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Preparation of enantiopure 2-acylazetidines and their reactions with chloroformates

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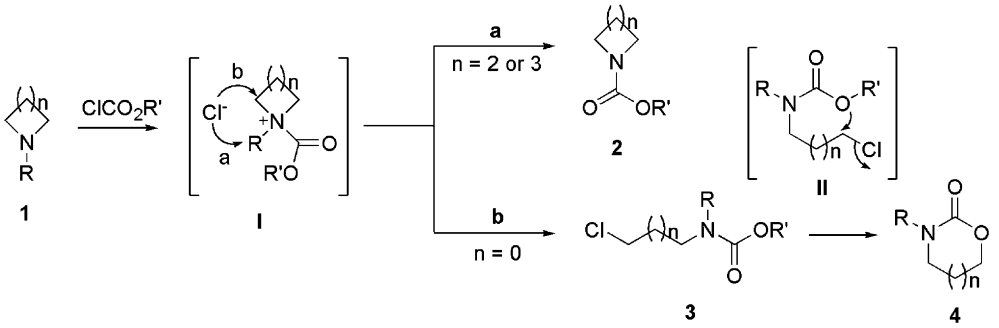
Abstract—Enantiopure 1-phenylethylazetidine-2-carboxylates and 2-acylazetidines were prepared and reacted with chloroformates to yield α-chloro-γ-amino butyric acid esters and ketones from ring opening reaction of azetidinium ion intermediate in a completely regio- and stereoselective manner.

Nitrogen containing cyclic compounds (**1**) with *N*-alkyl substituents react with chloroformate to yield ammonium ion intermediate (**I**) with free chloride (Scheme 1). This intermediate can take two different reaction pathways which would be either dealkylation (pathway 'a') or ring opening (pathway 'b'). When the ring size is five or six such as pyrrolidine ($n = 2$) and piperidine ($n = 3$), dealkylation reactions are dominant. This pathway 'a' has been used for debenzylation or demethylation.[1] However, when the ring size is small as aziridine ($n = 0$), only ring opening reaction occurs to afford chloroamine (**3**) that is further cyclized in the fashion of **II** to yield the cyclic carbamate (**4**).[2] However, the same reaction with azetidine ($n = 1$) remains to be undisclosed yet. Up to now disputable pieces of information are known.[3] Thereby, we decided to study the reaction of substituted azetidines with chloroformates to clarify the possible reaction pathways 'a' and 'b' in Scheme 1.

At first we elaborated azetidine-2-carboxylate and 2-acylazetidine in optically pure forms some of which are very valuable.[4] L-Azetidine-2-carboxylate is a representative example that was first isolated from *Convallaria majaris*.[5] It is also found in naturally occurring peptides such as mugineic acid,[6] nicotianamine[7] and in pharmacologically important melagatran.[8] Even though



Scheme 1.

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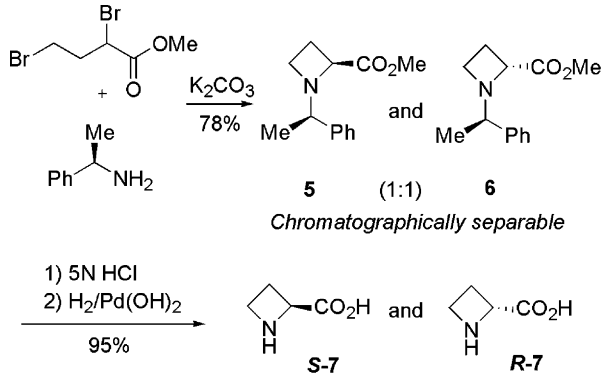
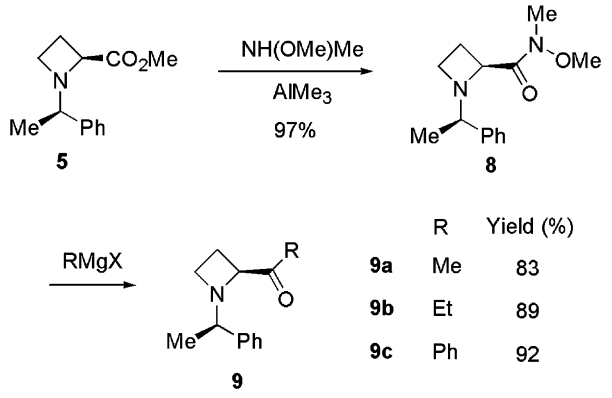
a few asymmetric syntheses of azetidine-2-carboxylate are reported,[9] a simple and easy route to obtain both enantiomers in optically pure forms is still necessary. Methyl 2,4-dibromobutanoate[10] was reacted with (2*R*)-phenylethylamine to yield orthogonally protected and chromatographically separable diastereomeric mixture of (2*S*,1*R*′)-(**5**) and (2*R*,1*R*′)-1-1-phenylethylazetidine-2-carboxylate (**6**) in 78% yield with almost 1:1 ratio. Each of those diastereomers were hydrolyzed in 5 N HCl and then hydrogenolysis yielded enantiomerically pure (2*S*)- (***S*-7**) and (2*R*)-azetidine-2-carboxylic acid (***R*-7**) in more than 95% yield (Scheme 2).[9]

Methyl (2*S*)-azetidine-2-carboxylate (**5**) was reacted with methoxymethylamine to yield the amide (**8**) that was readily reacted with methyl, ethyl, and phenylmagnesium bromide to afford the corresponding 2-acylaziridines (**9a**, **9b**, and **9c**) in 83%, 89%, and 92% yields, respectively (Scheme 3).[11]

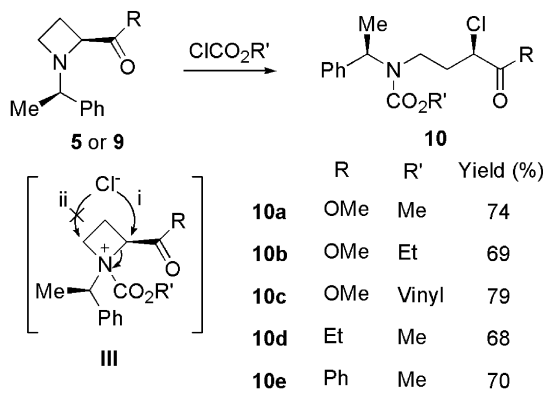
At first methyl (2*S*,1*R*′)-1-phenylethylazetidine-2-carboxylate (**5**) was reacted with methyl chloroformate to yield the acyclic chlorinated compound (**10a**) as a single isomer in 74% yield implying that the reaction is completely regio- and stereospecific.[12] We found that the reaction of *N*-alkylazetidine with methyl chloroformate took the ring opening pathway as 'b' in Scheme 1. Furthermore, the ring opening reaction occurred at the C-2 position regiospecifically with the inversion of configuration via azetidinium ion intermediate (**III**) as i and not as ii in Scheme 4. The same reactions with ethyl and vinyl chloroformates yielded the ring-opened products (**10b** and **10c**) in similar yields of 69% and 79%. The reactions for (2*S*,1*R*′)-1-phenylethyl-2-acylazetidines (**9b** or **9c**) proceeded in the same manner with methyl chloroformate to afford **10d** and **10e** in 68% and 70% yields, respectively (Scheme 4).



Scheme 2.



Scheme 3.

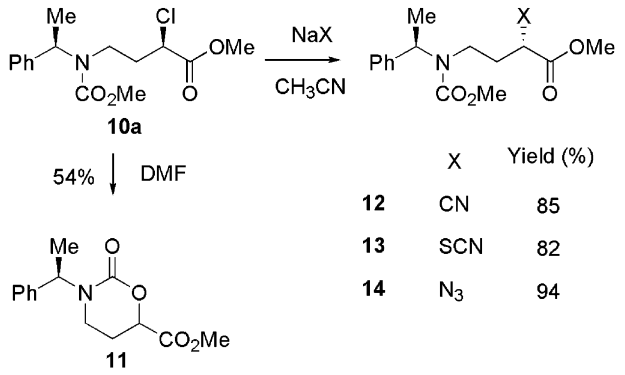


Scheme 4.

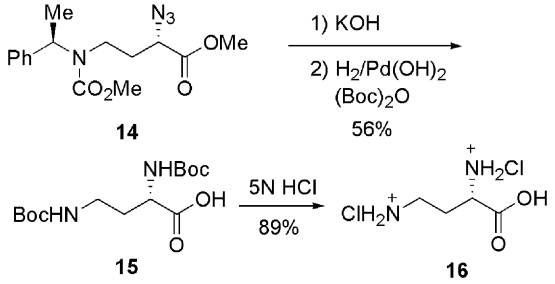
Recently we showed that the nucleophilic nitrogen in the small ring aziridine would react with acid chloride to yield ring-opened or ring-expanded products depending on the characteristic of the reactants.[13] All of the reactions show common pathways with the formation of aziridinium ion from the reaction of nucleophilic ring nitrogen with acid chloride and the subsequent ring opening by the chloride. What we observed in this study showed that the reaction of the substituted azetidines took the similar pathway as that of the substituted aziridines. The similar reaction pathways of azetidines and aziridines lead to the ring opening reaction with chloroformate which originates from the ring strain[14] of the intermediate **I** as shown in Scheme 1. The larger ring compounds than azetidine such as pyrrolidine and piperidine are free from ring strain. Thereby the same reaction proceeds to dealkylation instead of ring opening. We conclude that the ring strain energy would be the key to decide the direction between 'a' and 'b' in Scheme 1 for the reactions of nitrogen containing cyclic compounds with chloroformates.

In case of aziridines we observed that chlorinated acyclic product (**3**, $n = 0$) was readily cyclized in the manner **II** of Scheme 1 to yield oxazolidin-2-one (**4**, $n = 0$) in high yield.[2] The same reaction from azetidines yielded only acyclic products without the formation of any detectable amount of cyclic products. Instead we cyclized the chlorinated product (**10a**) under reflux in DMF to afford the cyclic 1,3-oxazinan-2-one (**11**) as a diastereomeric mixture with the ratio of 2:1. The reluctance of intramolecular cyclization gave an opportunity to prepare enantiopure α-substituted-γ-aminoketones by substitution of the chloride with various external nucleophiles. The reactions were successful to give optically pure α-cycano, α-thiocyano, and α-azidio-γ-aminobutyrates (**12**–**14**) in 85%, 82%, and 94% yields, respectively (Scheme 5).

The stereochemical pathways are expected to be inversion of configurations during ring opening and



Scheme 5.



Scheme 6.

the subsequent substitution with an external nucleophile. This was proved by conversion of methyl α-azido-γ-aminobutyrate (**14**) which originated from (2*S*,1*R*′)-1-phenylethylazetidine-2-carboxylate (**5**) into the known amino acid. Azidoamine (**14**) was hydrolyzed with KOH and hydrogenated in the presence of $(Boc)_2O$ to give 2,4-di-*t*-butyloxycarbonyldiaminobutanoic acid (**15**). This was further hydrolyzed with 5 N HCl to yield (2*S*)-diaminobutanoic acid dihydrochloride (**16**) in 50% yield. ($[\alpha]_D$ 12.1 (*c* 0.51, H_2O) lit.[15] $[\alpha]_D$ 12 (*c* 1, H_2O)). The configuration of the asymmetric carbon center at the α-position was completely retained to show that the ring opening reaction of the azetidine-2-carboxylates and the subsequent substitutions occurred in complete inversion manner (Scheme 6).

In summary, enantiopure 1-phenylethylazetidine-2-carboxylates and 2-acylazetidines were prepared and reacted with chloroformates to yield α-chloro-γ-amino butyric acid esters and ketones from ring opening reaction of azetidinium ion intermediates in completely regio- and stereoselective manner.

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12. Representative example of the formation of acyclic chlorinated compounds (**10a**). To a solution of methyl (2*S*,1*R*′)-1-phenylethylazetidine-2-carboxylate (**5**, 145 mg, 0.66 mmol) in 10 mL of CH_3CN was added methyl chloroformate (187 mg, 1.98 mmol), and the mixture was stirred for 8 h in refluxing CH_3CN. The mixture was cooled to room temperature and added by saturated $NaHCO_3$ solution slowly. The aqueous layer was washed with brine and extracted with EtOAc. The combined organic extracts were dried, filtered, and concentrated under reduced pressure. Purification by silica gel flash chromatography (EtOAc/*n*-hexane, 20:80) provided 153 mg (74%) of **10a** as a colorless oil: $[\alpha]_D^{22}$ +27.2 (*c* 2.4, EtOAc); ^1H NMR (200 MHz, $CDCl_3$) 7.34–7.22 (m, 5H), 5.59–5.43 (m, 1H), 4.13 (q, $J = 6.7$ Hz, 1H), 3.68 (s, 3H), 3.66 (s, 3H), 3.11 (t, $J = 7.2$ Hz, 2H), 1.98–2.13 (m, 2H), 1.53 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (50.3 MHz, $CDCl_3$) 169.5, 156.9, 140.9, 128.5, 128.0, 127.4, 79.6, 55.2, 53.9, 52.7, 40.3, 34.6, 17.2. Anal. Calcd for $C_{15}H_{20}ClNO_4$: C, 57.4; H, 6.42; N, 4.46. Found: C, 57.6; H, 6.29; N, 4.75.
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