Highly Efficient Methanolysis of Bicyclic *β*-Lactams to *β*-Amino Ester Using Silica Chloride

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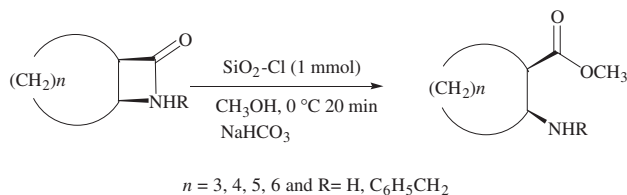*Jhansi Road, Gwalior-474002 (MP), India*

Silica chloride is used as an effective heterogeneous catalyst for the methanolysis of highly constrained cyclic *β*-lactam to afford *β*-amino ester under mild acidic conditions with quantitative yields.

β-Amino acids and their derivatives, such as amino esters, amides, or 1,3-amino alcohols, can serve as potential precursors for the synthesis of wide range of saturated heterocycles.[1–4] Several methods are reported in the literature[5] for the synthesis of *β*-amino esters but the most common method is the ring-opening reaction of *β*-lactam followed by methanolysis.[5a] Most of these methods require harsh acidic conditions, and under such conditions number of compounds containing constrained ring system like (+)-3-carene, decomposes and results in the formation of mixture of decomposed products.[5c] Recently, the use of reagents and catalyst supported on solid supports have received maximum attention.[6] Silica gel is one of such extensively used surface materials for different chemical transformations in organic chemistry.[7] Modified silica such as silica chloride (SiO$_2$–Cl), has been reported to be an efficient reagent for the synthesis of many organic compounds.[8] The efficiency of silica chloride under operationally simple conditions has prompted us to explore its use for the synthesis of *β*-amino esters and other organic transformations. During our recent work on the development of novel synthetic methodologies, we have observed that silica chloride also serves as an efficient catalyst for methanolysis of highly constrained cyclic *β*-lactams. Herein, we report a rapid, and easy to scale-up method for the synthesis of *β*-amino esters using silica chloride as heterogeneous catalyst Scheme 1.

Silica chloride can be prepared very easily and has been rarely applied in synthetic organic chemistry. The room temperature (20–25 °C) reaction of *β*-lactam with various alcohols in the presence of silica chloride afforded the corresponding *β*-amino ester in 20 min with excellent yields, Table 1.

The reactions were carried out by taking 1:1:4 molar ratio of *β*-lactam, silica chloride and alcohol; dry alcohol was added to the mixture drop wise at 0 °C and the derived *β*-amino ester hydrochloride was further basified with cold saturated sodium bicarbonate solution followed by the extraction with diethyl ether to afford *β*-amino ester in excellent yields.[9] However,

Table 1.

Entry	Substrate	Product[a]	Yield/%[b]
1		1b	80
2		2b	82
3		3b	80
4		4b	80
5		5b	82
6		6b	81
7		7b	78
8		8b	82
9		9b	80
10		No reaction	
11		11b	82

[a]All compounds have been characterized by IR, NMR, and MS spectroscopy. [b]Isolated yield.

when the reaction was carried out with cyclic amide (Entry 10, Table 1), reaction did not occur at all. This may be essentially because cyclic amides have less ring strain in comparison to that of cyclic *β*-lactam, which makes *β*-lactam more susceptible to ring-cleavage reactions. Hence, this method can be used specifically for the methanolysis of cyclic *β*-lactams to afford *β*-amino ester. The ring-opening mechanism goes by the cleavage of the amide bond by nucleophilic attack at N(1)–C(2) bond. The products were confirmed on the basis of their spectral data (¹H NMR, and MS).[10] The synthetic procedure for the *β*-lactams has been extensively documented in the literature[11] and can be applied to a large range of olefinic or diene-containing framework and was therefore ideal for our purposes. Advantage of using silica chloride was that it can be prepared by the readily available materials[12] and can also be removed easily from the reaction mixture by simple filtration. The recovered catalyst, however when applied again under the present experimental conditions has been

SiO$_2$-Cl (1 mmol)
CH$_3$OH, 0 °C 20 min
NaHCO$_3$

n = 3, 4, 5, 6 and R= H, C$_6$H$_5$CH$_2$

Scheme 1.

found to decrease the yields of esters (20–30% only). In conclusion, an efficient and simple method for the synthesis of β-amino esters from highly constrained β-lactams has been described using silica chloride as a heterogeneous catalyst. The main advantage of this method is that it requires mild reaction conditions, less reaction time and operational simplicity with excellent yields.

References and Notes

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9 *Typical Experimental procedure for the synthesis of β-amino esters.* To a mixture of β-lactam (1 mmol) and silica chloride (1 mmol), dry alcohol (4 mmol) was added drop wise at $0\,^\circ$C. The reaction mixture was stirred for 10–20 min. The progress of reaction was monitored by TLC (toluene:ethanol 9:1). After the disappearance of starting material in TLC the reaction mixture was further basified with cold saturated sodium bicarbonate solution followed by the extraction with diethyl ether (3×50 mL). The combined organic layer was dried (Na$_2$SO$_4$), filtered and evaporated. The oily residue obtained by flash chromatography on a silica-gel column (toluene:ethanol 9:1) to afford β-aminoester in excellent yield.
10 Analytical data for selected compounds have been reported here. **1b**: Viscous oil, IR ν_{max} 3344, 3223, 1730, 1260 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.27–1.35 (m, 2H), 1.70–1.86 (m, 4H), 1.88–2.0 (m, 2H), 2.65 (dd, 1H, $J = 4.1, 6.4$ Hz), 3.16 (m, 1H), 3.67 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 18.5, 20.3, 31.5, 47.2, 47.6, 50.8, 176. ESI-MS 144 (M + H); HRMS calcd for C$_7$H$_{13}$NO$_2$ 143.0946, found 143.0941. **3b**: Viscous oil, IR ν_{max} 3324, 3323, 1737, 1260 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.30–1.85 (m, 8H), 1.89–2.2 (m, 2H), 2.17 (dd, 1H, $J = 4.66, 6.04$ Hz), 3.17 (m, 1H), 3.68 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 21.8, 22.2, 24.3, 33.1, 45.1, 45.5, 50.7, 176; ESI-MS 158 (M + H); HRMS calcd for C$_8$H$_{15}$NO$_2$ 157.1103, found 157.1100. **5b**: Viscous oil, IR ν_{max} 3327, 3353, 1747, 1260 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.26–1.29 (m, 8H), 1.50–1.64 (m, 4H), 1.88–2.0 (m, 2H), 2.18 (dd, 1H, $J = 4.1, 6.6$ Hz), 3.25 (m, 1H), 3.68 (s, 3H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 24.7, 28.3, 29.9, 30.12, 30.2, 36.2, 43.42, 48.54, 50.7, 176; ESI-MS 186 (M + H); HRMS calcd for C$_{10}$H$_{19}$NO$_2$ 185.1416, found 185.1410. **6b**: Viscous oil, IR ν_{max} 3234, 3326, 1736, 1260 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.24–1.28 (m, 8H), 1.41–1.56 (m, 4H), 2.18 (dd, 1H, $J = 4.5, 6.8$ Hz), 3.17 (m, 1H), 3.67 (s, 3H), 4.06 (d, $J = 15.4$ Hz, 1H), 4.42 (d, $J = 15.4$ Hz, 1H), 6.17 (brs, 1H, NH), 7.23–7.28 (m, 5H); ^{13}C NMR (CDCl$_3$, 100 MHz) δ 25.2, 25.7, 27.2, 30.1, 30.6, 33.8, 46.5, 51.4, 52.3, 52.8, 127.6, 128.1, 128.7, 130.3, 131.1, 137.2, 176; ESI-MS 276 (M + H); HRMS calcd for C$_{17}$H$_{25}$NO$_2$ 275.1885 found 275.1881.
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12 *Typical procedure for the preparation of silica chloride.* To a well-stirred silica gel (20 g) in CH$_2$Cl$_2$ (50 mL) was added drop wise SOCl$_2$ (20 g) at room temperature. Evolution of copious amounts of HCl and SO$_2$ occurred instantaneously. After stirring for another 1 h, the solvent was removed to dryness under reduced pressure (1 torr) to get the silica chloride (SiO$_2$–Cl).