Pergamon

Tetrahedron Letters 42 (2001) 2119–2120

TETRAHEDRON LETTERS

Direct diastereoselective synthesis of (±)-*cis*- and (±)-*trans*-4-methylpipecolic acid and derivatives

Janine Cossy* and Damien Belotti

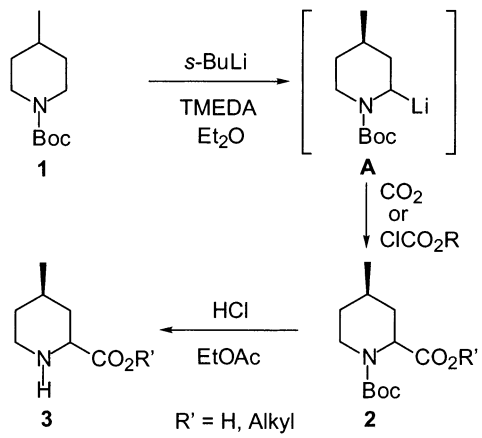
Laboratoire de Chimie Organique associé au CNRS, ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France

Received 17 November 2000; accepted 21 January 2001

Abstract—(±)-*cis*- or (±)-*trans*-4-Methylpipecolic acid and ester derivatives can be obtained directly by addition of electrophiles to α-lithiated *N*-Boc 4-methylpiperidine. © 2001 Elsevier Science Ltd. All rights reserved.

The synthesis of modified unnatural amino acids is still of great interest and of constant inspiration.[1] In particular much attention has been directed toward the diastereoselective synthesis of enantiomerically enriched 4-substituted pipecolic acids as they are constituents of biologically active compounds.[2] Access to the *cis* isomers is much easier than to the *trans* isomers as the former are the most conformationally stable.[3] One synthesis of alkyl (±)-*trans*-4-methylpipecolate was reported in five to six steps from 4-methylpyridine with an overall yield of 14%.[3]

It has been reported than the *N*-*tert*-butoxycarbonyl group (*N*-Boc) is an effective directing group for the α-lithiation of piperidines[4] and that the more thermodynamically stable isomer is the *trans N*-Boc 4-substituted pipecolic acid derivatives.[5] As alkyl (±)-*trans*-4-methylpipecolate was needed to synthesize argatroban,[6] carboxylation of 4-methylpiperidine was envisaged. Although, alkyl chloroformates as electrophiles were reported to give very low yields of α-aminoesters,[7] we report here that (±)-*cis*- and (±)-*trans*-4-methylpipecolic acid derivatives can be obtained diastereoselectively in a two-step sequence, in modest yield, from *N*-Boc 4-methylpiperidine by a lithiation–carboxylation sequence with CO_2 or alkyl chloroformates, followed by *N*-Boc deprotection.



N-Boc 4-methylpiperidine **1** was deprotonated with *sec*-BuLi (1.5 equiv., Et_2O, –90°C, 4–5 h) in the presence of TMEDA (1.5 equiv.). After the addition of the alkyl chloroformate (1.6 equiv.) or CO_2 at –90°C, the reaction mixture was allowed to slowly reach rt and stirred for 12 h to produce the desired carboxylic ester derivatives of type **2** in a modest yield (35–60%) (see Table 1). After deprotection of **2** with HCl in EtOAc, the 4-methylpipecolic acid **3** (R = H) or the ester derivatives were obtained in quantitative yield. The use of CO_2 as the electrophile produced exclusively the *cis* isomer. When the acylation was achieved with methyl or ethyl chloroformate, a mixture of (±)-*cis* and (±)-*trans N*-Boc 4-methylpipecolic esters was obtained in respective ratios of 35/65 and 30/70 in favor of the *trans*

Table 1. *cis*/*trans* Ratio of 4-methylpipecolic acid and derivatives

Electrophile	*cis*/*trans*	Yield (%)[a]
CO_2	100/0	60
$ClCO_2CH_3$	35/65	58
$ClCO_2C_2H_5$	30/70	60
$ClCO_2CH_2Ph$	5/95	35

[a] Yield for 50% conversion of the starting material which was recovered after chromatography on silica gel.

Keywords: piperidine; pipecolic acid; electrophile; 4-methylpipecolic acid.

* Corresponding author.

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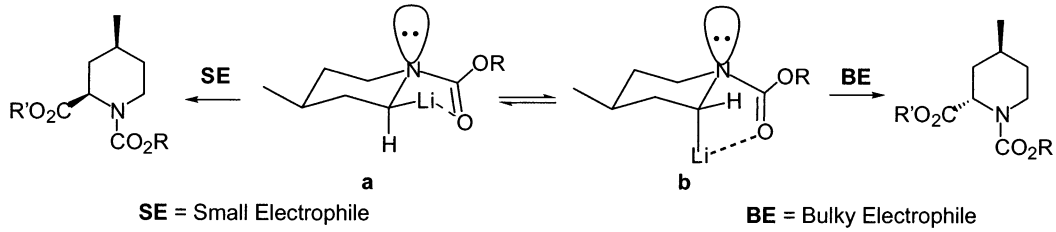
PII: S0040-4039(01)00138-1



Scheme 1. α-Lithiated *N*-Boc piperidines.

diastereomer. Benzyl chloroformate, afforded mainly the *trans* diastereomer (*cis*/*trans* = 5/95) possibly because of the increased steric bulk of this reagent. The results are summarized in Table 1.

We would expect the lithiated intermediates **a** and **b** to be favored as the *N*-Boc is in the equatorial orientation and well situated to coordinate with the α-lithiated anion.[4,8] As the reaction proceeds with an excess of alkyl chloroformate, equilibration between the *cis* and *trans* 4-methylpipecolic acid or derivatives should not occur. Furthermore, as it was assumed previously, the electrophilic substitution of equatorial α-lithiated piperidines is achieved with retention.[4] It would seem therefore that both equatorial and axial α-lithiated piperidines are formed under these conditions (Scheme 1). When a non-bulky acylating reagent is used as CO_2, an equatorial electrophilic substitution is preferred leading to the *cis*-2,4-disubstituted *N*-Boc piperidines. To minimize steric interactions with the *N*-Boc group, axial electrophilic substitution is preferred with sterically hindered acylating reagent such as benzyl chloroformate.

Although the yield of 4-methylpipecolic acid and their derivatives by using the carboxylation of α-lithiated piperidines is modest (30–60%), the method is direct (two steps) and efficient compared to the other routes.[3] Applications of this methodology to the synthesis of biologically active compounds such as argatroban[9] will be reported in due course.

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