Tetrahedron Letters 52 (2011) 2471–2472

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A facile synthesis of multigram quantity of ethyl 3-ethylmorpholine-3-carboxylate

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ARTICLE INFO

Article history:
Received 10 February 2011
Accepted 1 March 2011
Available online 12 March 2011

ABSTRACT

A five-step synthesis of ethyl 3-ethylmorpholine-3-carboxylate proceeding from readily available 2-aminobutyric acid is detailed herein.

The morpholine ring structure is a moiety found in a wide variety of natural products and many pharmaceutically relevant compounds.[1] Despite its increasing prevalence in molecules that display interesting biological and pharmacological properties, the synthetic utility of the morpholine ring is quite limited due to the combination of a lack of commercially available C-substituted morpholines as starting materials, as well as the fact that new synthetic approaches to C-functionalized morpholines remains a relatively unexplored synthetic area.[2] Recently, several methods detailing the preparation of 3-substituted morpholines have been described.[3] However, to our knowledge, few reports of 3,3-disubstituted morpholines have been described.[3c,4]

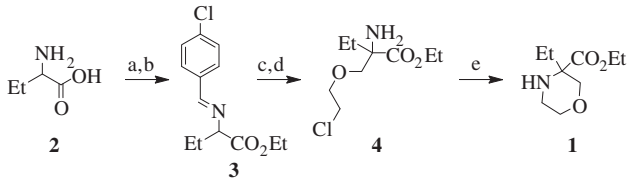
Recently, in connection with one of our research projects, multigram quantities of racemic ethyl 3-ethylmorpholine-3-carboxylate (**1**) were required. Surprisingly, no reports related to the preparation of this or similar 3,3-disubstituted morpholines were found in the literature. Reviews of possible synthetic approaches to **1** led to the selection of the route displayed in Scheme 1.

Proceeding from the readily available racemic 2-aminobutyric acid **2**, morpholine **1** can be obtained in a straightforward manner. Esterification of **2**, followed by condensation with 4-chlorobenzaldehyde provided imine **3** in 85% yield over two steps. Protection of the carboxylic acid **2** as an ethyl ester gave a significantly better yield than the methyl ester. This was attributed to the increased stability of the ethyl ester toward bases used during the synthesis. Additionally, imine **3** proved quite stable and could be stored at 4 °C for weeks. Alkylation of imine **3** proved to be the key intermediate reaction, and was achieved by reaction with 2-chloroethyl-chloromethyl ether in the presence of potassium *tert*-butoxide. The best results were obtained when deprotonation occurred at −78 °C in the presence of 2-chloroethyl-chloromethyl ether, and the reaction mixture was allowed to slowly warm to ambient temperature. The 4-chlorobenzyl group was removed by an aqueous hydrochloride acid work-up to provide amine **4** in 74% yield. Cyclization of amine **4** in the presence of sodium iodide and a catalytic amount of tetrabutylammonium iodide provided morpholine **1** in 65% yield.

The sequence proved easily reproducible and easy to carry out, even on a large scale, starting from 100 g of 2-aminobutyric acid. A single purification step for the entire five-step sequence was required. Neither imine **3** nor compound **4** required purification. However, purification of the final morpholine ester **1** was necessary to remove the low-level impurities that interfered with the subsequent chemistry. We speculate that there may have been present some carryover amounts of tetrabutylammonium salts and/or residual 2-chloroethyl-chloromethyl ether. The final product, **1**, is obtained as a viscous, pale-cream to colorless liquid in five steps in a 40% overall yield.

The Maruoka catalytic phase-transfer asymmetric alkylation[5] of imine **3** was briefly examined (Scheme 2).

The crude product of the reaction (**4a**, non-optimized conditions) was in turn subjected to cyclization to morpholine **1a.** Its optical purity was evaluated after preparation of respective *N*-benzoyl derivative (**1b**). It was found that the *N*-benzoyl-morpholine **1b** was ~40% ee, indicating that the opportunity exists for further optimization of imine alkylation conditions and eventually the



Scheme 1. Reagents and conditions: (a) EtOH/HCl, reflux; (b) 4-Cl-benzaldehyde, $MgSO_4$, Et_3N, CH_2Cl_2; (c) 2-chloroethyl–chloromethyl ether, KOtBu, THF, −78 °C to rt; (d) aq 1 N HCl, ambient, 2 h; (e) NaI, TBAI, K_2CO_3, CH_3CN, rt to 50 °C, 18 h.

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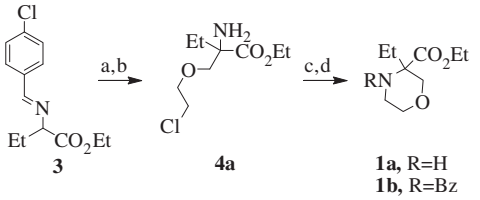
doi:10.1016/j.tetlet.2011.03.003



Scheme 2. Reagents and conditions: (a) 2-chloroethyl–chloromethyl ether, CsOH–H_2O, (*R*)-catalyst, toluene, 0 °C to rt, 24 h; (b) aq 1 N HCl, ambient, 2 h; (c) NaI, TBAI, K_2CO_3, CH_3CN, rt, 30 h; (d) benzoyl chloride, triethylamine, CH_2Cl_2, rt, 18 h.

morpholine **1** could be prepared as a non-racemic compound as well.

In conclusion, an efficient and scalable route to ethyl 3-ethylmorpholine-3-carboxylate, **1** was developed. The synthesis proceeds in five steps and 40% overall yield from readily available 2-aminobutyric acid, **2**, and requires only a single column chromatography purification of the final product.

Acknowledgements

We thank Donald Walker and John Maynard for their contributions to this work.

Supplementary data

Supplementary data (synthesis and characterization of the final product and intermediates) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.03.003.

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