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SYNTHESIS OF ETHYL 1-AZABICYCLO[2.2.1]HEPT-4-YL CARBOXYLATE

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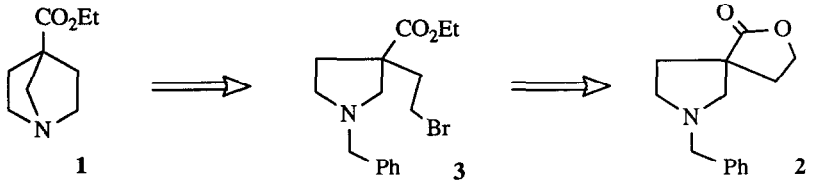
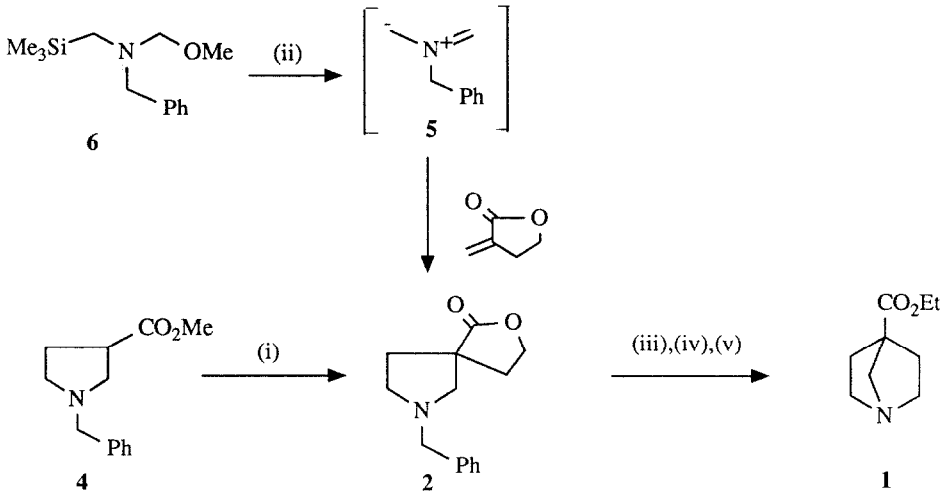
Summary - The dipolar cycloaddition reaction of α-methylene butyrolactone and N-benzyl azomethine ylid (5) affords the spirolactone (2) which rearranges to give ethyl 1-azabicyclo[2.2.1]hept-4-yl carboxylate (1) in excellent overall yield.

The synthesis of suitably functionalised 1-azabicyclo[2.2.1]heptanes has attracted considerable attention in recent years in view of the potent cholinomimetic activity associated with compounds incorporating this ring system[1]. In a previous letter[2] we described a diastereoselective approach to endo and exo 1-azabicyclo[2.2.1]hept-3-yl carboxylates based on the rearrangement of fused lactone precursors. We now wish to report the first synthesis of the isomeric 1-azabicyclo[2.2.1]hept-4-yl carboxylate (1).

The target ester (1) can be viewed as the rearrangement product of the N-benzyl protected spirolactone (2). Cleavage of lactone (2) with HBr/EtOH was expected to give the bromoethyl pyrrolidine (3) which is suitably arranged for cyclisation to the required bridgehead ester (1)[3].



We have investigated two approaches to the spirolactone (2). Initially, effort was focussed on the possibility of converting the readily available methyl N-benzylpyrrolidin-3-yl carboxylate (4)[4] into the required lactone (2). Treatment of (4) with LDA in the presence of TMEDA followed by reaction with ethylene oxide[5] afforded the required lactone (2). This constitutes a more direct method than conventional procedures which employ dicarboxylic acid ester intermediates[6]. However, yields were variable (36-85%), and the reaction appeared to be sensitive to the presence of low levels of impurity in the starting ester. A much improved route was developed which involved constructing the lactone by cycloaddition of the N-benzyl azomethine ylid (5) and α-methylene butyrolactone[7]. The ylid (5) was generated in situ by treatment of methoxymethyltrimethylsilylmethylbenzylamine (6) with trifluoroacetic acid as described by Terao *et al*[4]. The reaction of (5) with α-methylene butyrolactone proceeded in excellent yield (95%), providing a convenient convergent route to the spirolactone (2). Treatment of a solution of (2) in ethanol with HBr cleaved the lactone, and liberation of the free base with aqueous potassium carbonate resulted in spontaneous cyclisation. Debenzylation completed the synthesis. The overall yield of (1) based on α-methylenebutyrolactone was 79%.



Reagents: (i) LDA, TMEDA, Et_2O, -65°C then ethylene oxide, reflux (ii) CF_3CO_2H, CH_2Cl_2, rt (iii) EtOH saturated with HBr (iv) Aqueous K_2CO_3 (v) H_2, Pd-C, EtOH

In summary, this work demonstrates the versatility of dipolar cycloaddition methodology, and provides a short high yielding route to the novel azabicyclic ester (1).

References and Notes

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3. The synthesis of 4-ethoxycarbonyl quinuclidine using a similar strategy has been described by W. Eckhardt, C. A. Grob and W. D. Treffert Helv. Chim. Acta. 1972, 55(7), 2432.
4. Y. Terao, H. Kotake, N. Imai and K. Achiwa Chem. Pharm. Bull. 1985, 33, 2762.
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6. When this procedure was applied to ethyl N-benzyl nipecotate the corresponding spirolactone was obtained in good yield (50-70%). This represents a marked improvement on the method described in reference 3.
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