(Chloromethylene)dimethylammonium chloride: a highly efficient reagent for the synthesis of β-lactams from β-amino acids

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(Chloromethylene)dimethylammonium chloride **1**, is a unique reagent that conveniently and efficiently mediates the amide bond formation in β-lactams via cyclodehydration of β-amino acids leading to β-lactam formation. The process involves the formation of a highly reactive activated ester of a β-amino acid which gets cyclised to the corresponding β-lactam in excellent yield. The reaction proceeds smoothly and cleanly as the by-products formed are the water soluble-dimethyl formamide and triethylamine hydrochloride.

Keywords: (chloromethylene)dimethylammonium chloride, β-lactams, β-amino acids, cyclodehydration, intramolecular cyclisation

The well-recognised importance of β-lactams as antibiotics stimulated the pharmaceutical industry to develop new derivatives of this class of compounds possessing broader activity and enhanced resistance to biological degradation.[1] As a consequence; there is growing interest in improved synthetic methods that allow the assembly of an azetidin-2-one ring in a mild and selective fashion. The most obvious approach to the synthesis of the azetidinone structure is formation of amide bond via dehydration of β-amino acids. Unfortunately, in contrast to their γ and δ analogues β-amino acids do not normally cyclise thermally.[2] This is in part due to the high degree of strain present in the desired product, the possibility of intermolecular condensation, and the propensity of the starting material to undergo β-elimination. In spite of these complications, a limited number of specialised methods have been developed for the efficient cyclisation of β-amino acids and their derivatives through the use of several dehydrating reagents.[3]

In continuation of our studies in this direction[4-6] we present here a novel protocol for the cyclisation of β-amino acids using (chloromethylene)dimethylammonium chloride (**1,** Figure 1) as an effective acid activating agent. Since the discovery of (chloromethylene)dimethylammonium chloride, its reactivity and synthetic applications have been investigated in variety of transformations. Chloroformamidinium chlorides such as **1,** derived easily from *N,N*-dimethyl formamide and a chlorinating reagent, is known not only as a formylating agent,[7,8] but also as an activating reagent for carboxylic acids

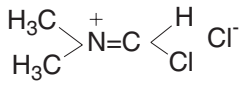

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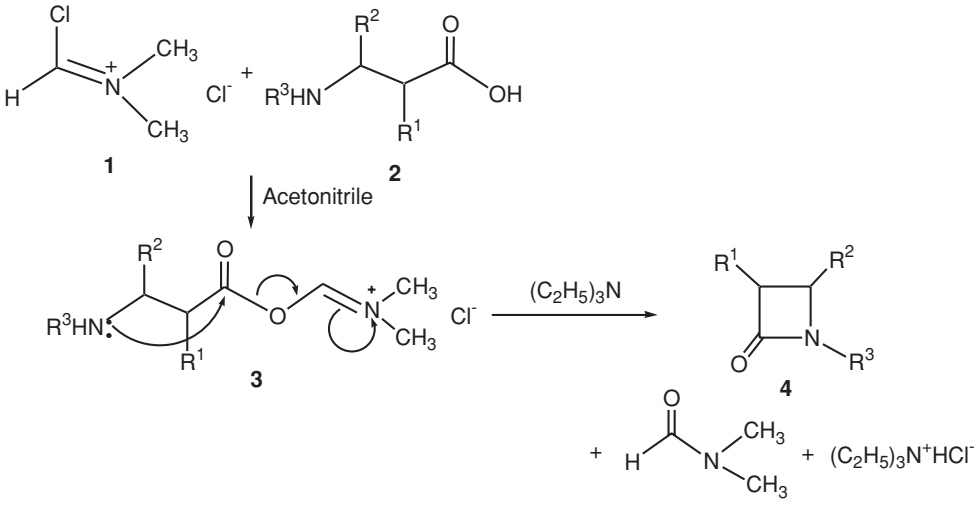
Fig. 1 (Chloromethylene)dimethyl ammonium chloride.

to give esters,[9,10] amides[11] and acid chlorides.[12] More recently, this iminium salt has also been reported to activate the alcohols for their transformation to alkyl chlorides,[13] esters[14] as well as imides.[15]

We felt the need to explore the potential of this reagent in the cyclodehydration reaction of β-amino acids and we observed that this compound is quite effective for the synthesis of β-lactams under mild reaction conditions. The effects of the solvents, quantity of reagent and reaction conditions were first examined in the synthesis of 1-benzylazetidin-2-one **4b** and found that appropriate solvent as well as reaction conditions are critical for the success of the present reaction (Table 1). Among the solvents examined were dichloromethane, THF and acetonitrile. Acetonitrile proved better than the other two in many cases, especially in terms of yield of the final product. The reaction is also temperature dependent and the high yields are obtained when the initial reaction of β-amino acid and reagent **1** is performed at 0 °C in acetonitrile solution (0.01 M) and cyclisation is carried out by stirring the reaction mixture overnight at room temperature in presence of a tertiary base (triethylamine). Usual workup furnished the



Scheme 1 Plausible mechanism for the formation of β-lactams.

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β-lactams in high yields. The process is efficient, cleaner and high yielding and the proposed mechanism of this reaction is shown in Scheme 1. No side reactions were observed under these reaction conditions. Where as in $POCl_3$ mediated cyclodehydration,[6] phosphorus containing mixed anhydride reacts via cyclic transition state but **1** reacts with carboxyl group of β-amino acid forming a highly reactive activated ester intermediate **3** that possess a new efficient leaving group, which facilitates the intramolecular amide bond formation resulting in the 2-azetidinone structure. The β-amino acids used in this study produced either 3 or 4 unsubstituted β-lactams in the racemic form.

A variety of structurally different β-amino acids[16-18] were used to study the scope and generality of this method (Table **2**) and it is clear that the reagent works well in cyclising N-substituted as well as N-unsubstituted β-amino acids in high yields. The structures of the products were confirmed on the basis of IR and ^{1}H NMR spectral data. IR spectrum showed the characteristic β-lactam carbonyl absorption peaks in the range generally found for monocyclic β-lactams *i.e.* 1740–1755 cm^{-1}.

In summary, we disclose here a new procedure for the preparation of 2-azetidinones using **1** as a novel reagent under mild conditions. Since the reagent is readily accessible and also commercially available, the reaction conditions mild, the procedure simple and the yields generally high, we believe that this method can also serve as a convenient route for the large scale preparation of useful monocyclic 2-azetidinones. Moreover, convenience of handling of this reagent can surpass the commonly used reagents in cyclisation of β-amino acids.

Table 1 Effect of reaction conditions

Entry	Solvent	Temperature /°C	Quantity of reagent /mmol	Yield/ %
1	Acetonitrile	25–30	< 5	45
		0	< 5	65
		25–30	6.4	75
		0	6.4	85
2	Dichloromethane	25–30	< 5	30
		0	< 5	60
		25–30	6.4	60
		0	6.4	75
3	Tetrahydrofuran	25–30	< 5	35
		0	< 5	55
		25–30	6.4	60
		0	6.4	70

Experimental

All melting points (m.p., °C) are uncorrected. The FT–IR spectra were recorded on a Perkin-Elmer Model 1430 spectrophotometer and were calibrated against polystyrene. Only the principal peaks of interest are reported and expressed in cm^{-1}. ^{1}H NMR spectra were recorded on a 300 MHz Bruker AC 300F spectrometer. Chemical shifts are expressed as δ values (ppm) downfield from tetramethylsilane (TMS). Elemental analysis (C, H, N) was recorded using a Perkin Elmer 2400 (C, H, N) elemental analyzer. Thin layer chromatography was performed using TLC grade Silica gel (G) and was developed in an atmosphere of iodine vapours.

Preparation of (cloromethylene)dimethylammonium chloride: To a solution of DMF (0.01 mmol) in dry dichloromethane (5 ml) at 0 °C, oxalyl chloride (0.1 mmol) was added dropwise with stirring under nitrogen atmosphere. During addition a white solid precipitated out in about 5 min, which was used as such for β-lactam formation.

Typical procedure for β-lactam formation (**4a–r**): suspension of β-amino acid (1 mmol) in dry acetonitrile (0.01M) was cooled to 0 °C under stirring. Freshly prepared reagent **1** (6.45 mmol) was added to this suspension at 0 °C under stirring during 30 min. At this time the reaction mixture became homogenous and triethylamine (2.10 mmol) in dry acetonitrile (50 ml) was added dropwise at 0 °C under stirring. The reaction mixture was stirred overnight at room temperature and quenched with saturated solution of sodium bicarbonate (50 ml) and finally washed with water (50 ml twice). The organic phase was separated, dried over anhydrous sodium sulfate and evaporated under reduced pressure. Chromatography of the residue on silica gel using ethyl acetate:hexane gradient afforded pure 2-azetidinone.

Azetidin-2-one (**4a**): Solid, m.p. 71–72 °C; FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 2900, 1740. ^{1}H NMR ($CDCl_3$; 300 MHz; δ/ppm): 2.00 (s, 1H, NH), 2.68 (m, 2H, CH_2CO), 3.12 (m, 2H, CH_2NH). Anal. Calcd for C_3H_5NO: C, 50.70; H, 7.04; N, 19.72. Found: C, 50.59; H, 7.00; N, 19.51.

4-Methyl-1-phenethylazetidin-2-one (**4d**): Pale yellow Oil, FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 1743.5. ^{1}H NMR ($CDCl_3$; 300 MHz; d/ppm): 1.29 (d, 3H, $CHCH_3$, J = 6.7 Hz), 2.11 (m, 2H, CH_2Ph), 2.53 (dd, 1H, C_3H, J = 14 Hz and 2.3 Hz), 3.22 (dd, 1H, C_3H, J = 14 Hz and 4.2 Hz), 3.71 (m, 1H, C_4H), 4.20 (dd, 1H, NCH_2, J = 15.2 Hz), 4.60 (dd, 1H, NCH_2, J = 15.1 Hz), 6.95–7.2 (m, 5H, ArH). Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 75.91; H, 7.23; N, 7.73.

3-Methyl-1-phenethylazetidin-2-one (**4j**): Oil, FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 1743. ^{1}H NMR ($CDCl_3$; 300 MHz; d/ppm): 1.99 (d, 3H, J = 6.5 Hz, CH_3), 2.81 (m, 2H, CH_2Ph), 2.95 (m, 1H, C_3H), 3.16 (m, 2H, NCH_2CH_2), 3.35 (dd, 1H, J = 5.4 Hz and 6.0 Hz, C_4H), 3.53 (dd, 1H, J = 6.0 Hz and 2.3 Hz, C_4H), 7.08–7.22 (m, 5H, ArH). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.19; H, 7.94; N, 7.41. Found: C, 75.93; H, 7.62; N, 7.31.

Table 2 β-Lactams obtained in (chloromethylene)dimethylammonium chloride mediated cyclodehydration

Product	R^1	R^2	R^3	Yield/%[a]	M.p./°C) Found (Reported)
4a	H	H	H	77	71–72 (73–74)[19]
4b	H	H	$CH_2C_6H_5$	85[20]	Oil
4c	H	CH_3	$CH_2C_6H_5$	82[6]	Oil
4d	H	CH_3	$CH_2CH_2C_6H_5$	84	Oil
4e	H	CH_3	$(CH_2)_3CH_3$	86[6]	Oil
4f	H	CH_3	$CH_2CH(CH_3)_2$	80[6]	Oil
4g	H	CH_3	CH_2CH_2OH	80[6]	Oil
4h	H	CH_3	$CH_2CH(OH)CH_3$	82[6]	Oil
4l	CH_3	H	$CH_2C_6H_5$	82[6]	Oil
4j	CH_3	H	$CH_2CH_2C_6H_5$	81	Oil
4k	CH_3	H	$(CH_2)_3CH_3$	82	Oil
4l	CH_3	H	$CH_2CH(CH_3)_2$	83[6]	Oil
4m	CH_3	H	CH_2CH_2OH	82[6]	Oil
4n	CH_3	H	$CH_2CH(OH)CH_3$	84	Oil
4o	H	C_6H_5	$CH_2C_6H_5$	75[6]	Oil
4p	H	C_6H_5	H	83[6]	114–116 (114–116)[6]
4q	H	piperonyl	H	83	118–119
4r	H	$C_6H_4OCH_3$(p)	H	81	160–162

[a]All products were identified by FT-IR, ^{1}H NMR and analytical data.

1-Butyl-3-methylazetidin-2-one (**4k**): Oil, FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 1748. ^1H NMR ($CDCl_3$; 300 MHz; d/ppm): 0.96–1.55 (m, 10H, CH_3, $CH_2CH_2CH_3$), 2.99 (m, 1H, C_3H), 3.16 (m, 2H, NCH_2CH_2), 3.20 (dd, 1H, *J* = 6.2 Hz ans 5.0 Hz, C_4H), 3.43 (dd, 1H, *J* = 6.2 Hz and 2.1 Hz, C_4H). Anal. Calcd for $C_8H_{15}NO$: C, 68.09; H, 10.64; N, 9.93. Found: C, 67.89; H, 10.59; N, 9.82.

1-(2-Hydroxy-propyl)-3-methylazetidin-2-one (**4n**): Oil, FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 3321, 1742. ^1H NMR ($CDCl_3$; 300 MHz; d/ppm): 1.21 (d, 3H, *J* = 7.0 Hz, CH_3), 1.30 (d, 3H, *J* = 7.1 Hz, CH_3), 2.11 (s, 1H, OH), 3.01 (m, 1H, C_3H), 3.21 (d, 2H, $CHCH_2N$), 3.42 (dd, 1H, *J* = 6.0 Hz and 4.2 Hz, C_4H), 3.51 (dd, 1H, *J* = 6.0 Hz and 2.0 Hz, C_4H), 4.02 (m, 1H, CHO). Anal. Calcd for $C_7H_{13}NO_2$: C, 58.74; H, 9.09; N, 9.79. Found: C, 58.64; H, 8.97; N, 9.99.

4-(Benzo[1,3]dioxol-5-yl)azetidin-2-one (**4q**): Solid, m.p. 118–119 °C; FT-IR ($CHCl_3$, ν_{max}/cm^{-1}): 3299, 1747. ^1H NMR ($CDCl_3$; 30 MHz d/ppm): d 3.21 (dd, 1H, *J* = 14 Hz and 2.0 Hz, C_3H), 3.30 (dd, 1H, *J* = 14 Hz and 5 Hz, C_3H), 4.59 (m, 1H, C_4H), 5.99 (s, 2H, OCH_2O), 6.1 (s, 1H, NH), 6.52–6.91 (m, 3H, ArH). (Anal. Calcd for $C_{10}H_9NO_3$: C, 62.83; H, 4.71; N, 7.33. Found: C, 62.79; H, 4.65; N, 7.29).

4-(4-Methoxyphenyl)azetidin-2-one (**4r**). Solid, m.p. 160–162 °C; FT-IR ($CHCl_3$, ν_{max}//cm^{-1}): 1745.9. ^1H NMR ($CDCl_3$; d/ppm): 3.11 (dd, 1H, *J* = 14.2 Hz, 2.3 Hz & 1.4 Hz, C_3H), 3.23 (dd, 1H, *J* = 14.2 Hz, 3.0 Hz and 4.5 Hz, C_3H), 3.73 (s, 3H, OCH_3), 4.72 (m, 1H, C_4H), 6.2 (s, 1H, NH), 6.91–7.23 (m, 4H, ArH). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.80; H, 6.22; N, 7.91. Found: C, 67.65; H, 6.12; N, 7.89.

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