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SYNTHESIS OF 1-AZIDOCYCLOPROPANECARBOXYLATES FROM 2-AZIDO-2-ALKENOATES

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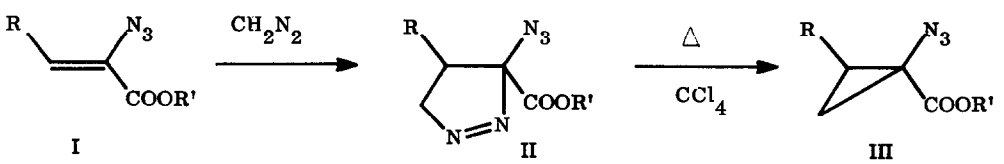
Addition of diazomethane to 2-azido-2-alkenoates followed by pyrolysis of the resulting pyrazoline derivatives affords the title compounds.

The title compounds III are logical precursors of 1-aminocyclopropanecarboxylic acids, some of which exhibit remarkable biological activity.[1-4] We wish to report these compounds are readily prepared by the cycloaddition of diazomethane to 2-azido-2-alkenoates (I) and subsequent selective thermal decomposition of the resulting pyrazoline derivatives II.

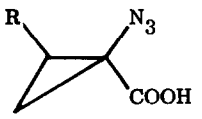
Ethyl 2-azidopropenoate (Ia)[5] was allowed to react with excess diazomethane in diethyl ether at room temperature for 2 h. Evaporation of the solvent gave the adduct IIa (93% yield) showing IR (neat): 2120, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.35 (q, J = 6 Hz, 3H), 1.4-1.7 (m, 1H), 2.0-2.3 (m, 1H), 4.30 (q, J = 6 Hz, 2H), 4.6-4.9 (m, 2H). Pyrolysis of IIa (toluene refluxing temperature) or photolysis (pyrex filter, high pressure mercury arc) gave intractable mixture of products. However, heating a carbon tetrachloride solution of IIa (0.38 mol/dm^3) at 80°C for 2 h induced smooth decomposition of IIa to give ethyl 1-azidocyclopropanecarboxylate (IIIa) in a quantitative yield. IR: 2120, 1740, 1320, 1200, 1150 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.0-1.5 (m +t, 7H), 4.15 (q, J = 6 Hz, 2H). Particularly noteworthy is that selective pyrazoline-cyclopropane ring-contraction took place at relatively low temperature with the azido group intact.[6] Hydrolysis (1 mol/dm^3 NaOH, EtOH, r.t., 5 h) of IIIa gave the carboxylic acid IVa (71%) which was reduced (10% Pd/C, EtOH, H_2 1 atm, 69% yield) to 1-aminocyclopropanecarboxylic acid (Va), mp 198-201°C (lit[1b] mp 224-231°C), a natural amino acid playing a role of plant growth regulator.[1]

Starting with ethyl (Z)-2-azido-2-butenoate (Ib),[5,7] we obtained ethyl 1-azido-2-methylcyclopropanecarboxylate (Ib→IIb, 90%, IIb→IIIb, 57% yield). ^1H NMR spectra suggest IIIb is consisted of two stereoisomers (ca 4:1), the major one presumably being that depicted (vide infra). Alkaline hydrolysis gave IVb in an 88% yield; IR (neat): 3000, 2120, 1710, 1440, 1270 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.85-2.15 [m +d (δ 1.28), 6H], 9.5-9.9 (br s, 1H).

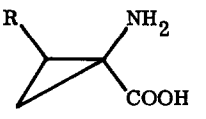


I II III

a: R = H, R' = Et, b: R = Me, R' = Et, c: R = Et, R' = Me, d: R = C_6H_5, R' = Et



IV



V

a: R = H, b: R = Me, c: R = Et, d: R = C_6H_5

This process is applicable to the synthesis of dl-allo-coronamic acid (Vc).[3] Reaction of methyl (Z)-2-azido-2-pentenoate (Ic)[5] with diazomethane (quantitative yield) and pyrolysis of the resulting pyrazoline IIc in refluxing carbon tetrachloride for 3 h gave methyl 1-azido-2-ethylcyclopropanecarboxylate (IIIc) in a 61% yield after chromatography. IR (neat): 2100, 1740, 1440, 1310, 1260, 1140 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.7-1.7 [m + t (δ 0.96, J = 7 Hz), 8H)], 3.70 (s, 3H). Stereochemical purity of IIIc was more than 90% based on the MeO signal of the ^1H-NMR spectra. Alkaline hydrolysis (87%) followed by hydrogenolysis (96%) gave allo-coronamic acid having consistent spectral data. The stereochemical confirmation was further made by reduction of IIIc (10% Pd/C, EtOH, H_2 1 atm) followed by methoxycarbonylation (ClCOOMe, pyridine, hexane, r.t., 1.5 h) to give methyl trans-2-ethyl-1-(N-methoxycarbonylamino)cyclopropanecarboxylate, mp 72-73°C (from hexane) (lit[3] mp 67.5-69°C), which exhibited correct spectra.

Finally, ethyl 1-azido-2-phenylcyclopropanecarboxylate (IIId, uniform by ^1H NMR) was prepared from ethyl (Z)-2-azido-3-phenylpropenoate (Id).[7] Both cycloaddition of diazomethane and pyrolysis of the pyrazoline IId turned out less effective (48% and 22% yield respectively), due possibly to steric and electronic effects of phenyl group. IId is readily transformed into Vd which is recorded to have hypotensive activity.[4]

Since the transformation of I into III or V could not be attained by other methods,[8] the process described herein should be widely applicable to the synthesis of 1-aminocyclopropanecarboxylic acids.

References and Notes

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