Conjugate Addition of Amines to α,β-Enones Promoted by $CeCl_3 \cdot 7H_2O$−NaI System Supported in Silica Gel

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The development of novel synthetic methods leading to β-amino ketones or their derivatives has attracted much attention in organic synthesis. These β-amino ketones are attractive targets for chemical synthesis because of their prevalence and wide utility. One of their earliest applications was in the preparation of important γ-amino alcohols, versatile synthetic intermediates for a large number of natural products,[1] antibiotics,[2] and chiral auxiliaries.[3] Further, the β-amino ketone moiety is common in a large variety of biologically active compounds[4] and finds use as an important intermediate for fine chemicals[5] and pharmaceuticals.[6] Among the methods for generating β-amino ketones, the Mannich reaction is a classical method for the preparation of these derivatives.[7] However, due to the drastic reaction conditions and the long reaction times, the classical Mannich reaction presents serious disadvantages.[7] Therefore, a variety of methods have been reported for the synthesis of β-amino ketones, and next to the elegant chemistry from the Gomtsyan[9] group on the addition of vinyl Grignard reagents to *N*-methoxyamides, the approach based on Michael addition of amines to α,β-unsaturated carbonyl compounds is one of the most simple and effective methods for preparing β-amino ketones.[10]

The conjugate addition of nucleophiles to α,β-unsaturated compounds usually requires basic conditions[11] or acid catalysis.[12] To avoid typical disadvantages resulting from the presence of such catalysts, a number of alternative procedures have been developed in the past few years,[13] and in particular, various Lewis acid-induced reactions have been studied. However, the fact that stoichiometric amounts of Lewis acids such as $AlCl_3$, $TiCl_4$, or $SnCl_4$ are required constitutes a serious drawback since these oxophilic promoters have a significant cost factor and cause environmental problems due to strongly acidic waste streams. The development of alternatives is therefore highly desirable, and herein, we report a new protocol that employs only air stable ingredients and is then distinguished by its practicalness.

Recently, during our studies on application of cerium compounds in organic synthesis,[14] we found that the $CeCl_3 \cdot 7H_2O$−NaI system is able to catalyze the Michael addition of 1,3-dicarbonyl compounds to α,β-unsaturated ketones and aldehydes.[15] Though this reaction without solvent satisfies the demands of environmentally benign "green" chemistry, in the case of conjugate addition of amines to α,β-enones the reaction has been sluggish and gave very low yields. These limitations prompted us to investigate further new convenient methodology, in which we can exploit the utility of $CeCl_3$ as a Lewis acid due to its ready availability and its price. The use of the combination of $CeCl_3 \cdot 7H_2O$ and NaI as Lewis acid is very well documented in the literature;[16] however, its utility has not been explored in Michael additions of amines to α,β-enones. By our continuing effort to improve the utility of $CeCl_3 \cdot 7H_2O$−NaI system,[17] we have revealed that, expanding the generality of our methodology, the Michael addition reaction of amines to electrondeficient olefins in refluxing acetonitrile mixture provided β-amino ketones **5** in moderate to good yields (Scheme 1).

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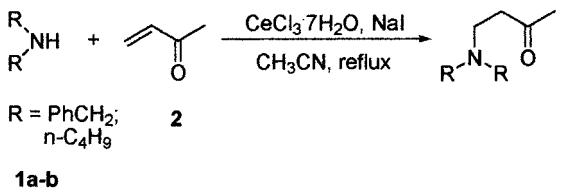
Scheme 1



Since several organic trasformations under solvent-free conditions have gained in popularity in recent years,[18] and papers on the use of rare earth on silica gel have been reported,[19] we further examined our Michael addition reaction on silica gel surface under no-solvent conditions. The $CeCl_3 \cdot 7H_2O-NaI$ system dispersed on chromatography silica gel (Baker Analyzed reagent) has been prepared by simple mixing of both reagents in acetonitrile followed by complete removal of the solvent.[20] Addition of amines **3** and α,β-unsaturated derivatives **4** to this mixture gave the desired Michael adduct in good to excellent yields (Table 1). The fact that the reaction can be carried out without solvent allowed us to adopt a very simple workup procedure for the recovery of the $CeCl_3-NaI-SiO_2$ system. The reaction mixture was treated with an organic solvent (Et_2O) able to dissolve the organic material, while the $CeCl_3-NaI$ silica gel support could be easily removed by filtration and it was found to be a recyclable reactive system. Thus, the recovered promoter, which was dried at room temperature for 2 h under reduced pressure, showed non appreciable decrease in activity for the reaction after being used three times. Unfortunately, every time it is necessary to use acetonitrile for preparing the $CeCl_3-NaI$ silica gel support. The amounts of $CeCl_3 \cdot 7H_2O$ and NaI used in the reaction have been tested and optimized. Neither $CeCl_3$ nor NaI alone could effect the conjugate addition even after 2 days. It has been found that the amount of $CeCl_3 \cdot 7H_2O$ has been decisive for completion of addition of amine. When less than 1 equiv of cerium salt was used, the addition proceeded rather slowly and after 3 days only 45% of Michael adduct was observed. The optimal molar ratio of enone, amine, $CeCl_3 \cdot 7H_2O$, and NaI is 1:1.25:1.35:1.15. The role of the sodium iodide remains to be established in the reaction, but one possibility includes the ability to enhance the activity of cerium trichloride as Lewis acid. It is probable that a halide-exchange reaction between $CeCl_3$ and NaI occurs during the preparation of $CeCl_3-NaI$ silica gel support, which is responsible for the enhancement of activity of system. Thus, the characterization of all components generated during the treatment of the $CeCl_3 \cdot 7H_2O$, NaI, and SiO_2 in acetonitrile is being carried out in our laboratories. So far, the results are too complicated and many kinds seem present.

These reactions have been also accomplished on $CeCl_3 \cdot 7H_2O-NaI$ system, i.e., without silica gel support, but the Michael adducts have been obtained in lower yields. In fact, the treatment of amines **3a** and **3b** with Michael acceptor **4a** in the presence of $CeCl_3-NaI$ system gave, under the same conditions, the desired adducts **5aa** and **5ba** only 45% in both cases after a much longer period of time, 3 and 4 days, respectively. Then, although the mechanism of this reaction is not clear, silica gel has an important role, and its presence was found to be essential for the high efficacy of the reaction. A reasonable explanation may be that the silica gel is mildly acidic and must interact favorably with $CeCl_3$ at its surface. The enones and the amines probably coordinate at a vacant coordination site of Ce metal that therefore promotes the reaction.

With regard to amines, secondary ones (Figure 1) are better reagents than primary amines since 1,4-conjugate addition products with primary amines undergo further additions giving rise to side products. The problem of double-conjugate addition is not observed in the reactions of secondary amines, evidently, because, protonation of the initially formed enolate anion is relatively fast compared with a second conjugate addition reaction, dodging so a possible dimerization or polimerization of the α,β-unsaturated ketone catalyzed by the amine.

This Michael addition reaction also works well for α,β-unsaturated esters and nitriles (Table 1, entries 9−11). The resulting β-amino derivatives are versatile synthons that can be converted into β-amino acids, which have been used in the synthesis of products with a wide range of biological activity[21] and pharmacological properties.[22] On the other hand, in the case of α,β-unsaturated aldehydes such as acrolein, the reaction suffers from regiochemical restriction caused by competing 1,2- versus 1,4-addition (Scheme 2). As is well know, iminium salts generally react faster and more regioselectively than the corresponding carbonyl compounds,[23] and thus, in α,β-unsaturated iminium salt **7** the hard electrophilic character of the N-linked carbon atom is enhanced, that 1,2-attack by a second molecule of amine **3a** takes place almost exclusively. In addition, it has been observed that although the conjugate additions of amines to enones of (*Z*)-configuration have been generally clean and efficient (Table 1, entries 6, 7, and 12), the attempt extend this

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(20) Studies showed that the yield of the Michael adduct was solvent dependent. Among a few solvents tested, acetonitrile was shown to be the best. In less polar solvents resulted in lower yields, CH_2Cl_2 (42%) and $CHCl_3$ (56%). A strongly coordinating solvent, i.e., DMF and THF, showed no reaction at all, probably due to the deactivation of $CeCl_3$ as Lewis acid.

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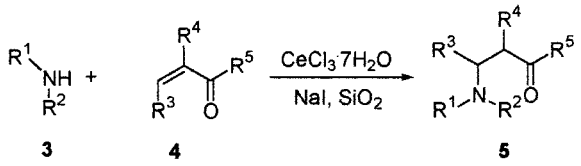
Table 1. Michael Addition of Secondary Amines to α,β-Enones Promoted by $CeCl_3 \cdot 7H_2O$–NaI System Supported in SiO_2



3 **4** **5**

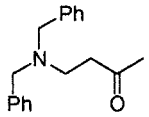
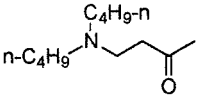
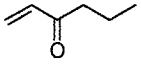
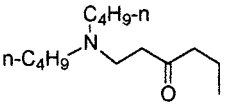
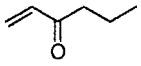
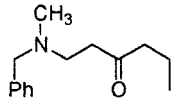
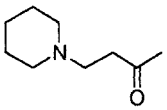
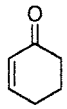
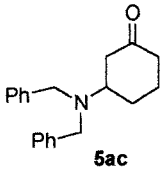
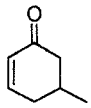
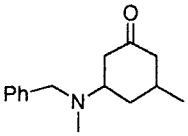
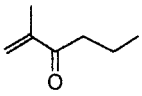
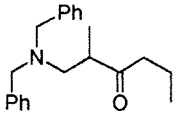
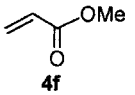
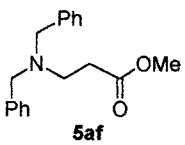
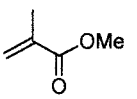
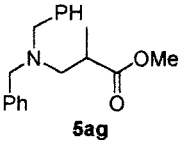
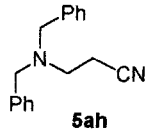
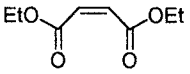
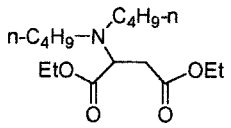
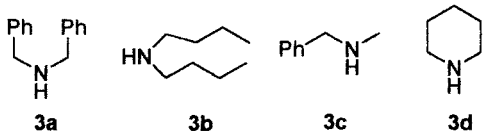
Entry	Amine	α,β-Enone	Time	Product[b]	Yield (%)[c]
1	**3a**	 **4a**	4.5 h	 **5aa**	91
2	**3b**	 **4a**	5 h	 **5ba**	84
3	**3b**	 **4b**	5 h	 **5bb**	87
4	**3c**	 **4b**	5 h	 **5cb**	88
5	**3d**	 **4a**	6 h	 **5da**	87
6	**3a**	 **4c**	5 h	 **5ac**	87
7	**3c**	 **4d**	5 h	 **5cd**	91
8	**3a**	 **4e**	5.5 h	 **5ae**	75
9	**3a**	 **4f**	6.5 h	 **5af**	90
10	**3a**	 **4g**	6.5 h	 **5ag**	90

Table 1 (Continued)

Entry	Amine	α,β-Enone	Time	Product[b]	Yield (%)[c]
11	**3a**	 **4h**	6.5 h	 **5ah**	87
12	**3b**	 **4i**	10 h	 **5ai**	80

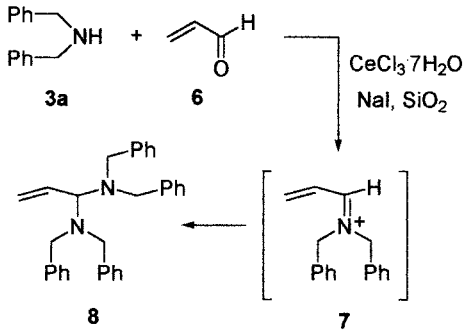
[a] All products were identified by their IR, NMR, and GC/MS spectra. [b] The rate and yields of this reaction are improved when it was warmed to 35 °C. [c] Yields of products isolated by column chromatography.



3a **3b** **3c** **3d**

Figure 1. Amines used as Michael donors.

Scheme 2



3a **6** **8** **7**

conjugate addition of amines to enones of (*E*)-configuration met with failure. In fact, the addition of amine **3a** and ethyl fumarate or (*E*)-3-nonen-2-one to $CeCl_3$−NaI−SiO_2 system gave only starting material in both cases. It is highly probable that these Michael adducts have been difficult to obtain as it is unstable on SiO_2 with respect to retro-conjugate addition,[24] and, thus, further investigations on this unfavorable selectivity for (*E*)-configuration are in progress in our laboratory.

In conclusion, we have shown that efficient conjugate addition of secondary amines to α,β-enones have been obtained with the use of amorphous silica gel. Its promoting role, although not well understood, is explained through the adsorption of the reactants that come into closer contact to each other on the silica surface. The efficiency of our $CeCl_3 \cdot 7H_2O$−NaI system supported on silica gel is remarkable: no inert conditions are required, since oxygen and moisture are tolerated. Further, the methodology does not require drastic and low temperature conditions as well as Brönstedt basic terms are avoided resulting excellent chemoselectivities. Then the mildness of the reaction conditions and simplicity of operation should make the present reaction highly synthetically useful. Thus, further explorations of the scope, selectivity, and mechanism of Michael addition of amines to α,β-enones by using inexpensive and commercially available salts such as $CeCl_3 \cdot 7H_2O$ and NaI on solid supports are in progress.

(24) Toda, F.; Takumi, H.; Nagami, M.; Tanaka, K. *Heterocycles* **1998**, *47*, 469−479.

Experimental Section

General Methods. General experimental details are provided as Supporting Information.

Typical Experimental Procedure. Silica gel (Baker 30−60 μm, 0.63 g) was added to a mixture of $CeCl_3 \cdot 7H_2O$ (0.50 g, 1.36 mmol) and NaI (0.17 g, 1.16 mmol) in acetonitrile (5 mL), and the mixture was stirred overnight at room temperature. The acetonitrile was removed by rotary evaporation and to the resulting reagent was added dibenzylamine (**3a**; 0.2 g, 1.01 mmol) and methyl vinyl ketone (**4a**; 88 mg, 1.26 mmol). Then, the mixture was mechanically stirred at an external temperature of 35 °C. After completion of the reaction (4.5 h) and addition of diethyl ether (75 mL), the mixture was passed through a short pad of Celite and the filtrate was washed with 10% aqueous citric acid to remove the possible excess amine, with aqueous saturated $NaHCO_3$ solution, and with saturated NaCl solution and finally dried over anhydrous Na_2SO_4. The extracts were then concentrated under reduced pressure and the crude purified by flash chromatography on a silica gel column (eluent: 30% EtOAc in hexanes) to give 0.24 g (91% yield) of the corresponding β-amino derivative **5aa** as oil.

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Supporting Information Available: Experimental procedures, ^1H NMR spectra, MS spectra, and other characterization data for new compounds, not reported previously, designated by their entries in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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