

# Synthesis of new 3,3-dimethoxyazetidine-2-carboxylic acid derivatives

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Received 8 July 2004; revised 21 October 2004; accepted 22 October 2004

**Abstract**—Cyclization of  $\gamma$ -amino- $\alpha$ -bromocarboxylic esters resulted in an efficient synthesis of new 3,3-dimethoxyazetidine-2-carboxylates, that is, methyl *N*-*t*-butyl-3,3-dimethoxyazetidine-2-carboxylic ester and 3,3-dimethoxyazetidine-2-carboxylic acid, or 3-bromo-4,4-dimethoxypyrrolidin-2-ones, depending on the substituent at nitrogen. Reduction of the 3,3-dimethoxyazetidine-2-carboxylates gave the corresponding 3,3-dimethoxy-2-(hydroxymethyl)azetidines. These novel cyclic amino acid derivatives, available on multigram scale, have a suitably protected carbonyl function at the 3-position, which enables further functionalization.

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## 1. Introduction

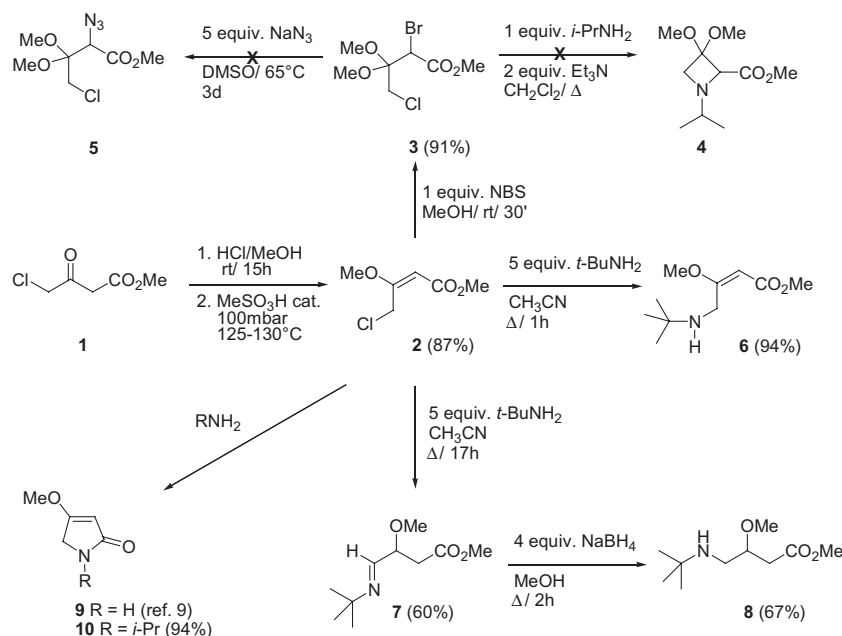
Compared to azetidin-2-ones ( $\beta$ -lactams), azetidin-3-ones are much less widespread.<sup>1</sup> The latter have been regarded as synthons for other natural *N*-heterocyclic four-membered rings, for example, 3-ethylideneazetidin-2-carboxylic acid (polyoximic acid).<sup>2</sup> More specifically, methyl 1-benzhydryl-3,3-dimethoxyazetidine-2-carboxylate has proven to be a useful building block in the synthesis of 4-alkyl-1-benzhydryl-2-(methoxymethyl)azetidin-3-ols.<sup>3</sup> These compounds are representatives of the class of 2,4-disubstituted azetidin-3-ols, which are found in nature as the alkaloids penarisidine A and B and penazetidine A.<sup>4</sup> In the present article we would like to disclose our results on the synthesis of 3,3-dimethoxyazetidine-2-carboxylic esters and 3,3-dimethoxyazetidine-2-carboxylic acids, which can be regarded as useful new building blocks for other azetidine derivatives.<sup>5</sup> This is the first time that such protected cyclic amino acids are made accessible.

## 2. Results and discussion

It has been shown that azetidine-2-carboxylic acid and its derivatives are easily accessible by a cyclocondensation reaction between primary amines and  $\alpha,\gamma$ -dibromoesters,<sup>6</sup> or, in an intramolecular version, from base treatment of  $\gamma$ -amino- $\alpha$ -halogenated acids<sup>7</sup> or  $\alpha$ -(*N*-tosyl)amino- $\gamma$ -halogenated carboxylic esters.<sup>8</sup> Initially, this more direct route towards azetidine-2-carboxylic acid derivatives through cyclocondensation was examined for the synthesis of 3,3-dimethoxyazetidine-2-carboxylates. The substrate for this reaction, that is, the  $\alpha,\gamma$ -dihalo ester **3**, was prepared starting from the commercial methyl 4-chloro acetoacetate **1** (Scheme 1). The latter reaction included alkoxybromination of 4-chloro-3-methoxy-2-butenate **2**, prepared from **1** as described in the literature.<sup>9</sup> Despite the presence of an inductively activated halogen no reaction could be established between the  $\alpha$ -bromo- $\gamma$ -chloro ester **3** and a primary amine. Even sodium azide, successfully applied in structurally related cases, was found to be unreactive under a series of reaction conditions.<sup>10</sup> In a second approach, nitrogen was introduced via nucleophilic substitution of the allylic halogen in **2** prior to alkoxyhalogenation.<sup>11</sup> Treatment of **2** with an excess of *t*-butylamine in acetonitrile under reflux for 1 h afforded pure  $\gamma$ -aminocrotonate **6** in 94% yield. The excess of primary amine was used to minimize the reaction time, as prolonged heating

**Keywords:** Azetidin-3-ones; Azetidine-2-carboxylates; Pyrrolidin-2-ones.

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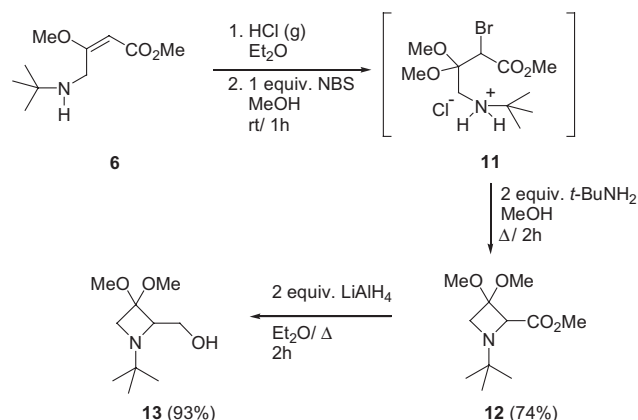
Scheme 1.

resulted in the formation of the regioisomeric  $\gamma$ -imino butanoate **7** as the sole product, originating from two double bond migrations.

The use of the more sterically hindered *t*-butylamine was of prime importance in more than one way. In the case of lower analogues such as isopropylamine and ammonia<sup>9</sup> substitution of the allylic halogen was accompanied by lactam formation. The *t*-butyl group thus clearly prevented cyclization of the crotonate formed. The same accounted for similar saturated compounds, like  $\gamma$ -amino ester **8**.<sup>12</sup> The latter was the only compound observed upon reduction of the  $\gamma$ -imino butanoate **7** with sodium borohydride in methanol under reflux.

The vicinal methoxybromination of the amino crotonate **6** proceeded smoothly, provided the hydrochloride salt of the free base **6** was applied. Since the *t*-alkyl substituent precluded lactam formation, reflux of **11** in methanol in the presence of *t*-butylamine exclusively afforded the desired azetidinecarboxylic ester **12** (Scheme 2).<sup>11</sup> The electrophilic addition and consecutive ring closure could be run as a one pot reaction without isolation of the intermediate  $\gamma$ -amino ester **11**. Even though this approach was restricted to an amine bearing a *t*-butyl substituent, it was an important achievement. The reactions involved are feasible on a large scale. Substantial amounts of the azetidine **12** (38 g) in a 60% overall yield starting from methyl 4-chloroacetoacetate **1** could be obtained. Reduction of the azetidine ester **12** with lithium aluminium hydride finally afforded 3,3-dimethoxy-2-(hydroxymethyl)azetidene **13** in 93% yield.

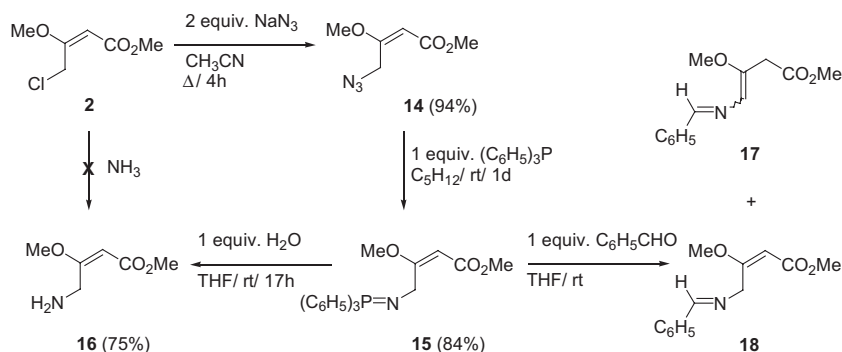
After successfully having accomplished the synthesis of azetidinecarboxylic ester **12**, our attention was focussed on the  $\gamma$ -azidobutenoate **14**, which was used in the synthesis of methyl 1-benzhydryl-3,3-dimethoxyazetidene-2-carboxylate.<sup>3</sup> Staudinger reduction of  $\gamma$ -azidobutenoate



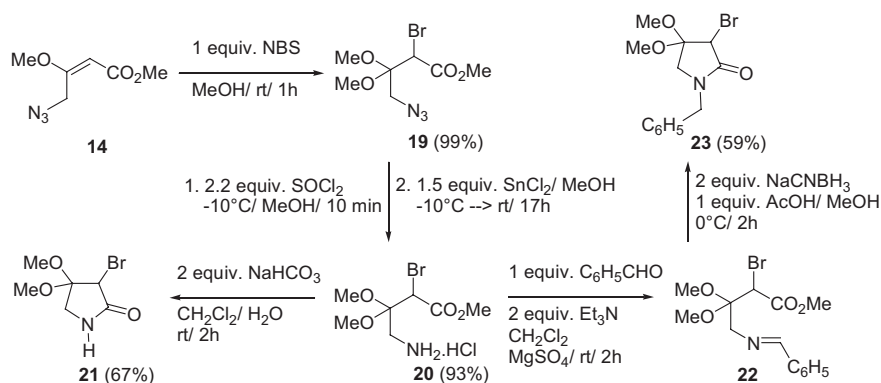
Scheme 2.

**14**<sup>3</sup> generated the iminophosphorane **15**,<sup>13</sup> which precipitated from pentane as a white amorphous solid (Scheme 3). By hydrolysis of **15** with 1 equiv of water in THF, a primary amino group was introduced<sup>13</sup> while circumventing lactam formation in contrast to direct displacement with ammonia.<sup>9</sup> Somewhat disappointingly, an aza-Wittig reaction of the phosphorane **15** with aromatic aldehydes was always accompanied by isomerization of the imino compound to the 2-azadiene **17**. Alkoxyhalogenation of *N*-(arylidene)aminobutenoate **18** and hydride-induced cyclization would have lead again to an azetidene-2-carboxylic ester bearing a removable *N*-substituent.

Efforts were then concentrated on 4-azido-2-bromo-3,3-dimethoxybutanoate **19**, obtained by methoxybromination of  $\gamma$ -azidobutenoate **14** (Scheme 4). Reduction of the azido group with tin(II) chloride in dry methanol containing dry hydrogen chloride provided the hydrochloride salt of the  $\gamma$ -amino ester **20**. The propensity



Scheme 3.



Scheme 4.

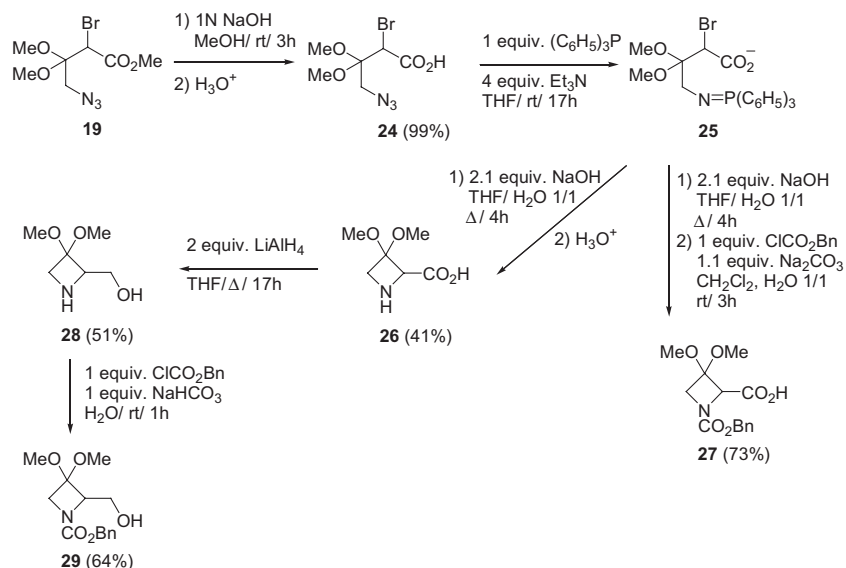
of *N*-unsubstituted  $\gamma$ -amino esters to cyclize was manifested by the neutralization of the hydrochloride salt **20** in a biphasic liquid system of aqueous sodium bicarbonate and dichloromethane. Stirring at room temperature for 1 h was sufficient to obtain the  $\gamma$ -lactam **21** as the sole product. Another possibility to establish the synthesis of an *N*-arylidene- $\gamma$ -amino ester entailed the condensation of **20** with benzaldehyde. The latter was however not so successful as the condensation with benzophenone imine.<sup>3</sup>

As expected, the presence of triethylamine led to the formation of lactam **21** as side reaction. Only the *N*-benzylidene- $\gamma$ -aminoester **22** together with the unreacted benzaldehyde was isolated after aqueous workup. Due to the polarity of the lactam **21** and the alkaline workup, none of it was extracted into the organic layer. Reduction of **22** with NaBH<sub>4</sub> in methanol at room temperature or even with NaCNBH<sub>3</sub> at 0°C finally showed that the propensity for lactam formation is equally valid for  $\gamma$ -amino esters with a primary *N*-substituent.

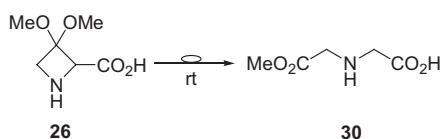
Up to now attention was focussed on the nucleophilic part of the azetidine precursors. In order to prevent the amino function from attacking the ester carbonyl with concomitant lactam formation, the electrophilic part was rendered less attractive towards nucleophilic attack. The best way to do this was to increase its electron density, that is, to protect it as its corresponding carboxylic acid salt. For this purpose, the ester moiety

of the  $\gamma$ -azido ester **19** was hydrolyzed in alkaline medium prior to generation of the amino function (Scheme 5).<sup>12</sup> In the next step a Staudinger reaction was performed to reduce the azido group. Treatment of the  $\gamma$ -azido acid **24** with triphenylphosphine in THF provided a simple way to control the course of the reaction. The intermediate iminophosphorane **25** precipitated from the THF solution as soon as it was formed and could be collected as a white amorphous solid. Hydrolysis of the intermediate **25** with a small excess of base and simultaneous ring closure then offered the free 3,3-dimethoxyazetidine-2-carboxylic acid **26**.<sup>14</sup>

Removal of any inorganic material by means of ion exchange chromatography (Dowex 50  $\times$  8, H<sup>+</sup>) led to considerable loss of material. This is probably due to hydrolysis of the acetal moiety and concomitant ring opening through a retro-Dieckmann reaction.<sup>15</sup> The reaction sequence, leading to *N*-(methoxycarbonylmethyl)glycine **30**, slowly occurred upon storage of the amino acid at room temperature (Scheme 6). It is not inconceivable that the column material works as a catalyst and accelerates the reaction. Direct *N*-protection of amino acid **26** with a benzyloxycarbonyl group however, was possible under Schotten–Baumann conditions, which resulted in carbamate **27** in good yield starting from  $\gamma$ -azido acid **24**. Reduction of the amino acid **26** with lithium aluminium hydride finally yielded the free amino alcohol **28**, which could be benzyloxycarbonylated selectively at nitrogen to afford carbamate **29**.



Scheme 5.



Scheme 6.

The most important advantage of this pathway clearly is the direct access to the free amino acid **26**.

In conclusion, starting from functionalized  $\gamma$ -amino esters, new 3,3-dimethoxyazetidine-2-carboxylates were made accessible, along with the corresponding 2-(hydroxymethyl)azetidines obtained by reduction of the former. These compounds possess the appropriate azetidine skeleton required for further total synthesis of several natural products.

### Acknowledgements

The authors are indebted to the IWT, the FWO and Ghent University (GOA) for financial support of this research.

### References and notes

- Dejaegher, Y.; Kuz'menok, N. M.; Zvonok, A. M.; De Kimpe, N. *Chem. Rev.* **2002**, *102*, 29–60.
- (a) Emmer, G. *Tetrahedron* **1992**, *48*, 7165–7172; (b) Hanessian, S.; Fu, J.-M.; Isono, K. *Tetrahedron Lett.* **1993**, *34*, 4153–4156; (c) Hanessian, S.; Fu, J.-M.; Chiara, J.-L.; Di Fabio, R. *Tetrahedron Lett.* **1993**, *34*, 4157–4160; (d) Isono, K.; Asahi, K.; Suzuki, S. *J. Am. Chem. Soc.* **1969**, *91*, 7490–7505; (e) Baumann, H.; Duthaler, R. O. *Helv. Chim. Acta* **1988**, *71*, 1035–1041.
- Salgado, A.; Boeykens, M.; Gauthier, C.; Declercq, J.-P.; De Kimpe, N. *Tetrahedron* **2002**, *58*, 2763–2775.
- (a) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M. R.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135–1137; (b) Takikawa, H.; Maeda, T.; Seki, M.; Koshino, H.; Mori, K. *J. Chem. Soc., Perkin Trans. 1* **1997**, 97–111; (c) Knapp, S.; Dong, Y. *Tetrahedron Lett.* **1997**, *38*, 3813–3816.
- For a review on the synthesis of azetidin-3-ols and of other azetidines, see: (a) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331–358; (b) De Kimpe, N. Azetidines, Azetines and Azetes: Monocyclic. In *Three and Four-Membered Rings, with all Fused Systems Containing Four-Membered Rings*; Padwa, A., Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive Heterocyclic Chemistry II; Elsevier: Oxford, UK, 1996; Vol. 1B, Chapter 1.18, pp 507–589.
- (a) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1968**, *5*, 309–311; (b) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1969**, *6*, 435–437; (c) Phillips, B. A.; Cromwell, N. H. *J. Heterocycl. Chem.* **1973**, *10*, 795–799; (d) Wasserman, H. H.; Lipshutz, B.; Tremper, A. W.; Wu, J. S. *J. Org. Chem.* **1981**, *46*, 2991–2999; (e) Kulkarni, S. B.; Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1976**, *13*, 329–332; (f) Soriano, D. S.; Podraza, K. F.; Cromwell, N. H. *J. Heterocycl. Chem.* **1980**, *17*, 1389–1392.
- (a) Fowden, L. *Nature (London)* **1955**, *176*, 347–348; (b) Fowden, L. *Biochem. J.* **1956**, *64*, 323–332; (c) Pichat, L.; Liem, P. N.; Guermont, J. P. *Bull. Soc. Chim. Fr.* **1968**, 4079–4081; (d) Yamada, S.; Emori, T.; Kinoshita, S.; Okada, H. *Agric. Biol. Chem.* **1973**, *37*, 649–652.
- (a) Chen, T.; Sanjiki, T.; Kato, H.; Ohta, M. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2398–2401; (b) Miyoshi, M.; Sugano, H.; Fujii, T.; Ishihara, T.; Yoneda, N. *Chem. Lett.* **1973**, 5–6.
- Duc, L.; McGarrity, J. F.; Meul, T.; Warm, A. *Synthesis* **1992**, 391–394.
- (a) Micetich, R. G.; Maiti, S. N.; Spevak, P.; Tanaka, M.; Yamazaki, T.; Ogawa, K. *Synthesis* **1986**, 292–296; (b) Durst, T.; Koh, K. *Tetrahedron Lett.* **1992**, *33*, 6799–6802.
- Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1971**, *8*, 19–24.
- Khoukhi, N.; Vaultier, M.; Carrié, R. *Tetrahedron* **1987**, *43*, 1811–1822.

13. Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, 24, 763–764.
14. 3,3-Dimethoxyazetidine-2-carboxylic acid **26**:  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ , 270 MHz):  $\delta$  (ppm) 3.20 (s, 3H), 3.32 (s, 3H), 4.04 (d,  $J = 11.2$  Hz, 1H), 4.17 (d,  $J = 11.2$  Hz, 1H), 4.79 (s, 1H);  $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ , 67.5 MHz):  $\delta$  (ppm) 48.8, 49.3, 53.2, 68.7, 97.7, 167.5; IR (KBr,  $\text{cm}^{-1}$ ): 3600–2200, 1680; MS (70 eV)  $m/z$  (%): no  $\text{M}^+$ , 149 (4), 132 (15), 115 (8), 101 (7), 89 (5), 88 (98), 87 (29), 86 (11), 84 (8), 75 (11), 74 (13), 73 (8), 71 (5), 70 (5), 69 (12), 60 (9), 59 (11), 58 (46), 57 (17), 56 (7), 55 (12), 47 (4), 45 (14), 44 (33), 43 (100), 42 (21), 41 (18), 40 (26).
15. Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, 50, 5223–5230.