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AN IMPROVED ROUTE TO CYCLOALKA[b]PYRROLE 2- CARBOXYLATES

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AN IMPROVED ROUTE TO CYCLOALKA[b]PYRROLE 2-CARBOXYLATES

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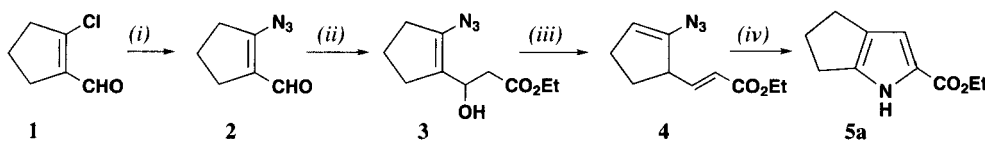
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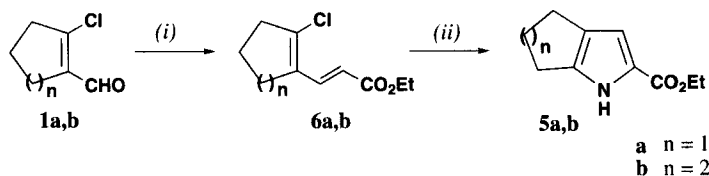
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Cyclopenta- and cyclohexa[b]-pyrrole-2-carboxylate derivatives are key intermediates in the synthesis of angiotensin II antagonists¹ and of angiotensin converting enzyme inhibitors.² In the course of a project, we needed cycloalka[b]-pyrrole-2-carboxylates **5a** and **5b**. Thus we considered the synthesis of ethyl cyclopenta[b]-pyrrole-2-carboxylate **5a**³ which is reported as involving condensation of active methylene aliphatic esters with the aldehyde group of the 2-azidocyclopent-1-ene-1-carbaldehyde **2**, followed by thermal cyclization *via* nitrene attack to the unsaturated side-chain. We have now achieved a two-step synthesis of **5a** (and of its cyclohexa analogue **5b**⁴) based on a modification of this literature method.³



(i) NaN₃, DMSO, 10°; (ii) 1. LDA, THF, -78°; 2. CH₃CO₂Et; (iii) POCl₃, PhH, pyridine, 0°; (iv) Δ, xylene

Thus β-cycloalkenyl acrylates **6a,b** were easily prepared by a Wittig reaction of **1a,b** with ethoxycarbonylmethylene triphenylphosphorane which were then cyclized in one-step by heating in DMSO with sodium azide. In comparison with the former method, our procedure has the advantages of consisting of fewer steps (2 vs 4) and simpler and safer reaction conditions which avoid LDA at low temperature (-78°) and the isolation of the potentially explosive azide **2**.⁵ Starting from **1a**, both methods gave **5a** in an identical overall yield (29%), whereas a 60% overall yield of **5b** was obtained from **1b**. This represents an improvement on the synthesis of **5b** from 2-formylcyclohexanone, where an isomeric mixture of alkyl cyclohexa[b]- and alkyl cyclohexa[c]pyrrole-2-carboxylate are obtained,^{4,6} and provides an useful alternative to the methods for **5b** starting from 4H-2-oxazines.⁷⁻⁹



EXPERIMENTAL SECTION

Melting point were determined on a Buchi SMP-510 capillary apparatus and are uncorrected. ^1H NMR spectra were recorded on a Varian EM 60 spectrometer and are reported in ppm (δ) with TMS as the internal standard. EI-MS spectra (70eV) were taken on a Fisons TRIO 1000 instrument. **Proper precautions should be used when working with azides.**

Ethyl β -(2-Chlorocyclopenten-1-yl)acrylate (6a) and Ethyl β -(2-Chlorocyclohexen-1-yl)acrylate (6b).— To the appropriate aldehyde **1a,b** (2 mmol)¹⁰ dissolved in dry benzene (2 mL), was added ethoxycarbonylmethylene triphenylphosphorane (2 mmol); the strongly exothermic reaction mixture was stirred at room temperature (**1a**: 6 h; **1b**: 4 h). The solvent was evaporated and the residues were purified by flash chromatography (cyclohexane-EtOAc 8:2 as eluent) to give pure compounds as yellowish oils.

TABLE. β -Cycloalkenyl Acrylates **6a,b**

Cmpd	Yield (%)	MS (70eV) (mz, %)	^1H NMR (CDCl_3) (δ)
6a	99	200(16), 137(100)	7.60 (d, 1H), 5.75 (d, 1H), 4.25 (q, 2H), 2.9-1.8 (m, 6H), 1.30 (t, 3H).
6b	93	214(29), 151(100)	7.95 (d, 1H), 5.85 (d, 1H), 4.2 (q, 2H), 2.7-1.5 (m, 8H), 1.3 (t, 3H).

Ethyl Cyclopenta- and cyclohexa[b]pyrrole-2-carboxylate (5a,b).— To a solution of a suitable acrylate (**6a,b**, 1 mmol) in DMSO (1.4 mL), was added NaN_3 (1.5 mmol) and the mixture was heated (**6a**: 65°, **6b**: 105°) with stirring until the starting material had disappeared by TLC analysis (**6a**: 8 h; **6b**: 4h). The mixture was cooled, water (14 mL) was added, and the mixture was extracted with CH_2Cl_2 ; the organic phase was dried (NaSO_4), evaporated to dryness to give a tar. Flash column chromatography (cyclohexane-EtOAc 7:3 as eluent) furnished pure compounds (Yields: **5a** 29%; **5b** 64%).

Compound **5a**: mp. 120-121° (cyclohexane), lit.³ 124° (heptane). Compound **5b**: mp. 108-109° (Et_2O /light petr.), lit.⁴ 98-100° (ethanol); the mass spectrum of **5b** is in agreement with the reported data.⁴

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SYNTHESES AND STEREOCHEMISTRY OF TETRAHYDROFURAN DERIVATIVES FROM α -PINENE

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Tetrahydrofuran derivatives have been utilized as intermediates for the synthesis of α -haloesters^{1,2} and γ -lactones³ and terpenoid tetrahydrofuran derivatives have been useful as perfumes. Only a few papers have been reported the synthesis of terpenoid tetrahydrofuran derivatives.⁴ In 1985, Kula⁵ synthesized 2,2,5-trimethyl-3-(3-methyl-2-butenyl)tetrahydrofuran (**4b**) in several steps *via* diol **3b** derived from α -pinene (**1**) and found it to be endowed with good flowery-woody scent. However, the stereochemistry of **4b** was not investigated.

This paper reports a new one-pot method for the synthesis of a terpenoid tetrahydrofuran derivative (**4a**) *via* ozonization of α -pinene (**1**) and sodium borohydride reduction followed by treat-