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SYNTHESIS OF 2,2-DIMETHYL-1-AMINOCYCLOPROPANECARBOXYLIC ACID FROM β-CHLOROIMINES

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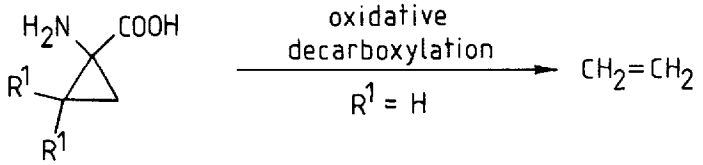
Abstract
2,2-Dimethyl-ACC, a potential plant growth regulator, was synthesized by cyclopropanation of β-chloroimines.

Ethylene is a plant hormone that initiates fruit ripening and regulates many aspects of plant growth, development, and senescence. It has been shown that the ethylene biosynthesis proceeds from methionine via 1-aminocyclopropanecarboxylic acid (ACC) 1 through interaction of two enzymes, i.e. the ACC synthase and the socalled ethylene forming enzyme (EFE).[1]

Recently, various studies have been conducted towards unraveling the mechanistic details of the



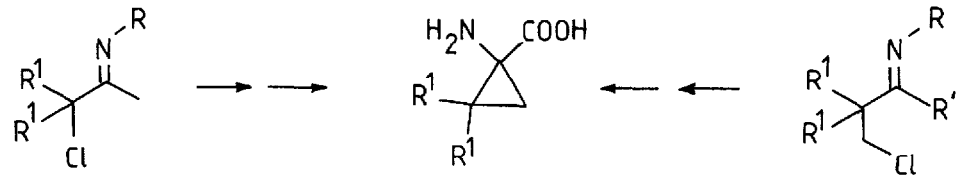
1 R^1 = H (ACC)
2 R^1 ≠ H

3

conversion of ACC 1 into ethylene 3[2] and several research groups have devoted much efforts to the synthesis of ACC-analogues in the hope of effecting a potential control of the enzymatic processes in plants.[3,4] Various syntheses of monoalkyl-ACC derivatives have been performed,[3-5] some of which were substrates of the ethylene forming enzyme.

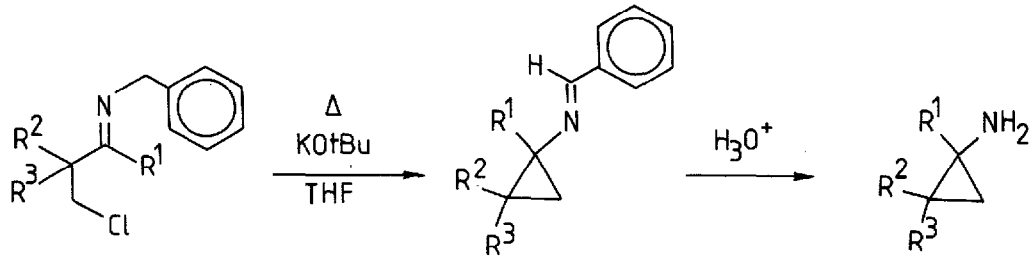
We reported recently on the first synthesis of 2,2-dialkyl-1-aminocyclopropanecarboxylic acids 2 by straightforward cyclopropanation of chloroketimines 4[6]. In the present communication, an alternative synthesis of the potentially plant growth regulating 2,2-dialkyl-1-aminocyclopropanecarboxylic acids 2

from β-chloroimines 5 is disclosed. In order to convert β-chloroimines 5 into 2,2-dialkyl-ACC derivatives 2, a proper choice of the substituents (R and R'), linked to the imino moiety, is required in view of further elaboration of appropriate functional group transformations. 1,5-Dehydrochlorination of β-chloro



4 2 5

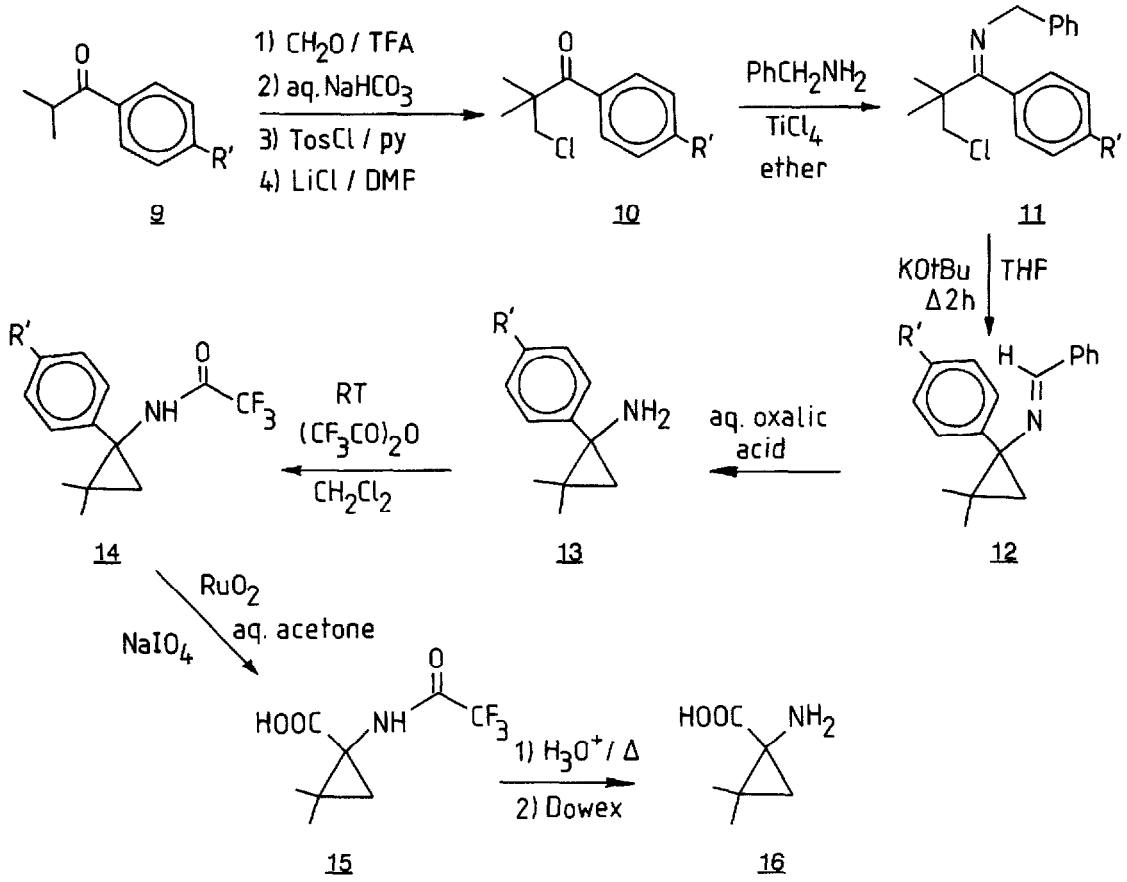
N-benzylimines 6 can be accomplished by strong bases, e.g. potassium t-butoxide, and the resulting N-(benzylidene)cyclopropylamines 7 can be hydrolytically converted into the corresponding cyclopropylamines 8.[7] This cyclopropanation process is suitable for the synthesis of 2,2-dialkyl-ACC derivatives 2



6 7 8

provided the R^1 group is transformable into a carboxylic group. Accordingly, a phenyl or a p-tolyl group was selected as R^1 substituent because, after appropriate protection of the amino substituent of cyclopropylamine 8, oxidation of the aromatic group with ruthenium tetroxide[8] offers a possibility for the generation of the requisite carboxylic acid. β-Chloroketimines 11 (R' = H, Me) were prepared in good yields from the corresponding isobutyrophenones 9 by subsequent hydroxymethylation (85-95%),[9] tosylation,[10] chloride substitution (82-94%),[10] and imination using titanium tetrachloride (72-93%).[10] The base-induced cyclopropanation of β-chloroimines 11 into N-(benzylidene)cyclopropylamines 12 was easily performed with potassium t-butoxide in tetrahydrofuran for 1-3 days at room temperature or for 2 hours under reflux (83-97% yield), after which hydrolysis with aqueous oxalic acid at room temperature afforded cyclopropylamines 13 (82-90%)[7]. The oxidative conversion of the aromatic substituent of 13 into a carboxylic group requires protection of the amino group as the trifluoroacetamide 14[8]. The oxidation of the protected cyclopropylamine 14 into the ACC derivative 15 was executed with catalytic

ruthenium tetroxide, generated from oxidation of ruthenium dioxide by means of sodium periodate in aqueous acetone. The resulting N-(trifluoroacetyl)amino acid 15 was not purified but was immediately hydrolyzed with aqueous acid under reflux (6 h) to afford the free α-amino acid 16, which was purified in



the usual way via chromatography over a Dowex column. The overall yield of the conversion of the cyclopropylamine 13 into 1-amino-2,2-dimethylcyclopropanecarboxylic acid 16 was 20-30% (3 steps). The purity of the α-aminoacid 16 was verified by HPLC (sulphonated polystyrene-divinylbenzene column) and by capillary gaschromatography [after silylation with N,O-bis(trimethylsilyl)trifluoroacetamide].

By this novel synthesis a new route to 1-amino-2,2-dialkylcyclopropanecarboxylic acids 2 becomes available. These 2,2-dialkyl-ACC derivatives 2, having potential plant growth regulating properties, are now accessible from α-chloroketimines 4[6] as well as from β-chloroketimines 5 by different cyclopropanation strategies.

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