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Silica gel accelerated aza-Michael addition of amines to α,β-unsaturated amides

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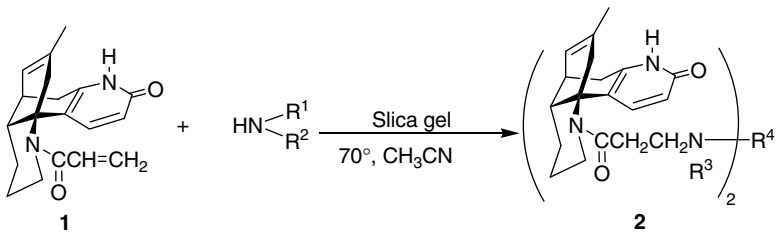
ABSTRACT

A novel method to synthesize β-amino amide has been developed via conjugated addition of amine to bulky α,β-unsaturated amides promoted by silica gel. The silica gel worked efficiently to accelerate the reaction and afforded the related adduct in good to excellent yield.

β-Amino amides and derivatives play an important role on natural and synthetic products with a wide range of biological activities[1] and pharmacological properties.[2] The synthesis of β-amino amides has gained considerable attention due to their biologically important application.[3] Among the reported synthetic methodologies to β-amino amides, the simplest and most widely used method is the conjugate addition of amines to α,β-unsaturated amides and derivatives.[4]

Michael reactions promoted by Lewis acids or base catalyst is one of the most important carbon–nitrogen bond-forming reactions in organic synthesis.[5] In particular, they are atom-efficient procedures and thus are inherently 'green' transformations. Several Lewis acids, such as $AlCl_3$, $TiCl_4$, or $SnCl_4$ have been employed to this addition.[6] However, their use in stoichiometric amount often caused severe environmental problems. Over last few years, several groups have reported sub-stoichiometric use of some Lewis acids such as $Yb(OTf)_3$, $Bi(OTf)_3$, $Bi(NO_3)_3$, hydrated $CeCl_3$–NaI supported on silica gel or clay.[7] Despite their remarkable success, however, the literature reveals that these catalysts are very substrate-selective. In addition, use of these heavy metal salts coupled with solvents are not desirable for a 'green' reaction. Herein, we developed an efficient and practical procedure for the conjugate addition of amines to α,β-unsaturated amides and derivatives promoted on a surface of silica gel.

Compared with other methodologies, easy recycling of the catalyst and scaling up of the reactions are important attributes of silica gel. Meanwhile, the reaction was relatively more facile than other catalysis system. Potassium fluoride supported on



1 2

R^1=R^3= alkyl, R^2=alkyl amine , R^4= alkyl

Scheme 1. The synthesis of bis-huperzine B via Michael addition promoted by silica gel.

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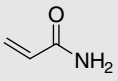
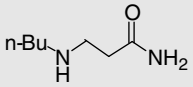
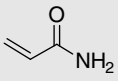
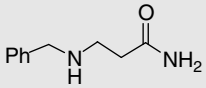
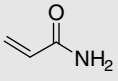
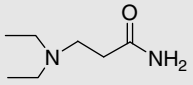
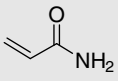
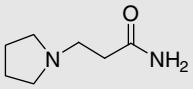
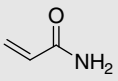
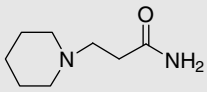
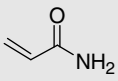
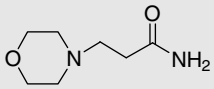
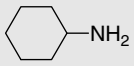
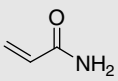
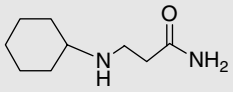
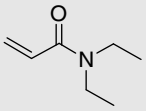
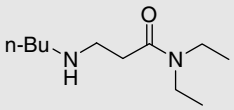
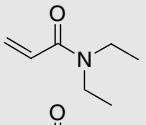
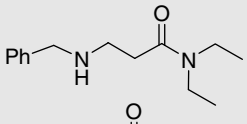
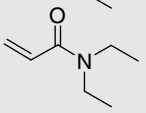
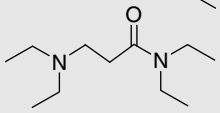
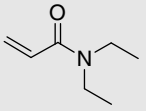
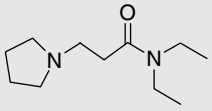
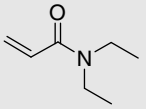
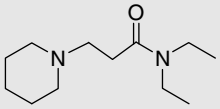
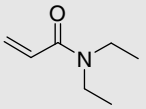
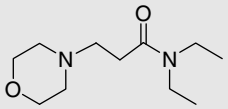
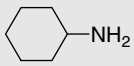
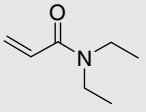
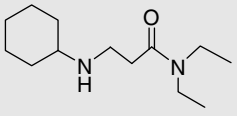
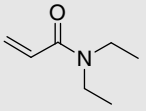
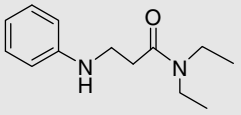
Table 1
Michael addition of amines to α, β-unsaturated amides

Entry	Amines	Amides	Product[a]	Yield[b] (%) (time, h)
1	*n*-$BuNH_2$			92(3)[11]
2	$PhCH_2NH_2$			93(5)[11]
3				89(5)[11]
4				95(5)[11]
5				93(5)[11]
6				92(5)[11]
7				90(8)
8	*n*-$BuNH_2$			94(5)
9	$PhCH_2NH_2$			90(5)
10				88(10)
11				87(10)
12				72(10)
13				84(10)
14				65(16)
15	$PhNH_2$			62(24)
16	PhNHMe			55(24)

[a] All products were characterized by IR, ^1H NMR, and ^{13}C NMR spectra data.[12]
[b] Isolated yield.

alumina was reported to exhibit similar effects.[8] So far only few papers have reported the interesting function of silica gel in Michael addition and its application (see Scheme 1).

In our previous reports on the preparation of dual acetylcholinesterase (AChE) inhibitors,[9] several methods which have been employed to build the carbon–nitrogen bond and link the two Huperzine B molecules failed to furnish the target compound bishuperzine B. It was the strong steric hindrance at the huperzine B molecule which made it very difficult to link the two parts of target compounds by usual methods. The problem was solved occasionally by using silica gel to accelerate the conjugated addition of amines to α,β-unsaturated amides and derivatives of huperzine B(**1**). The method was utilized repeatedly to afford many other highly potent and selective AChE dual inhibitors (**2**).[5] The successful applications on this case encouraged us to further explore the silica gel's effects on conjugated addition of amine to α,β-unsaturated amides. Therefore, we report the method using silica gel as promoter to accelerate this kind of aza-Michael addition.

In order to make our method be successful, the type of silica gel used is critical, herein, 200–300 mesh of GF254 silica gel (Qingdao, China) normally used for flash chromatography was employed in corresponding experiments. In a typical experiment, a mixture of amine and α,β-unsaturated amide in a ratio of 1.1:1.0 was mixed with silica gel (0.1–1 g, GF254, 200–300 mesh). To the mixture was added acetonitrile, and the resulting mixture was heated at reflux for 3–24 h. The mixture was concentrated under reduced pressure to afford a solid residue. The desired product was then isolated by flash column chromatography over silica gel.[10]

Our investigations showed that aromatic and aliphatic amines reacted smoothly with α,β-unsaturated amides in the presence of silica gel. The corresponding Michael addition adducts were obtained in high to excellent yields. To obtain the optimized reaction condition, different types of solvents were examined. Acetonitrile was found to be the favorite solvent for this reaction. A series of aliphatic and aromatic amines were employed as substrates to perform conjugate addition with α,β-unsaturated amides promoted by silica gel, and the results was summarized in Table 1.

Several aliphatic primary amines (entries 1, 2 and 7–9) underwent nucleophilic addition to α,β-unsaturated amides in the presence of silica gel to yield the desired adducts in excellent yields. Aliphatic secondary amines, for example, piperidine (entries 3–6) on treatment with acrylamide on silica gel afforded the target adduct in good yield. Encouraged by these good results, we turned our attention to aromatic amines, which were proved inefficient according to many reports. To our satisfaction, the aromatic amines under similar conditions also gave corresponding adducts in reasonable yields (entries 15 and 16). The slight difference in Michael addition yields in the presence of silica gel between aliphatic and aromatic amine with α,β-unsaturated amides might be caused by the electron-donating effects. It has also been observed that the reaction is greatly influenced by the steric hinderance of the conjugated amides; that is, N-substituted acrylamide reacts slower than the nonsubstituted acrylamide on the N-position (Table 1, entries 1, 8, 3 and10). The recovered silica gel was washed with methanol and dried under vacuum (0.5 mmHg) at 120–130 °C, then employed for further reaction. The recycled silica gel was tested for a particular reaction, the loss of obvious activity was not observed.

In conclusion, we have developed a mild and efficient method for the synthesis of β-amino amides and derivatives via conjugated addition of amines to α,β-unsaturated amides promoted on a surface of silica gel. The best results are realized by using the silica gel usually used for flash chromatography. The applicability of this 'green' methodology to a variety of amines including aromatic and hindered amines is an attractive feature, which can be beneficial for synthetic and industrial chemists.

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10. General procedure for Michael additions: Representative one is as follows. To a solution of the amine (2 mmol) in acetonitrile (10 mL) was added α,β-unsaturated amide (2 mmol), followed by silica gel (GF254, 200–300 mesh, 1 g). The resulting mixture was heated at reflux for 4 h. After cooled to rt, the mixture was concentrated under reduced pressure. The solid residue was washed with EtOAc/methanol (5:1) for three times, the combined organic phase was concentrated and the crude was purified by chromatography eluting with various ratios of EOAc to petroleum to afford the product. These compounds are identified by IR, ^{1}H NMR, and ^{13}C NMR spectra data.
11. (a) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991; (b) Azizi, N.; Saidi, M. R. *Tetrahedron* **2004**, *60*, 383.
12. Selected NMR (300 M, $CDCl_3$) spectral data for the products:
Entry 8: ^{1}H NMR: δ = 0.96 (t, 3H, *J* = 7.1 Hz), 1.22 (t, 6H, *J* = 6.8 Hz), 1.33–1.41 (m, 4H), 2.30 (t, 2H, *J* = 7.6 Hz), 2.55 (t, 2H, *J* = 7.1 Hz), 2.83 (t, 2H, *J* = 7.8 Hz), 3.24 (q, 4H, *J* = 6.8 Hz). ^{13}C NMR: δ = 12.0, 13.2, 20.1, 32.5, 33.1, 41.0, 48.9, 49.5, 170.5. *Entry 10*: ^{1}H NMR: δ = 0.96 (t, 3H, *J* = 7.1 Hz), 1.22 (t, 6H, *J* = 6.8 Hz), 2.30–2.52 (m, 6H), 2.64 (t, 2H, *J* = 7.8 Hz), 3.24 (q, 4H, *J* = 6.8 Hz), ^{13}C NMR: δ = 12.8, 13.2, 31.5, 41.0, 48.9, 49.5, 171.7. *Entry 12*: ^{1}H NMR: δ = 1.24 (t, 6H, *J* = 6.8 Hz), 1.4–1.5 (m, 6H), 2.21–2.40 (m, 6H), 2.64 (t, 2H, *J* = 7.8 Hz), 3.28 (q, 4H, *J* = 6.8 Hz). ^{13}C NMR: δ = 12.9, 25.1, 31.5, 41.6, 51.7 171.5. *Entry 15*: ^{1}H NMR: δ = 1.21 (t, 6H, *J*=6.8 Hz), 2.40 (t, 2H, *J* = 7.0 Hz), 2.64 (t, 2H, *J* = 7.8 Hz), 3.34 (t, 2H, *J* = 7.0 Hz), 6.7–7.1 (m, 5H), ^{13}C NMR: δ = 12.9, 33.2, 38.7, 41.3, 51.7, 113.0, 117.1, 130.4, 147.6, 171.5.