Tetrahedron Vol. 47, No.20/21, pp. 3389-3406, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

SYNTHESIS OF 2,2-DIALKYLCYCLOPROPYLAMINES FROM β-CHLOROIMINES AND APPLICATION TOWARDS THE SYNTHESIS OF 1-AMINO-2,2-DIALKYLCYCLOPROPANE-CARBOXYLIC ACIDS

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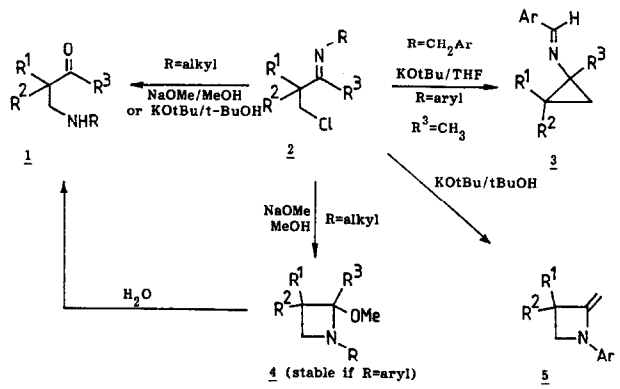
(*Received in UK* 31 *December* 1990)

Abstract

Base-induced 1,5-dehydrochlorination of β-chloroimines, having a relatively acidic hydrogen atom at carbon-1 of the N-substituent (e.g. benzyl, methoxycarbonylmethyl, α-methylbenzyl), afforded N-cyclopropylimines which were easily hydrolyzed into cyclopropylamines. This synthetic methodology was applied to the synthesis of the potentially plant growth regulating 1-amino-2,2-dialkylcyclopropanecarboxylic acids via oxidation with catalytic ruthenium(IV)oxide/ sodium periodate of suitably N-protected 1-aryl-2,2-dialkylcyclopropylamines.

Introduction

β-Chloroimines **2** have been shown to be versatile building blocks for the synthesis of a great variety of useful compounds including azetidines,[1] 2-cyanoazetidines,[1] 2-alkoxyazetidines **4**,[2] β-aminoketones **1**,[2] β-aminoacetals,[3] perhydro-1,3-diazine-2-thiones[3] and 2-methyleneazetidines **5**.[4] The nitrogen substituent of β-chloroimines **2** plays a dominant role in the outcome of the reactions with bases. N-Alkyl β-chloroimines **2** (R=alkyl) react with sodium methoxide in methanol to afford β-(N-alkyl)aminoketones **1** via the intermediacy of 2-methoxyazetidines **4**, which are only stable with an aromatic N-substituent.[2] When substrates having an aromatic substituent are involved, the reaction of β-chloroketimines **2** (R^3=Me) can be directed towards stable 2-methyleneazetidines **5** by using potassium t-butoxide in t-butanol. However, β-chloroimines **2**, having a nitrogen substituent carrying a relatively activated α-position, with potassium t-butoxide undergo a completely different reaction from the usual nucleophilic addition across the imino bond or deprotonation at the α-position of alkyl chain R^3. Instead, the exclusive formation of N-cyclopropylimines **3** is observed.[5] In this paper, a detailed description of this new synthesis of functionalized cyclopropanes is reported and attention will be paid to the application of this new method for the synthesis of new nonproteinogenic α-aminoacids.



Results and Discussion

β-Chloroimines 6 are able to undergo a 1,5-dehydrochlorination into N-cyclopropylimines 7, provided a suitable activating group (R^4 or R^5) is present in the nitrogen substituent and on condition that the nucleophilic action of the base used is prohibited. These conditions are met with N-benzyl-, N-α-methylbenzyl- and N-(methoxycarbonyl)methyl-imines 6 using potassium t-butoxide as base in tetrahydrofuran. Subsequent hydrolysis with aqueous oxalic acid of the resulting benzylidenecyclopropylamines 7 and related compounds, which were obtained in 82-97% yield, gave rise to cyclopropylamines 8 in high yields. It should be stressed that if nucleophilic conditions are employed, e.g. sodium methoxide in methanol, N-benzylimines 6 undergo nucleophilic addition across the imino bond followed by intramolecular nucleophilic substitution, the resulting intermediate 2-methoxyazetidine being hydrolyzed during the aqueous workup into β-(N-benzyl)aminoketones 11.[2]

The formation of N-cyclopropylamines 7 can be interpreted as the result of an initial deprotonation at the activated α-carbon of the N-substituent, affording a 2-azaallylic anion, the extreme forms of the polarization being represented as 9 and 10. Subsequent chloride expulsion gives the final N-cyclopropylimines 7. The net result of the conversion of β-chloroimines into N-cyclopropylimines 7 comprises a base-induced 1,5-dehydrochlorination. This type of reaction only takes place if R^4 (or R^5) is an activating group (e.g. Ph or COOMe), capable of enhancing the acidity of the α-hydrogens of the N-substituent.

Table I shows the various N-cyclopropylimines 7 prepared while Table II gives an overview of the synthesis of cyclopropylamines 8.
As can be judged from the tables, a great variety of N-(benzylidene)-2,2-dialkylcyclopropylamines 7 (and related compounds) are accessible by the 1,5-dehydrochlorination process of β-chloroimines 6. 1-Unsubstituted

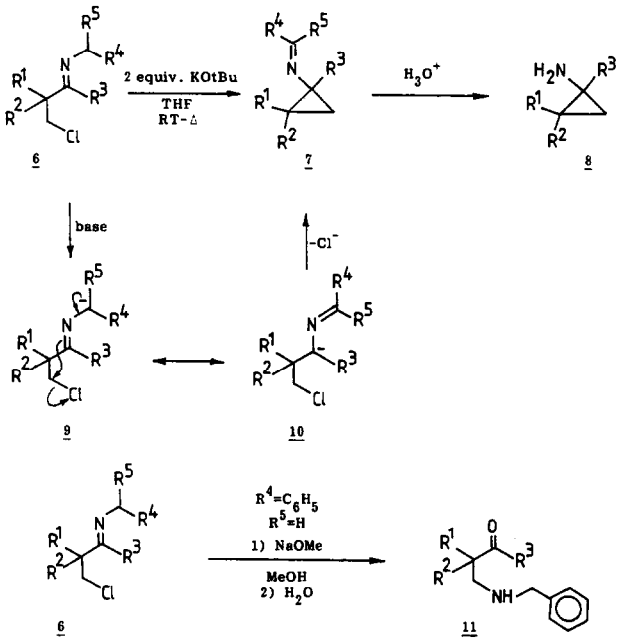


Table I : Synthesis of N-Cyclopropylimines 7

	R^1	R^2	R^3	R^4	R^5	Reaction[a] Conditions	Yield
7a	Me	Me	Me	Ph	H	Δ 2h	95%[b]
7b	Me	Me	Ph	Ph	H	Δ 3h	92%[b]
7c	Me	Me	H	Ph	H	Δ 2h	93%[b]
7d	Me	Me	H	Ph	Me	RT 3d	83%[c]
7e	Me	Me	$pMeC_6H_4$	Ph	H	RT 1d	95%[b]
7f	Et	Et	H	Ph	H	RT 2d	97%[b]
7g	Et	Me	H	Ph	H	RT 1d	90%[b]
7h	Me	Me	H	COOMe	H	RT 12h	82%[c]
7i	$(CH_2)_5$		Me	Ph	H	RT 3d	96%[c]
7j	Me	Me	H	$CH_2=CH$	H	RT 3d	-[d]

a. Use of 2 molar equivalents of potassium t-butoxide in tetrahydrofuran; Δ = reflux; RT = room temperature; d = day(s). The reaction time was not optimized.

b. Crude reaction mixture (purity > 95%; checked by GC and ^1H NMR).

c. Contained small amounts (≈ 7%) of unidentified products.

d. No cyclopropane formation; instead, 2-azadienes 13 and 14 was formed (E/Z 45:55; 92% yield).

Table II : Synthesis of Cyclopropylamines 8

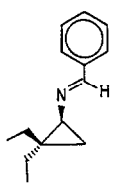
Starting Material	Product	R^1	R^2	R^3	Yield of 8 from 7
7a	8a	Me	Me	Me	92%[a]
7b	8b	Me	Me	Ph	90%[a]
7e	8c	Me	Me	$pMeC_6H_4$	82%[b]
7c	8d	Me	Me	H	70%[c]
7i	8e	$(CH_2)_5$		Me	91%[a]

a. Yield of the crude reaction mixture (purity > 95%; checked by GC and ^1H NMR).

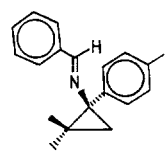
b. Yield after distillation (bp. 50-52°C/0.7 mmHg).

c. Purity 85% (GC; ^1H NMR); bp. 85-86°C[6].

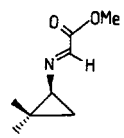
(R^3=H), e.g. 7f, as well as 1-substituted (R^3=Me, Ph, $pMeC_6H_4$) derivatives, e.g. 7e, can be synthesized via this route. In addition, this method is suitable for the synthesis of N-cyclopropyl α-iminoester 7h and spiro compound 7i. If the geminal dialkyl group contains two different alkyl



7f



7e



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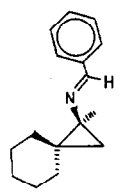

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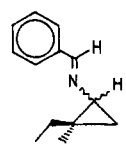


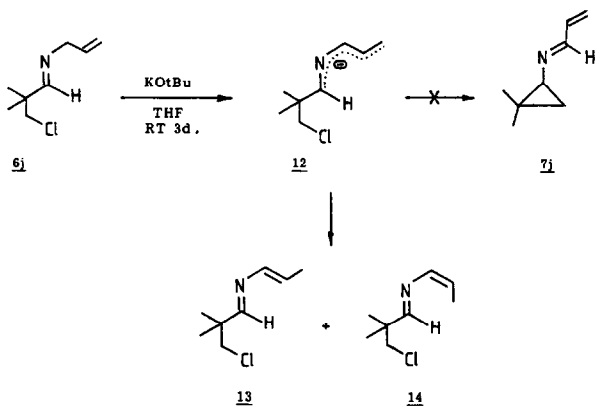
7g

groups, then a mixture of cis- and trans-isomers was formed as found for 7g in a 1:1 ratio (capillary GC). Based on accepted concepts of steric hindrance the stereochemistry at the carbon nitrogen double bond of N-cyclopropylimines 7 is E exclusively (the presence of only one stereoisomer is clear from the ^1H NMR and ^{13}C NMR).

The hydrolysis of N-cyclopropylimines 7 was easily performed with oxalic acid (5 equiv.) in 20% aqueous methanol at room temperature to afford cyclopropylamines 8 and the corresponding carbonyl compounds (R^4COR^5 :

benzaldehyde, acetophenone and methylglyoxylate), which were separated from each other by acidic and basic extractive workup.

As shown above, β-chloroimines 6 having an acidic α-hydrogen in the N-substituent undergo the 1,5-dehydrochlorination under the influence of potassium t-butoxide. Activating groups (R^4) such as phenyl and methoxycarbonyl are required for this process. Unexpectedly, the corresponding N-allyl β-chloroimines (R^4 = vinyl; R^5 = H) do not seem to give the desired 1,5-dehydrochlorination. For instance, N-(3-chloro-2,2-dimethyl-1-propylidene)allylamine 6j, when treated with potassium t-butoxide (5 molar equiv.) in tetrahydrofuran for three days at room temperature, only afforded the conjugated 2-aza-1,3-dienes 13 and 14 (E/Z 45:55) in 92% yield. Both isomers 13 and 14 can be easily separated by preparative gas chromatography.



6j 12 7j

13 14

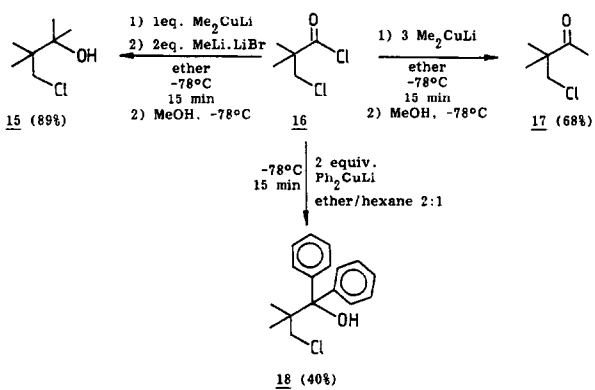
The characterization of the N-cyclopropylimines 7 and the cyclopropylamines 8 was performed by ^1H NMR spectroscopy. Tetrasubstituted cyclopropanes ($R^3 \neq H$) exhibited an AB system in the ^1H NMR spectrum, corresponding to the methylene group of the cyclopropane (J=4-4.4 Hz). Trisubstituted cyclopropanes (R^3=H) showed an ABX pattern for the cyclopropane protons ($J_{AB} \approx 4.5$ Hz; $J_{BX} \approx 3.8$ Hz; $J_{AX} \approx 7$ Hz).

The synthesis of cyclopropylamines 8 from β-chloroimines 6 provides an elegant and straightforward approach to these potentially physiologically active compounds, which received considerable attention in view of their inhibition of monoamine oxidases.[7-11] Cyclopropylamines are most renowned as suicide substrates for those enzymes containing the cytochrome P-450 cofactor,[7-11] while the aminocyclopropyl group is often present in pesticides,[12] activiral[12] and antibacterial agents.[12]

It should be stressed that the present synthesis of N-cyclopropylimines and cyclopropylamines occurs via a straightforward process. Many aminocyclopropanes have been reported in the literature[12] but the great majo-

rity of derivatives originated from transformation of substrates in which the cyclopropane group is already present. Very often, these syntheses make use of Hofmann and Curtius rearrangements of derivatives of cyclopropanecarboxylic acids.[12] Accordingly not that many processes incorporating a construction of the cyclopropane ring have been developped for aminocyclopropanes.

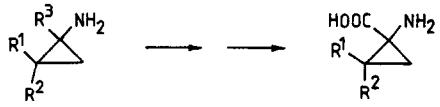
The present synthesis of cyclopropylamines calls for a convenient availability of β-chloroimines 6. The latter compounds are accessible from imination of the corresponding β-chloroketones and β-chloroaldehydes.[13] β-Chloroketones themselves are available by hydroxymethylation (CH_2O/TFA) of ketones followed by O-tosylation (TosCl/py) and chloride substitution (LiCl/DMF).[14] As an alternative for this 3-step synthesis, we have developed now a more direct way to 4-chloro-3,3-dimethyl-2-butanone 17 by reaction of the commercially available 3-chloropivaloylchloride 16 with lithium dimethylcuprate in ether at -78°C during 15 minutes. Using 3 molar equivalents of the cuprate (-78°C) a 68% yield of the β-chloroketone 17 was obtained, while the use of 1 molar equivalent of the cuprate (-78°C) in addition to 2 molar equivalents of methyllithium led to a complete conversion into the tertiary alcohol 15 (89% yield). However, the reaction of lithium diphenylcuprate in ether/hexane (2:1) at -78°C did not afford the expec-



ted 3-chloro-2,2-dimethyl-1-phenyl-1-propanone. In addition to biphenyl, the major reaction product appeared to be 3-chloro-2,2-dimethyl-1,1-diphenyl-1-propanol 18 (40% yield). It seems that the previously developed synthesis of ketones from carboxylic acid chlorides and cuprates[15] is amenable for the synthesis of functionalized ketones.

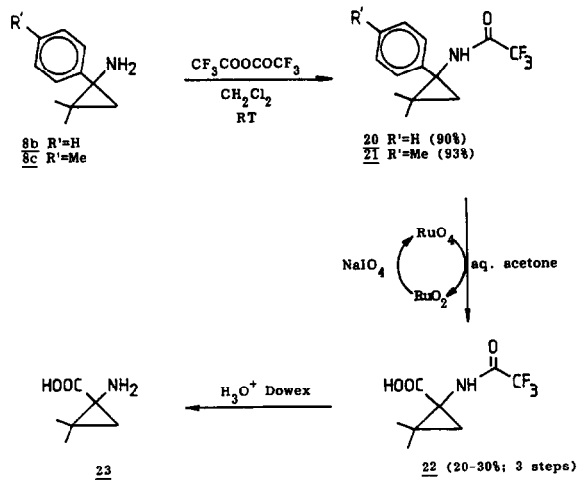
The second part of this paper will focus on the utilization of this synthesis of cyclopropylamines (8) in a route leading to 1-amino-2,2-dialkylcyclopropanecarboxylic acids. Cyclopropylamines 8 would be good precur-

sors for the synthesis of the potentially plant growth regulating 1-amino-2,2-dialkylcyclopropanecarboxylic acids 19 provided that the substituent at the 1-position of the cyclopropane (R^3) is transformable into a carboxylic group. Accordingly, a phenyl or a p-tolyl group was selected as the R^3 substituent because, after appropriate protection of the amino substituent



8 19

of the cyclopropylamine 8, oxidation of the aromatic group with ruthenium tetroxide[16] offers a possibility for the generation of the requisite carboxylic acid.[17] Cyclopropylamines 8b,c, obtained from the corresponding isobutyrophenones via a sequence involving hydroxymethylation, tosylation, chloride substitution, imination, 1,5-dehydrochlorination and acidic hydrolysis as discussed above, were protected at the nitrogen atom as the corresponding trifluoroacetamide. Reaction of cyclopropylamines 8b,c with trifluoroacetic anhydride in dichloromethane at room temperature (1 d.) afforded the trifluoroacetamides 20 and 21 in 90-93% yield. The oxidation



of the aromatic substituent (R^3 = phenyl or p-tolyl) of the trifluoroacetamides 20 and 21 was executed with catalytic ruthenium tetroxide, generated from ruthenium dioxide and sodium periodate in aqueous acetone. Due to difficulties in the isolation of the oxidation product, i.e. cyclopropanecarboxylic acid 22, the latter was not purified but was immediately hydrolyzed with aqueous acid under reflux (6 h) to afford the α-amino acid 23. This α-amino acid was purified in the usual way via chromatography over a

Dowex column as described previously in detail.[18] The overall yield of the conversion of the 1-arylcyclopropylamines 8b,c into 1-amino-2,2-dimethylcyclopropanecarboxylic acid 23 was 20-30% (3 steps). The purity of α-amino acid 23 was verified by HPLC (sulphonated polystyrene-divinylbenzene column using gradients of 0,2 N and 1 N sodium citrate buffers). Further characterization of the amino acid 23 was established by mass spectrometric and gas chromatographic analysis of carbamate and silyl derivatives, i.e. N-methoxycarbonyl derivatives (using methyl chloroformate) and O- and N,O-silylated derivatives (using N,O-bis(trimethylsilyl)trifluoroacetamide, BSTFA) respectively. The recent interest in the ring-substituted 1-aminocyclopropanecarboxylic acids 19 (R^1, R^2=H, alkyl) stems from their potential use as plant growth regulators and as structural unit in enzyme inhibitors.[19] While the majority of such ACC analogues are monosubstituted,[18] only few reports dealt with 1-amino-2,2-dialkylcyclopropanecarboxylic acids 19 (R^1, R^2 = alkyl).[17,18,20-22]

Experimental part

IR spectra were measured with a Perkin Elmer Model 1310 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian T-60 NMR spectrometer (60 MHz) and a Bruker WH 360 (360 MHz) NMR spectrometer. ^{13}C NMR spectra were obtained from a Varian FT-80 NMR spectrometer (20 MHz). Mass spectra were recorded with a Varian-MAT 112 mass spectrometer (direct inlet system or GC-MS coupling, 70 eV). Gas chromatographic analyses were performed with Varian 1700, Varian 1400 and Varian 920 gas chromatographs using preparative stainless steel columns (1.5 m, 5-10% SE-30, Chromosorb W 60-80, H_2 carrier gas) or glass capillary columns (30 m, i.d. 0.5 mm, SE-30, He carrier gas).

β-Chloroimines 6 were synthesized from the corresponding β-chloroketones as previously reported.[1,13] The spectral data of compounds 6a-d,f,h,i were published previously,[1,13] while β-chloroimines 6e,g,j are new compounds whose spectral data are given below.

N-[3-Chloro-2,2-dimethyl-1-(4-methylphenyl)-1-propylidene]benzylamine 6e

IR (NaCl) : 1640 cm^{-1} (C=N); ^{1}H NMR (CCl_4) : 1.23 (6H,s,Me_2); 2.29 (3H,s, $\underline{Me}C_6H_4$); 3.69 (2H,s,CH_2Cl); 4.23 (2H,s,$C\underline{H}_2Ph$); 6.7-7.4 (4H,C_6H_4); 7.2 (5H,s,$CH_2C_6\underline{H}_5$). ^{13}C NMR ($CDCl_3$) : 24.6 (q,Me_2); 45.1 (s,$\underline{C}Me_2$); 54.0 and 56.7 (each t, $\underline{C}H_2Cl$ and $\underline{C}H_2Ph$); 176.0 (s,C=N); 140.6, 137.6 and 133.5 (3xs, 2xCq and Cp); 129.0, 128.1, 127.3, 126.6 and 126.2 (5xd,2xCo,2xCm and Cp); 21.2 (q,$\underline{Me}C_6H_4$).

Elemental analysis : calcd 4.67% N and 11.82% Cl; found 4.76% N and 11.64% Cl.

N-(3-chloro-2-ethyl-2-methyl-1-propylidene)benzylamine 6g

IR (NaCl) : 1665 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : 0.83 (3H,t,J=7.2Hz,$\underline{Me}CH_2$); 1.19 (3H,s,CH_3); 1.3-1.8 (2H,m,$C\underline{H_2}Me$); 3.65 (2H,s,CH_2Cl); 4.61 (2H,d,J=1.2 Hz,$C\underline{H_2}Ph$); 7.28 (5H,s,Ph); 7.66 (1H,t,J=1.2Hz,CH=N). Mass spectrum m/z (%) : no M^+; 195(3); 188(10); 161(4); 160(24); 133(16); 92(14); 91(100); 90(3); 89(4); 83(4); 70(14); 69(16); 65(15); 63(4); 55(16); 53(3); 51(3); 43(11); 42(5); 41(20); 39(8). ^{13}C NMR ($CDCl_3$) : 8.2 (q,Me); 28.9 (t,CH_2); 20.8 (q,Me); 44.0 (s,$\underline{C}Me_2$); 51.0 (t,CH_2Cl); 64.8 (t,NCH_2); 169.3 (d,$\underline{C}H$=N); 128.4, 127.6 and 126.8 (each d, =$\underline{C}H$ arom); 139.3 (s,Cq).

Bp. 90-95°C/0.1 mmHg.

Elemental analysis : calcd 6.26% N and 15.48% Cl; found 6.39% N and 15.61% Cl.

N-(3-chloro-2,2-dimethyl-1-propylidene)allylamine 6j

IR (NaCl) : 1670 cm^{-1} (C=N). ^1H NMR (CCl_4) : 1.14 (6H,s,Me_2); 3.49 (2H,s, CH_2Cl); 3.8-4 (2H,m,CH_2-C=); 4.8-5.2 (2H,m,CH_2=C); 5.4-6.2 (1H,m,CH=C); 7.54 (1H,t,J=1.4Hz,CH=N). ^{13}C NMR ($CDCl_3$) : 23.2 (q,Me_2); 41.0 (s,CMe_2); 52.9 (t,CH_2Cl); 63.0 (t,NCH_2); 135.9 (d,$\underline{C}H$=C); 115.5 (t,$\underline{C}H_2$=C); 169.3 (d,CH=N).

Elemental analysis : calcd 8.77% N and 22.20% Cl; found : 8.66% N and 22.05% Cl.

Synthesis of N-Cyclopropylimines 7 from β-Chloroimines 6

To a solution of 0.05 mol of β-chloroimine 6 in freshly distilled tetrahydrofuran (distilled from sodium benzophenone ketyl under nitrogen) (10% w/v) was added 0.1 mol of potassium t-butoxide. The reaction mixture was stirred at room temperature or under reflux for the time given in Table I, after which it was poured into aqueous sodium hydroxide (1N). Extraction was performed three times with dichloromethane and the combined extracts (after drying with magnesium sulfate) were evaporated in vacuo. The remaining reaction product consisted of N-cyclopropylimines 7 in sufficient purity (> 95% as evidenced by ^1H NMR and GC analysis) for further elaboration in the next hydrolysis step. Analytical samples were obtained by preparative gas chromatography or column chromatography (silica gel; ether-pentane 1:1). The spectroscopic data of N-cyclopropylimines 7 are given below.

N-(Benzylidene)-1,2,2-trimethylcyclopropylamine 7a

IR (NaCl) : 1640 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : 1.15 (3H,s,CH_3); 1.19 (3H,s, CH_3); 1.37 (3H,s,CH_3); 7.0-7.8 (5H,m,C_6H_5); 8.14 (1H,s,CH=N); 0.58 and 1.02 (2H,2xd,AB,J=4.4Hz,CH_2). Mass spectrum m/z (%) : 187 (M^+, 7); 172(19);

146(15); 132(12); 131(100); 130(92); 105(10); 104(18); 91(15); 90(58); 89(35); 77(14); 62(9); 57(7); 55(7); 51(8); 43(8); 42(8); 41(20); 40(58); 39(13).
Elemental analysis : calcd 7.47% N; found 7.61% N.

N-(Benzylidene)-2,2-dimethyl-1-phenylcyclopropylamine 7b
IR (NaCl) : 1640 cm^{-1} (C=N). ^1H NMR (C_6D_6); 0.94 (3H,s,CH_3); 1.28 and 1.44 (2H,2xd,AB,J=4.4Hz,CH_2); 1.70 (3H,s,CH_3); 7.0-7.8 (5H,m,C_6H_5); 7.22 (5H,s,C_6H_5); 7.87 (1H,s,CH=N). Mass spectrum m/z (%) : 249 (M^+, 10); 234(12); 194(20); 193(100); 192(12); 166(7); 165(15); 146(6); 120(6); 119(4); 116(5); 115(5); 107(5); 105(11); 104(9); 103(9); 91(30); 90(35); 89(40); 77(13); 65(7); 64(6); 63(8); 56(7); 51(10); 44(20); 41(11).
Elemental analysis : calcd 5.62% N; found 5.69% N.

N-(Benzylidene)-2,2-dimethylcyclopropylamine 7c
IR (NaCl) : 1639 cm^{-1} (C=N). ^1H NMR (60 MHz; $CDCl_3$) : 0.5-1.2 (2H,AB,part of ABX system,C<u>H</u>$_2$); 1.10 (3H,s,CH_3); 1.31 (3H,s,CH_3); 2.76 (1H,dxd,X part of ABX system,C<u>H</u>); 7.2-7.8 (5H,m,C_6H_5); 8.34 (1H,s,CH=N). Mass spectrum m/z (%) : 173 (M^+,15); 172(3); 159(9); 158(36); 131(3); 130(9); 118(15); 117(100); 106(3); 105(7); 104(17); 91(13); 90(73); 89(35); 78(3); 77(12); 69(5); 68(7); 67(3); 65(3); 64(6); 63(13); 55(5); 53(7); 51(13); 41(30); 40(12); 39(23).
Elemental analysis : calcd 8.08% N; found 8.20% N.

N-(1-Phenylethylidene)-2,2-dimethylcyclopropylamine 7d
IR (NaCl) : 1630 cm^{-1} (C=N). ^1H NMR (60 MHz; $CDCl_3$) : 0.5-1.2 (2H,AB,part of ABX system,CH_2); 1.15 (3H,s,CH_3); 1.28 (3H,s,CH_3); 2.30 (3H,s,CH_3); 2.83 (1H,dxd,X part of ABX system,C<u>H</u>); 7.1-7.9 (5H,m,C_6H_5). Mass spectrum m/z (%) 187 (M^+, 32); 186(9); 172(30); 144(9); 132(15); 131(85); 130(71); 120(21); 110(9); 105(47); 104(100); 103(35); 81(9); 78(29); 77(44); 69(12); 51(12); 42(12); 41(18); 39(9).
Elemental analysis : calcd 7.47% N; found 7.39% N.

N-(Benzylidene)-2,2-dimethyl-1-(4-methyl)phenylcyclopropylamine 7e
IR (NaCl) : 1639 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : 0.90 (3H,s,CH_3); 1.50 (3H,s,CH_3); 1.24 and 1.30 (2H,2xd,AB,J=4Hz,CH_2); 2.30 (3H,s,CH_3); 6.8-7.7 (5H,m,C_6H_5); 7.09 (4H,s,C_6H_4); 7.67 (1H,s,CH=N). Mass spectrum m/z (%) : 263 (M^+, 18); 248(18); 208(23); 207(100); 206(18); 192(14); 171(18); 165(14); 149(23); 120(18); 119(27); 117(14); 106(23); 105(41); 95(23); 91(54); 90(32); 89(45); 83(14); 77(23); 72(27); 71(36); 70(18); 57(36); 56(27); 55(23); 51(14); 44(14); 43(59); 42(77); 41(72); 40(23); 39(23).

Elemental analysis : calcd 5.32% N; found 5.28% N.

N-(Benzylidene)-2,2-diethylcyclopropylamine 7f

IR (NaCl) : 1637 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : 0.7-2.0 (6H,m,CH_2 (ring) and 2x($C\underline{H}_2CH_3$); 0.93 (6H,t,J=6Hz,2x($CH_2C\underline{H}_3$)); 2.85 (1H,dxd,X part of ABX system, C<u>H</u>); 7.2-8.0 (5H,m,C_6H_5); 8.37 (1H,s,CH=N). Mass spectrum m/z (%) : 201 (M^+, 4); 186(4); 173(6); 172(35); 119(8); 118(13); 117(48); 106(9); 105(7); 104(10); 91(16); 90(26); 89(12); 87(17); 75(7); 69(11); 67(7); 57(100); 56(16); 55(16); 53(4); 45(37); 43(12); 42(7); 41(56); 39(11).
Elemental analysis : calcd 6.96% N; found 6.84% N.

N-(Benzylidene)-2-ethyl-1-methylcyclopropylamine 7g (E+Z)

IR (NaCl) : 1632 cm^{-1}. ^1H NMR ($CDCl_3$) : 0.65-2.4 (10H,m,$C\underline{H}_3$-$C\underline{H}_2$,$C\underline{H}_3$ and $C\underline{H}_2$ ring); 2.6-3.0 (1H,m,X part of ABX system,J_{AX} 3.8Hz,J_{BX} 7Hz,J_{AB} 4.5Hz, C<u>H</u>); 7.2-7.9 (5H,m,C_6H_5); 8.39 (1H,s,CH=N). Mass spectrum m/z (%) (cis and trans may be reversed) : <u>cis</u> : 187 (M^+; 11); 172(16); 158(35); 130(6); 119(6); 118(26); 117(100); 106(14); 104(14); 91(19); 90(59); 89(24); 82(6); 77(6); 70(6); 67(9); 63(6); 55(11); 53(5); 51(5); 44(11); 43(5); 41(13); 40(16); 39(8).
<u>trans</u> : 187 (M^+, 11); 172(19); 159(6); 158(35); 144(6); 130(7); 119(7); 118(26); 117(100); 106(11); 104(15); 91(17); 90(52); 89(26); 82(6); 77(6); 70(6); 67(7); 63(6); 55(9); 44(13); 41(11); 40(20); 39(9).
Elemental analysis : calcd 7.47% N; found 7.63% N.

N-(Methoxycarbonylmethylene)-2,2-dimethylcyclopropylamine 7h

IR (NaCl) : 1635 cm^{-1} (C=N); 1725-1755 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) : 0.5-1.4 (2H,AB part of ABX,$C\underline{H}_2$); 1.13 (3H,s,$C\underline{H}_3$); 1.28 (3H,s,CH_3); 2.83 (1H, dxd,X part of ABX system,J_{AX} 3.8Hz,J_{BX} 7Hz,J_{AB} 4.5Hz,C<u>H</u>); 3.87 (3H,s,CH_3); 7.85 (1H,s,CH=N).
Elemental analysis : calcd 9.02% N; found 9.14% N.

N-(Benzylidene)-1-methylspiro[2.5]-1-octylamine 7i

IR (NaCl) : 1641 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : 0.61 and 1.05 (2H,2xd,AB, J=4.4Hz,$C\underline{H}_2$); 1.43 (3H,s,CH_3); 1.2-2.0 (10H,m,C_6H_{10}); 7.1-7.9 (5H,m,C_6H_5); 8.30 (1H,s,CH=N). Mass spectrum m/z (%) : 227 (M^+, 26); 226(7); 212(3); 186(3); 184(6); 170(9); 150(11); 146(6); 136(12); 132(12); 131(100); 130(70); 129(3); 122(3); 117(4); 106(16); 105(13); 104(19); 103(6); 95(3); 94(3); 91(21); 90(52); 89(28); 81(6); 79(8); 78(4); 77(17); 67(7); 65(4); 63(5); 58(4); 57(8); 55(7); 53(6); 51(8); 43(3); 42(8); 41(17); 39(10).
Elemental analysis : calcd 6.16% N; found 6.25% N.

Table III : ^{13}C NMR Data (δ, $CDCl_3$) of N-Cyclopropylimines 7

	C=N	CR^3	CH_2 (t)	C R^1 R^2 (s)	If R^1=R^2=Me $(CH_3)_2$ (q)	Cq (s)	Co, Cm, Cp (3xd)	Other signals
7a	155.8 (d)	49.4 (s)	29.4	25.3	22.6 21.8	137.3	129.7 128.4 127.5	17.5 (q, CH_3)
7b	156.8 (d)	58.7 (s)	28.8	27.1	24.9 21.3	138.5 137.3	131.2 128.0 129.7 127.5 128.3 127.0	-
7c	157.6 (d)	54.1 (d)	24.0	21.4	25.8 20.2	136.9	129.7 128.4 127.5	-
7d	163.2 (s)	46.2 (d)	24.4	21.2	26.0 20.1	141.5	129.0 128.1 126.3	15.5 (q, CH_3)
7e	156.6 (d)	58.4 (d)	29.0	27.1	24.9 21.3	137.3[a] 136.5[a]	135.4[a,b] 129.0 131.1 128.3 129.6 127.5	21.1 (q, CH_3)
7f	157.7 (d)	53.9 (d)	28.3	31.5	-	137.1	129.7 128.4 127.5	23.2 and 22.6 (2xt, $(CH_2CH_3)_2$); 10.7 and 10.1 (2 x q, $(CH_2CH_3)_2$)
7h	149.9 (d)	54.5 (d)	26.2	24.5	25.7 20.1	-	-	163.6 (s, C=O); 52.3 (q, CH_3O)
7i	155.7 (d)	49.7 (s)	28.1	32.8	-	137.4	129.7 128.4 127.5	17.1 (q, CH_3); 33.0; 32.0; 26.6, 26.1 and 25.7 (5xt, $-(CH_2)_5-$)

a : or vice versa

b : singlet

Synthesis of Cyclopropylamines 8

A 10% solution (w/v) of 0.01 mol of N-cyclopropylimine 7 in 20% aqueous methanol was treated with 0.05 mol of oxalic acid. The mixture was stirred at room temperature during 1-3 days. The reaction mixture was extracted

with 3x30 ml carbon tetrachloride in order to remove all non-basic reaction products. Afterwards the reaction mixture was made alkaline with concentrated sodium hydroxide and extraction was performed with ether or dichloromethane. After drying ($MgSO_4$) of the combined extracts, evaporation of the solvent afforded cyclopropylamines 8, which were obtained free of side products (^1H NMR, GC; purity > 95%). Analytical samples were obtained from preparative gas chromatography. Cyclopropylamines 8 were synthesized in yields of 70-92% (Table II).

1,2,2-Trimethylcyclopropylamine 8a

IR (NaCl) : 3375 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : 0.21 and 0.25 (2H,2xd,AB,J= 4.6Hz,$C\underline{H}_2$); 1.07 (3H,s,CH_3); 1.17 (3H,s,CH_3); 1.30 (3H,s,CH_3); 1.53 (2H,s, NH_2). Mass spectrum m/z (%) : 99 (M^+; 0.5); 98(1); 85(1); 84(10); 83(2); 82(1); 81(0.5); 67(1); 58(2); 57(4); 55(1); 44(14); 43(6); 42(13); 41(5); 40(100); 39(2).
Elemental analysis : calcd 14.12% N; found 14.03% N.

2,2-Dimethyl-1-phenylcyclopropylamine 8b

IR (NaCl) : 3380 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : 0.65 and 1.01 (2H,2xd,AB,J= 4.5Hz,CH_2); 0.78 (3H,s,CH_3); 1.44 (3H,s,CH_3); 1.75 (2H,s,br,NH_2); 7.40 (5H,s,C_6H_5). Mass spectrum m/z (%) : 161 (M^+, 20); 160(50); 147(14); 146(88); 145(6); 144(12); 143(8); 131(8); 130(12); 129(20); 128(20); 127(10); 119(6); 117(6); 115(6); 106(12); 105(34); 104(100); 103(14); 91(14); 84(8); 78(18); 77(54); 76(8); 68(10); 65(16); 51(21); 50(6); 44(16); 42(9); 41(19); 40(8); 39(11).

2,2-Dimethyl-1-(4-methylphenyl)cyclopropylamine 8c

IR (NaCl) : 3415 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : 0.73 (3H,s,CH_3); 1.35 (3H,s,CH_3); 1.45 (2H,s,br,NH_2); 2.30 (3H,s,CH_3); 7.07 (4H,s,C_6H_4); 0.51 and 0.81 (2H,2xd,AB,J=4.4Hz,$C\underline{H}_2$). Mass spectrum m/z (%) : 175 (M^+, 2); 174(9); 161(10); 160(79); 159(2); 158(6); 145(10); 144(10); 143(15); 142(4); 141(4); 133(4); 130(11); 128(17); 120(6); 119(25); 118(100); 117(13); 116(8); 115(13); 105(8); 91(58); 90(6); 89(12); 84(4); 77(17); 68(15); 63(12); 58(8); 55(10); 54(8); 53(11); 52(11); 51(12); 44(31); 43(15); 42(31); 41(50); 40(8); 39(46).
Elemental analysis : calcd 7.93% N; found 7.88% N.

2,2-Dimethyl-1-(4-methylphenyl)cyclopropylamine Hydrochloride 8c'

IR (KBr) : 3420-2500 cm^{-1} (broad; $-NH_3^+$). ^1H NMR ($CDCl_3$) : 0.73 (3H,s, CH_3); 1.0-1.3 (2H,2xd,≈AB broadened,CH_2); 1.37 (3H,s,CH_3); 2.33 (3H,s,CH_3); 7.08 and 7.26 (4H,2xd,AB,J=8Hz,C_6H_4); 8.63 (3H,s,br,NH_3^+).

1-Amino-1-Methylspiro[2,5]octaan 8e

IR (NaCl) : 3370 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : 0.20 and 0.26 (2H,2xd,AB,J= 4.4Hz,CH_2); 1.34 (3H,s,CH_3); 1.2-1.8 (10H,m,C_6H_{10}); NH_2 invisible. Mass spectrum m/z (%) : 139 (M^+, 20); 138(5); 124(11); 110(9); 107(4); 97(19); 96(100); 94(4); 93(4); 84(11); 83(18); 82(11); 81(13); 80(4); 79(11); 77(4); 70(22); 69(4); 68(6); 67(5); 58(11); 57(81); 56(6); 55(15); 54(5); 53(8); 44(19); 43(15); 42(67); 41(22).

Elemental analysis : calcd 10.06% N; found 9.93% N.

Table IV : ^{13}C NMR Data (δ, $CDCl_3$) of Cyclopropylamines 8

	$\underline{C}H_2$ (t)	$\underline{C}R^1$ (s)	$\underline{C}(R^2R^3)$ (s)	R^1=R^2=Me $(\underline{C}H_3)_2C$ (q)	Other signals
8a	27.9	37.6	21.2	23.8[a] 21.2[a]	22.4[a] (q,$\underline{C}H_3$)
8b	25.7	45.8	22.8	24.2 20.6	145.4 (s,$\underline{C}q$); 128.3 (2x) and 126.3 (3xd;$\underline{C}o$,$\underline{C}m$ and $\underline{C}p$)
8c	25.7	45.5	22.8	24.2[a] 20.7[a]	21.0[a] (q,$\underline{C}H_3$); 142.4 and 135.7 (2xs, $\underline{C}q$ and $\underline{C}p$); 129.0 and 128.2 (2xd,$\underline{C}o$ and $\underline{C}m$)
8c'[c]	22.6[a]	44.8	21.6	23.4[a] 20.5[a]	21.2[a] (q,$\underline{C}H_3$); 138.0 and 132.0 (2xs, $\underline{C}q$ and $\underline{C}p$); 129.5 and 129.3 (2xd,$\underline{C}o$ and $\underline{C}m$)
8e	26.3[b]	38.1	28.7	-	23.3 (q,$\underline{C}H_3$); 32.7; 31.3; 26.5; 26.3[b]; 26.1 (5xt,$(\underline{C}H_2)_5$)

a : or vice versa

b : overlap of signals

c : cyclopropylamine hydrochloride

Reaction of N-(3-chloro-2,2-dimethyl-1-propylidene)allylamine 6j with Potassium t-Butoxide in Tetrahydrofuran

A solution of 1.59g (0.01 mol) of β-chloroaldimine 6j in 16 ml tetrahydrofuran was treated with 0.05 mol of potassium t-butoxide and stirred for 3 days at room temperature. The reaction mixture was poured into water and extracted twice with ether. The combined extracts were dried (K_2CO_3) and evaporated to give an oil (1.46 g), which consisted of two isomeric compounds 13 (45%) and 14 (55%) as evidenced by GC and ^1H NMR. Both compounds were separated by preparative gas chromatography.

(E)-N-(3-Chloro-2,2-dimethyl-1-propylidene)-1-propenylamine 13

IR (NaCl) : 1665 cm^{-1} (C=N;C=C;broad). ^1H NMR ($CDCl_3$) : 1.20 (6H,s, $C(C\underline{H}_3)_2$); 1.75 (3H,dxd,J=6.8Hz,J=1.2Hz,$C\underline{H}_3CH$=CH); 3.57 (2H,s,CH_2Cl); 5.97 (1H,qxd,J=6.8Hz,J=13Hz,C$\underline{H}$-CH_3); 6.60 (1H,dxq,J=13Hz,J=1.2Hz,C$\underline{H}$=CH-CH_3); 7.50 (1H,s,CH=N). ^{13}C NMR ($CDCl_3$) : 167.3 (d,$\underline{C}$=N); 143.0 and 126.4 (2xd, $\underline{C}$H=$\underline{C}$H); 53.1 (t,$\underline{C}H_2$); 40.8 (s,$\underline{C}(CH_3)_2$); 23.3 (q,$C(\underline{C}H_3)_2$); 15.2 (q,$\underline{C}H_3$).
Elemental analysis : calcd 8.77% N; found 8.59% N.

(Z)-N-(3-Chloro-2,2-dimethyl-1-propylidene)-1-propenylamine 14

IR (NaCl) : 1625 cm^{-1} (C=N;C=C;broad). ^1H NMR ($CDCl_3$) : 1.21 (6H,s, $C(C\underline{H}_3)_2$); 1.90 (3H,dxd,J=6.8Hz,J=1.6Hz,$\underline{C}H_3CH$=CH); 3.61 (2H,s,$C\underline{H}_2Cl$); 5.37 (1H,qxd,J=6.8Hz,J=6.8Hz,=C$\underline{H}$-CH_3); 6.48 (1H,dxq,J=6.8Hz,J=1.6Hz,C$\underline{H}$=CH-CH_3); 7.50 (1H,s,C$\underline{H}$=N). ^{13}C NMR ($CDCl_3$) : 167.6 (d,$\underline{C}$=N); 140.5 and 124.4 (2xd,$\underline{C}$H=$\underline{C}$H); 53.2 (t,$\underline{C}H_2$); 41.1 (s,$\underline{C}(CH_3)_2$); 23.2 (q,$C(\underline{C}H_3)_2$); 12.2 (q, $\underline{C}H_3$).
Elemental analysis : 8.77% N; found 8.65% N.

Synthesis of 4-Chloro-3,3-dimethyl-2-butanone 17 from 3-Chloropivaloylchloride 16

Under an inert atmosphere and at 0°C, a mixture of 1.71 g (9 mmol) copper (I) iodide and 15 ml of dry ether was treated with 9 ml (18 mmol) of 2M methyllithium (lithium bromide complex) in ether. After stirring for 10 minutes at 0°C, the resulting lithium dimethylcuprate was cooled to -78°C and treated dropwise by syringe with 0.46 g (3 mmol) of 3-chloropivaloylchloride 16, dissolved in 2 ml of ether. The stirred reaction mixture was quenched at -78°C after 15 minutes by the addition of 2 ml of methanol. The reaction mixture was then poured into 30 ml of water. The ether phase was isolated and the aqueous phase was extracted once more. The combined extracts were dried ($MgSO_4$) and evaporated to afford pure 4-chloro-3,3-dimethyl-2-butanone 17 (0.27 g; 68%).[14] The purity was more than 97% as evidenced by GC and ^1H NMR analysis.

Synthesis of 4-Chloro-2,3,3-trimethyl-2-butanol 15

In analogous way as described in the previous experiment, 0.57 g (3 mmol) of copper(I) iodide and 15 ml of ether were treated (0°C, N_2 atmosphere) with 6 ml of 2M methyllithium (lithium bromide complex) (12 mmol) in ether. The organometallic reagents were reacted at -78°C with 0.46 g (3 mmol) of 3-chloropivaloylchloride 16 during 15 min after which quenching was performed with methanol at -78°C. After similar workup as above, the resulting oil (0.40 g; 89%) was identified as 4-chloro-2,3,3-trimethyl-2-butanol 15 (purity > 95%).

IR (NaCl) : 3430 cm^{-1} (OH). ^1H NMR ($CDCl_3$) : 1.10 (6H,s,Me_2); 1.30 (6H,s, Me_2); 1.67 (1H,s,OH); 3.70 (2H,s,CH_2Cl). Mass spectrum m/z (%) : no M^+; 135/7(10); 101(10); 90(1); 83(8); 81(1); 71(1); 60(3); 59(100); 57(5); 56(40); 55(11); 43(47); 41(18); 40(7); 39(4).

Synthesis of 3-Chloro-2,2-dimethyl-1,1-diphenyl-1-propanol 18

Under a nitrogen atmosphere, a stirred and cooled (0°C) mixture of 5.70 g (0.03 mmol) of copper (I) iodide in 60 ml ether was treated dropwise by syringe with 30 ml 2M phenyllithium (0.06 mol) in hexane. After stirring at 0°C for 10 minutes, the mixture was cooled to -78°C and treated dropwise by syringe with 2.32 g (0.015 mol) of 3-chloropivaloylchloride 16. After stirring for 15 min at -78°C, the reaction was quenched with 30 ml of methanol. After pouring into water, extraction with ether, drying of the combined extracts ($MgSO_4$) and evaporation, the residual reaction products were dissolved in little pentane. Crystallisation at -20°C afforded first biphenyl. Further crystallisation afforded 1.6 g (40%) of 3-chloro-2,2-dimethyl-1,1-diphenyl-1-propanol 18, mp. 57°C.

IR (NaCl) : 3540 cm^{-1} (OH). ^1H NMR (CCl_4) : 1.23 (6H,s,Me_2); 2.57 (1H,s, OH); 3.67 (2H,s,CH_2Cl); 6.9-7.7 (10H,m,2xC_6H_5). ^{13}C NMR ($CDCl_3$) : 145.01 (s,Cq); 128.14 and 127.46 (each d,Co and Cm); 126.87 (d,Cp); 82.79 (s, C-OH); 54.45 (t,CH_2Cl); 43.67 (s,$\underline{C}Me_2$); 22.61 (q,Me_2). Mass spectrum m/z (%) : no M^+; 183(87); 105(100); 91(6); 77(52); 55(5); 51(10); 49(4); 44(6); 43(6); 40(23).

Synthesis of N-(1-Aryl-2,2-dimethyl-1-cyclopropyl)trifluoroacetamides 20 and 21

A cooled solution (0°C) of 0.01 mol of cyclopropylamines 8b (R'=H) or 8c (R'=Me) in 50 ml dichloromethane, containing 0.015 mol of triethylamine, was treated cautiously with 0.015 mol of trifluoroacetic anhydride. The mixture was stirred overnight at room temperature and then poured into water. The organic phase was isolated and the aqueous phase was extracted twice with 15 ml of dichloromethane. The combined extracts were washed successively with 2N hydrogen chloride and with saturated sodium bicarbonate. After drying ($MgSO_4$) and evaporation of the solvent, pure trifluoroacetamides 20 (90%) and 21 (93%) were obtained. Compound 21 was recrystallized from hexane to given mp. 111°C, while compound 20 was used as such in the next oxidation step.

N-(2,2-Dimethyl-1-phenyl-1-cyclopropyl)trifluoroacetamide 20

IR (NaCl) : 3330 cm^{-1} (NH); 1735 cm^{-1} (C=O). ^1H NMR ($CDCl_3$) : 1.20 and 1.36 (2H,2xd,AB,J=5.8Hz,CH_2); 0.97 (3H,s,CH_3); 1.36 (3H,s,CH_3); 7.0-8.0

(5H,m,C_6H_5); NH invisible.

N-[2,2-Dimethyl-1-(4-methylphenyl)-1-cyclopropyl]trifluoroacetamide 21
IR (KBr) : 3300 cm^{-1} (NH); 1722 (C=O). ^1H NMR (C_6D_6); 0.65 and 1.10 (2H,2xd,AB,J=5.5Hz,CH_2); 0.78 (3H,s,CH_3); 1.20 (3H,s,CH_3); 2.07 (3H,s,CH_3); 6.94 and 7.40 (4H,2xd,AB,J=8.0Hz,C_6H_4); NH invisible. ^{13}C NMR ($CDCl_3$) : 157.6 (q,J=36.14Hz,C=O); 137.3 and 136.0 (2xd;Cq and Cp); 129.6 and 129.1 (2xd,Co and Cm); 116.0 (q,J=288.74Hz,CF_3); 43.8 (s,C); 25.2 (t,CH_2); 24.1 (s,C); 23.1; 21.3 and 21.1 (3xq,3xCH_3).
Elemental analysis : calcd 5.16% N; found 5.08% N.

Synthesis of 1-Amino-2,2-dimethylcyclopropanecarboxylic Acid 23
To a yellow solution of ruthenium tetroxide, continuously generated in situ from 500 mg (0.003 mol) of rutheniumdioxide and 5 g of sodium periodate in 200 ml of acetone and 50 ml of water, was added at room temperature 0.01 mol of trifluoroacetamide 20 or 21, dissolved in 10 ml of acetone. The mixture was stirred at room temperature for 72 h, during which a total amount of 30 g of sodium periodate (dissolved in 300 ml 50% aqueous acetone) was added at regular intervals. The reaction mixture was filtered, cooled to 0°C during 1 h and filtered again. The filtrate was evaporated in vacuo in order to remove the acetone and the residual liquid was continuously extracted with ether during 36 h. The extract was evaporated in vacuo and the residue was refluxed with 10 ml of 5N hydrogen chloride during 4 h. Water was evaporated in vacuo and the solid residue was loaded on a cation exchange resin (Dowex 50 X8-100, H^+ form, 15 g). The column was eluted with 100 ml of water and with 100 ml aqueous ammonia (0.5N). The first fractions contain impurities while the desired compound 23 was eluted with the aqueous ammonia. The yield of 23 ranged from 20-30%. The ACC derivative 23 was recrystallised from aqueous ethanol at -20°C. The compound was identical in all aspects with a sample prepared from the corresponding α-chloroketimines.[17,18]

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* "Research Director" (Onderzoeksdirecteur) of the Belgian "National Fund for Scientific Research".

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