Cl	H	H	7.5	81	114–117	115–116[20]
4r	4-Cl	H	3-Cl	2.5	75	105–108	109–110[20]
4s	4-Cl	H	4-Cl	1.4	64	126–128	128–130[20]
4t	4-Cl	3-NO_2	4-Cl	18	82	133–135	136–138[20]
4u	4-NO_2	H	4-Cl	3	75	145–147	146–148[20]

[a] The structures of all the products were characterized by mp, ^1H NMR, IR, MS, and elemental analysis. The physical and spectroscopic data of our samples were identical with those reported in the literature.

as an aldehyde component (**4p**). As to aromatic amines, either electron-withdrawing or electron-donating groups were all suitable to the reactions. The position of a *meta*-substituent or *para*-substituent on the aromatic ring shows little effect on this conversion. One of the outstanding advantages of this method is its efficiency for the conversion in moderate yield of *ortho*-substituted aromatic amine to the corresponding Mannich base (**4b**), a reaction that generally fails to yield any product in the presence of the previously reported catalysts because of steric hindrance. As to aromatic ketones, 4-chloroacetophenone and 4-nitroacetophenone were also investigated and provided good yields.

CONCLUSIONS

In summary, $SnCl_4 \cdot 5H_2O$ was found to be an efficient catalyst for the three-component, one-pot Mannich-type reaction of aromatic ketones, aromatic aldehydes, and aromatic amines. The catalyst is cheap and stable. The protocol could make a valuable contribution to the existing processes in the field of β-amino carbonyl compounds synthesis.

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