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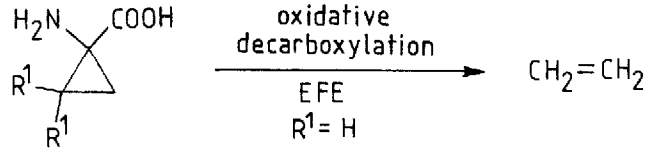
SYNTHESIS OF 2,2-DIALKYL-1-AMINOCYCLOPROPANECARBOXYLIC ACIDS FROM α-CHLOROIMINES

Norbert De Kimpe,* Paul Sulmon,[¶] Pascal Brunet, Fernand Lambein[§]
and Niceas Schamp
Laboratory of Organic Chemistry, Faculty of Agricultural Sciences,
State University of Gent, Coupure Links 653, B-9000 Gent, BELGIUM

Abstract

2,2-Dialkyl-ACC analogues, i.e. potential plant growth regulators, were synthesized via straightforward cyclopropanation of α-chloroimines.

1-Aminocyclopropanecarboxylic acid 1 (ACC) holds a prime position in plant physiology as it is oxidatively decarboxylated by the so-called "ethylene forming enzyme" (EFE) to produce ethylene 3, which is a major plant hormone.[1] Ethylene plays an important role in the germination, ripening of fruits, abscission of fruits and leaves, and senescence of plants. The physiological importance of ACC 1 and ethylene 3 has stimulated much efforts in the develop-

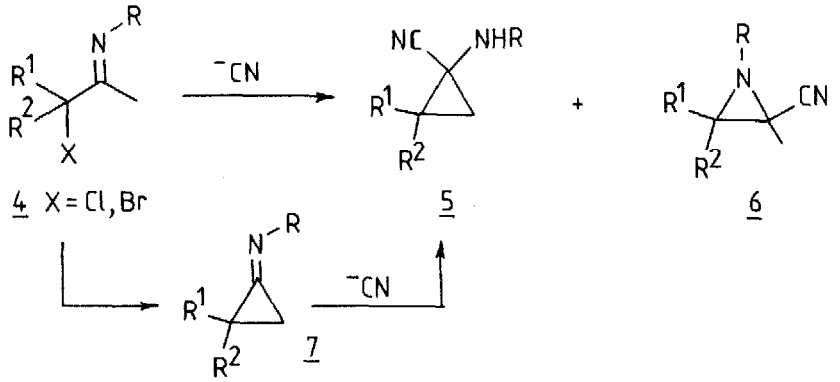


1 R^1 = H (ACC)
2 $R^1 \neq$ H

3

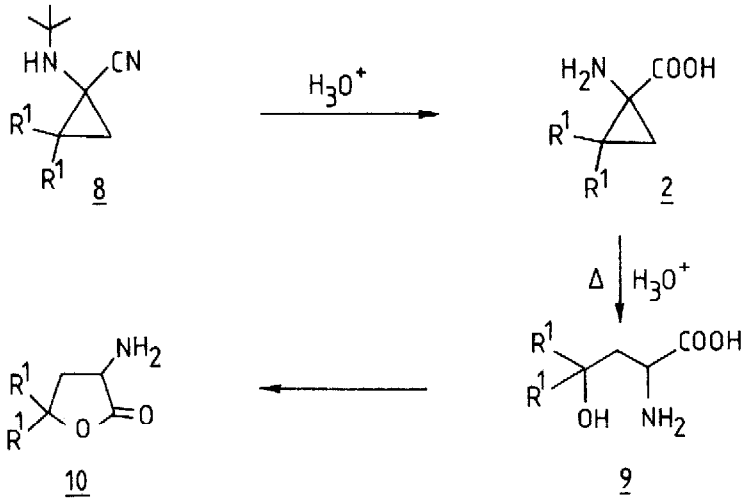
ment of substrates which might induce an inhibition of the ethylene production, thus allowing a potential control of the ripening process. Major synthetic efforts have been directed towards monoalkylated ACC-analogues, some of which showed inhibition of the EFE.[2] Up to now, the reported syntheses of monoalkyl-ACC's did not allow to generate geminal dialkylation at the cyclopropane moiety of ACC. Because of the fact that geminally dialkylated ACC-analogues 2 have a potential plant growth regulating activity, the synthesis of these target molecules was performed starting from α-chloroimines 4 (X=Cl).

Previous studies revealed that cyanation of α-haloimines 4 under Favorskii conditions entailed a useful cyclopropanation to form 5 via cyclopropylideneamines 7, but α-cyanoaziridine formation (see 6) was most of all the major reaction.[3] A detailed study of the cyanation of α-haloimines 4 unraveled that the nature of the cyanide, the α-halogen and the solvent played an important role, but that especially the introduction of steric bulk in the starting compound directed the reactivity towards cyclopropanation, i.e. formation of 1-(N-alkylamino)cyclopropanecarbonitriles 5.[3] This led us to use N-t-butyl α,α-dialkyl-α-chloroketimines 3 (X=Cl; R=t-Bu) in the generation of cyclopropanecarbonitriles 5. The tertiary halide moiety in 4 would allow the synthesis of geminally dialkylated cyclopropanes and the t-butyl group on nitrogen would enable removal in acid medium.



Reaction of N-t-butyl α-chloroketimines 4 (X=Cl; R=t-Bu; R^1=R^2=Me, Et, n-Pr) with potassium cyanide in methanol under reflux (5-6h) gave rise to 1-(N-t-butylamino)-2,2-dialkylcyclopropanecarbonitriles 5 (R^1=R^2=Me : 47%; R^1=R^2=Et : 93%; R^1=R^2=n-Pr : 92%) and, to a minor extent, α-cyanoaziridines 6. After separation of both compounds by distillation, the 1-(N-t-butylamino)-2,2-dialkylcyclopropanecarbonitriles 8 were treated with aqueous hydrogen chloride under reflux (10 molar equiv. 2-5N aq. HCl; Δ 3-5 days), which hydrolyzed the nitrile function to the carboxylic acid and which removed the t-butyl substituent on nitrogen. Under these conditions, 1-amino-2,2-dimethylcyclopropanecarboxylic acid 2a (R^1=Me) was obtained in 40-60% yield but an increasing geminal substitution (R^1=Et, n-Pr) caused, not unexpectedly, the three-membered ring to open in a competitive reaction resulting in the formation of γ-hydroxy-α-aminoacids 9 (0-26%) and the cyclized α-aminolactones 10 (3-24%). Accor-

dingly, yields of the higher ACC-analogues 2 dropped dramatically to 17-27%. The various intrinsic reactions of the hydrolysis step, namely hydrolysis of the nitrile, deprotection on nitrogen and cleavage of the cyclopropane ring,



are plausible to occur in a mixed, undefined order. However, monitoring of the reaction by tlc revealed that ACC-analogues 2 are the initial reaction products, which are cleaved in the acid medium. This statement is supported by the conversion of 1-amino-2,2-dimethylcyclopropanecarboxylic acid 2a (R^1= Me) with 5N aqueous hydrogen chloride (10 equivalents) under reflux (18.5 days) into 3-amino-5,5-dimethylbutyrolactone hydrochloride 10a in 92% yield.

The mixture of α-aminoacids 2 and 9 and α-aminolactones 10 were separated by the usual chromatographic techniques (DOWEX 50X8-100; tlc monitoring of the eluates; 1,2-epoxypropane treatment; gel filtration with Bio Gel P-2 200-400 mesh). All compounds were characterized by ^{1}H NMR (360 MHz)[4], ^{13}C NMR and IR spectrometry. The purity of the new ACC-analogues 2 was verified by HPLC analysis (sulphonated polystyrene-divinylbenzene column using gradients of 0.2N and 1N sodium citrate buffers). Further characterization was established by mass spectrometric and gas chromatographic analysis of derivatives of the ACC-analogues, e.g. N-methoxycarbonyl derivatives and silylated derivatives [N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA) converted ACC-analogues 2 into O-silylated and O,N-silylated derivatives].

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References

* N. De Kimpe : "Onderzoeksleider" (Senior Research Associate) of the Belgian National Fund for Scientific Research (Nationaal Fonds voor Wetenschappelijk Onderzoek).

¶ Present address : DSM Limburg b.v., Geleen (The Netherlands).

§ Laboratory of Physiological Chemistry, State Univ. of Gent, K.L. Ledeganckstraat 35, B-9000 Gent, Belgium.

1. S.F. Yang, N.E. Hoffman, Ann. Rev. Plant Physiol., 35, 155 (1984).

2. For some leading references on the synthesis of 2-substituted-1-aminocyclopropanecarboxylic acids, see : A. Ichihara, K. Shiraishi, S. Sakamura, Tetrahedron Lett., 269 (1977); H. Liu, R. Auchus, C.T. Walsh, J. Am. Chem. Soc., 106, 5335 (1984); M.L. Izquierdo, I. Arenal, M. Bernabe, E. Fernandez Alvarez, Tetrahedron, 41, 215 (1985); J.E. Baldwin, R.M. Adlington, B.J. Rawlings, Tetrahedron Lett., 26, 481 (1985); M.C. Pirrung, G.M. McGeehan, Angew. Chem., 97, 1074 (1985); U. Schöllkopf, B. Hupfeld, R. Gull, Angew. Chem. Int. Ed. Engl., 25, 754 (1986); M. Suzuki, E.E. Gooch, C.H. Stammer, Tetrahedron Lett., 24, 3839 (1983); M.C. Pirrung, G.M. McGeehan, J. Org. Chem., 51, 2103 (1986).

3. N. De Kimpe, P. Sulmon, R. Verhé, L. De Buyck, N. Schamp, J. Org. Chem., 48, 4320 (1983); N. De Kimpe, P. Sulmon, N. Schamp, Bull. Soc. Chim. Belg., 95, 567 (1986).

4. The ^{1}H NMR spectra (360 MHz, D_2O) of ACC-analogues 2 exhibited the typical AX spin system of both ring protons (J=6.4-6.7Hz). In addition, the characteristic ^{13}C chemical shifts of the cyclopropane carbons were indicative of a correct structural assignment. The ^{1}H NMR and ^{13}C NMR data of 2a (R^1=Me) are exemplified here : ^{1}H NMR (360 MHz; D_2O; ref. 1,4-dioxane) : δ 0.93 (1H,d,AX,J_{ab}=6.4Hz,C(3)H_a); 1.11 and 1.14 (each 3H, each s, 2xCH_3); 1.29 (1H,d,AX,J_{ab}=6.4Hz, C(3)H_b). ^{13}C NMR (D_2O; ref. 1,4-dioxane) : 20.2 and 21.1 (2xq,2xCH_3); 23.8 (s,$\underline{C}Me_2$); 24.4 (t,CH_2); 45.7 (s,$\underline{C}$-NH_2); 175.0 (s,$\underline{C}OOH$).

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