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SYNTHESIS OF 1-AMINO-2,2-DIALKYLCYCLOPROPANECARBOXYLIC ACIDS FROM β-CHLOROALDIMINES

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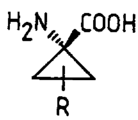
Abstract

A variety of hydrogen cyanide adducts of β-chloroaldimines using acetone cyanohydrin were prepared. The reactive behaviour of these α-amino-γ-chloronitriles towards bases was investigated with the aim to generate 1-aminocyclopropanecarbonitriles, which are precursors for the potentially plant growth regulating 1-aminocyclopropanecarboxylic acids. The synthesis of 1-amino-2,2-dimethylcyclopropanecarboxylic acid (= 2,3-methanovaline) by a reaction sequence involving addition of hydrogen cyanide across β-chloroaldimines, ring closure to functionalized cyclopropanes and acidic hydrolysis was accomplished. Alternatively the hydrogen cyanide adducts of β-chloroaldimines were converted into α-(N-benzylidene)amino-γ-chloronitriles, which were ring closed with base and hydrolyzed to afford 1-amino-2,2-dialkylcyclopropanecarbonitriles, the latter serving again as substrates for the hydrolytic conversion into the corresponding 1-amino-2,2-dialkylcyclopropanecarboxylic acids (exemplified for 1-amino-2,2-dimethylcyclopropanecarboxylic acid).

Introduction

In recent years there has been a considerable interest in 1-aminocyclopropanecarboxylic acids 1 due to their occurrence in nature (1-aminocyclopropanecarboxylic acid = ACC,[1] coronamic acid,[2,3] carnosadine[4,5]), their potential plant growth regulating properties[6,7] and their ability to exert conformationally controlling features in oligopeptides.[8] Various syntheses



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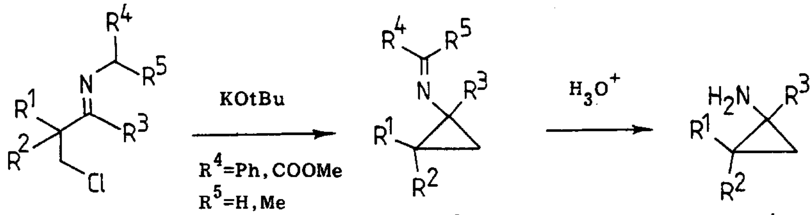
of these 1-aminocyclopropanecarboxylic acids have been published,[7-10] mainly based on strategies involving (a) double alkylation of glycine anion equivalents, (b) cyclopropanation of protected α,β-dehydro-α-aminocarboxylic acids and (c) Hofmann or Curtius rearrangements of cyclopropane 1,1-dicarboxylic acid derivatives. Geminally dialkylated 1-aminocyclopropanecarboxylic acids have been scarcely reported, among others from 1,3-dehydrochlorination of α-chloroketimines[11] or from cycloaddition of 2-diazopropane across diprotected methyleneglycine.[12] In this paper the synthesis of 2,2-dialkyl-1-aminocyclopropanecarboxylic acids, e.g. 11, from β-chloroimines and β-chloroaldehydes is reported.[13] The interest in these dialkylated ACC analogues stems from their potential to act as plant growth regulators. In addition, peptides containing these geminally dialkylated ACC's, e.g. 2,2-dimethyl-ACC 11 (also referred to as 2,3-methanovaline), might be enzyme inhibitors.[8,12]

Results and Discussion

β-Chloroimines 2 having an acidic hydrogen at the α-carbon of the N-substituent are known to undergo a base-induced 1,5-dehydrochlorination to afford N-cyclopropylimines 3 which are easily hydrolyzed into the corresponding cyclopropylamines 4.[14] This methodology for the construction of cyclo-



2 3 4

propylamines would be suitable for the synthesis of geminally dialkylated 1-aminocyclopropanecarboxylic acids provided the R^3 substituent, linked to the imino functionality, is convertable into a carboxylic group. Therefore, the synthesis of 1-aminocyclopropanecarbonitriles 4 (R^3 = CN) was investigated utilizing the cyanation of β-chloroimines 2.

The cyanation of β-chloroaldimines 6, easily accessible from the corresponding β-chloroaldehydes 5 and primary amines,[15] with acetone cyanohydrin in acetone at room temperature furnished N-substituted γ-chloro-α-aminonitriles 7 in 51-92% yield (Table I). Good yields (83-92%) of hydrogen cyanide adducts 7 were obtained for N-alkyl (R = i-Pr, t-Bu) or N-benzylic [R=CH_2Ph,CH(Me)Ph] derivatives, but the synthesis of the N-phenyl derivative 7b required an additional heating which caused some decomposition of the end product (51% yield). The cyanation using potassium cyanide in methanol under reflux could not be used as it led to ring closure affording azetidine-2-carbonitriles.[16] An alternative approach to hydrogen cyanide adducts 7 consisted of a Strecker-type synthesis involving the successive treatment of β-chloroaldehydes 5 with sodium bisulfite, an appropriate primary amine and potassium cyanide in aqueous medium (Table I). The reaction of 3-chloro-2,2-dimethylpropanal 5a (R^1=R^2=Me) with dimethylamine in the presence of sodium bisulfite and potassium cyanide afforded the α,γ-bis(dimethylamino)-nitrile 8 in 87% yield.

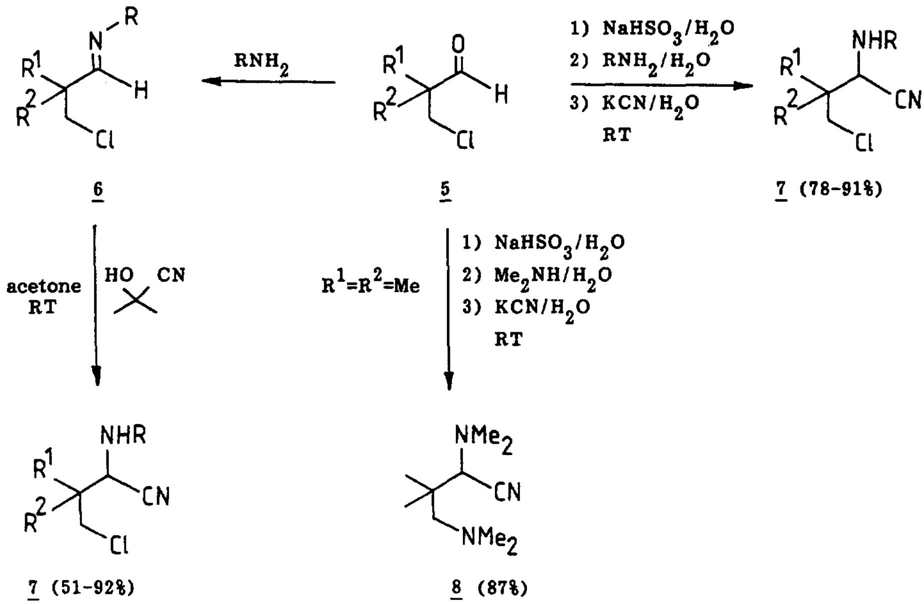
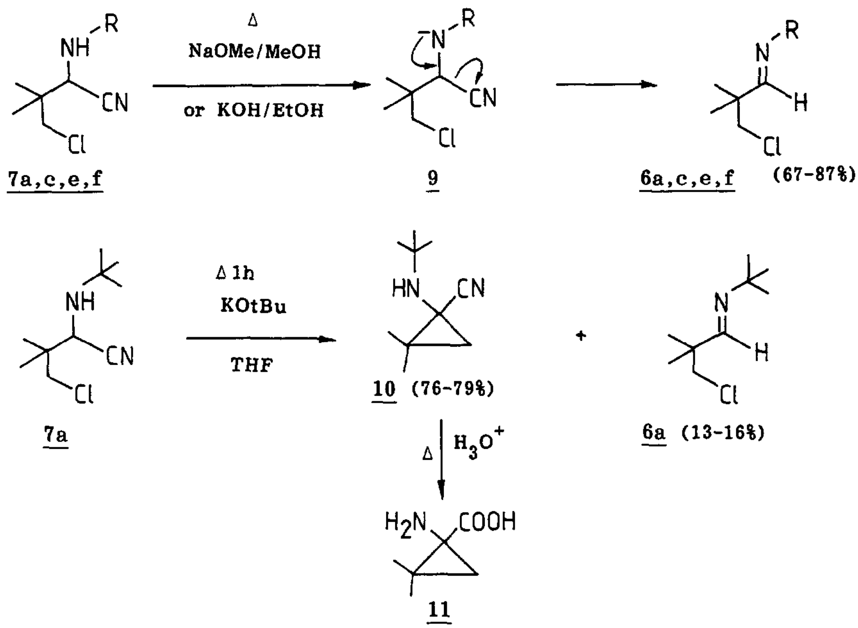


Table I : Syntheses of γ-Chloro-α-aminonitriles 7 from β-Chloroaldimines 6 and β-Chloroaldehydes 5

Starting Material	R^1	R^2	R	R'	Reaction Conditions[a]	Product	Yield (%)	Mp. (°C)
6a	Me	Me	t-Bu	-	2E $Me_2C(OH)CN$ acetone; RT 15h	7a	92	76
6b	Me	Me	Ph	-	2E $Me_2C(OH)CN$ acetone; RT 3d + Δ 1h	7b	51	72[b]
6c	Me	Me	i-Pr	-	2E $Me_2C(OH)CN$ acetone; RT 3d	7c	91	35
6d	Me	Me	CH(Me)Ph	-	1,5E $Me_2C(OH)CN$ acetone; RT 3d	7d	83	76
6e	Me	Me	CH_2Ph	-	5E $Me_2C(OH)CN$ acetone; RT 2d	7e	90	-
5a	Me	Me	Me	H	2E $NaHSO_3$/2E amine 2E KCN/H_2O/RT 1d	7f	87-91	-
5a	Me	Me	H	H	2E $NaHSO_3$/10E amine 2E KCN/H_2O/RT 1d	7g	89	-
5b	Et	Et	H	H	2E $NaHSO_3$/10E amine 2E KCN/H_2O/RT 1d	7h	78	-
5a	Me	Me	Me	Me	2E $NaHSO_3$/10E amine 2E KCN/H_2O/RT 1d	8	87	-

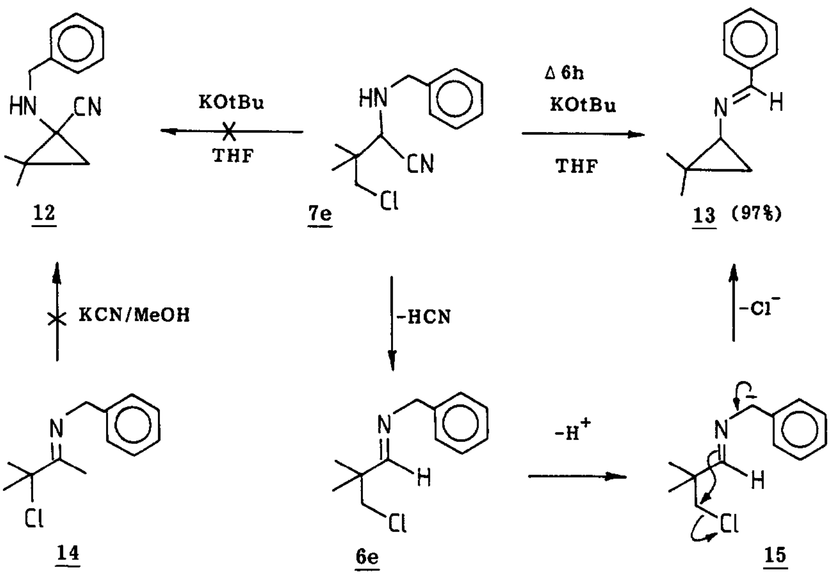
a) E : molar equivalents; b) partial decomposition

Reaction of hydrogen cyanide adducts 7 with sodium methoxide in methanol or with potassium hydroxide in ethanol regenerated β-chloroaldimines 6 as the only reaction products by base-induced dehydrocyanation (67-87% yield). Stronger bases in less polar medium, such as potassium t-butoxide in tetrahydrofuran, induced dehydrocyanation to a minor extent, but gave 1,3-dehydrochlorination as the major reaction pathway. Accordingly, 2-(N-t-butyl)-amino-4-chloro-3,3-dimethylbutanenitrile 7a reacted with two molar equivalents of potassium t-butoxide in tetrahydrofuran under reflux for 1h to provide 76-79% of 1-(N-t-butyl)amino-2,2-dimethylcyclopropanecarbonitrile 10 and 13-16% N-(3-chloro-2,2-dimethyl-1-propylidene)t-butylamine 6a. This reaction is most useful in terms of the synthesis of ACC-analogous because



it represents a better entry to 10 than starting from α-chloroketimines,[11,17] which gave rise to an important side reaction (formation of α-cyanoaziridines). As reported previously, 1-(N-t-butyl)-2,2-dimethylcyclopropanecarbonitrile 10 (and higher homologues) has been converted by hydrolysis into 1-amino-2,2-dimethylcyclopropanecarboxylic acid 11.[11,17]

Cyclopropanecarbonitriles having a N-benzylamino substituent at the 1-position are not accessible via 1,3-dehydrochlorination of α-chloroketimines.[17] This is regretful because the N-benzyl group would be more easily removable from nitrogen than the t-butyl substituent. Therefore the synthesis of 1-(N-benzyl)amino-2,2-dimethylcarbonitrile 12 was attempted by reaction of the functionalized nitrile 7e with potassium t-butoxide in tetrahydrofuran under reflux. However, a nearly quantitative conversion into N-(benzylidene)cyclopropylamine 13 was obtained, indicative of an initial 1,2-dehydrocyanation into β-chloroaldimine 6e, which underwent 1,5-dehydrochlorination under the influence of the base.



A base-induced 1,5-dehydrochlorination of β-chloroimidoylcyanides 16 (the deprotonation site being carbon-1 of the N-substituent) would generate geminally dialkylated cyclopropanes with a nitrile moiety and an alkylideneamino group at the 1-position. This would easily allow further conversion into ACC analogues by hydrolysis of the imino function and the nitrile group. Therefore, some efforts were performed in the direction of β-chloroimidoylcyanides 16. N-Chlorination of N-alkyl α-amino-γ-chloronitriles 7a,c with t-butylhypochlorite in ether, followed by dehydrochlorination with triethylamine afforded β-chloroimidoylcyanides 16a,c in 37-48% yield, together with the undesired β-chloroaldimines 6a,c (48-58%), making this process less attractive.

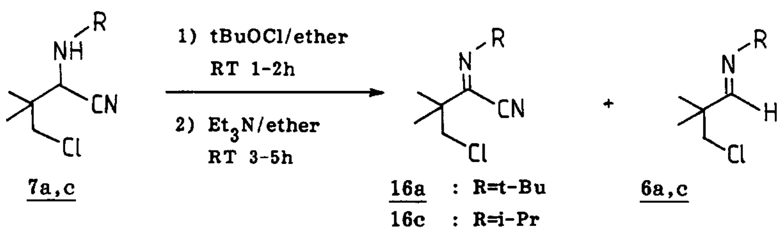


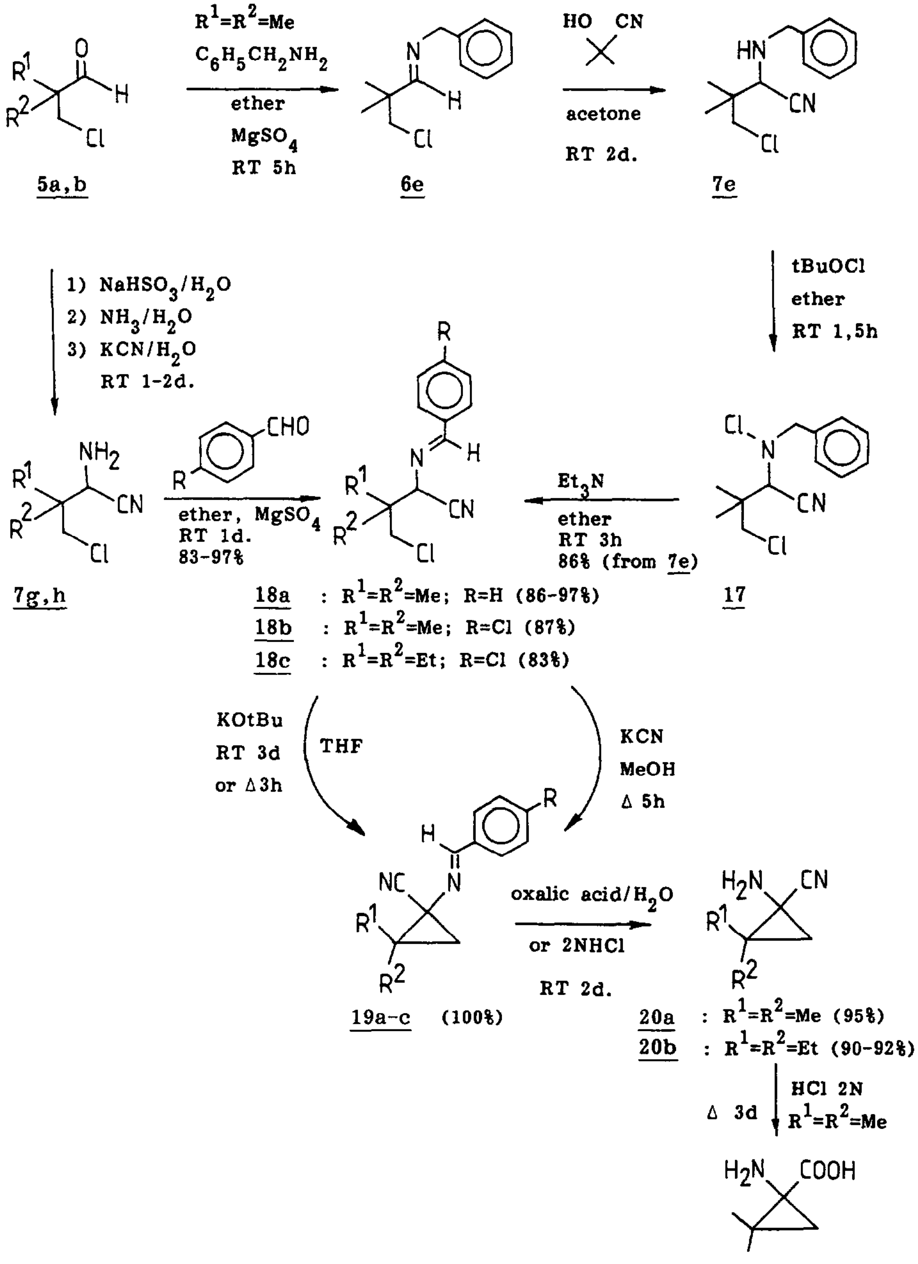
Table II gives a compilation of the various reactions of the hydrogen cyanide adducts 7.

Table II : Reaction of Hydrogen Cyanide Adducts with Various Reagents

Starting Material	Reaction Conditions[a]	Product(s)	Yield
7a	NaOMe/MeOH/2E 2N; Δ 1d	6a	87%
7e	NaOMe/MeOH/2E 2N; Δ 15h	6e	82%
7f	NaOH/EtOH/2E (10% soln); RT 1d	6e	77%
7c	KOH/EtOH/2E (10% soln); Δ 1d	6c	67%
7a	KOt-Bu/THF/2E (10% soln); Δ 1h	10	76-79%
		6a	13-16%
7e	KOt-Bu/THF/2E (10% soln); Δ 6h	13	97%
7c	Et_3N/ether/5E (10% soln); Δ 3d	-[b]	-[b]
7a	1) t-BuOCl/ether/2E; RT 1h	6a	58%
	2) Et_3N 5E; RT 3h	16a	37%
7c	1) t-BuOCl/ether/2E, RT 2h	6c	48%
	2) Et_3N 5E; RT 5h	16c	48%

[a] E = molar equivalents; = reflux; d = days; [b] No reaction.

The N-benzyl α-amino-γ-chloronitrile 6e could be conveniently N-chlorinated and dehydrochlorinated, but the final compound was not the imidoylcyanide 16 ($R=CH_2Ph$). Instead, the dehydrochlorination of N-chloro derivative 17 with triethylamine in ether at room temperature afforded the functionalized aldimine 18a in 86% overall yield from 7e (two steps). These functionalized aldimines 18 are also accessible via an alternative route involving a Strecker-type conversion of β-chloroaldehydes 5a,b into γ-chloro-α-aminonitriles 7g,h (vide supra) and subsequent reaction of the latter with benzaldehyde or 4-chlorobenzaldehyde (83-97%). These functionalized aldimines 18 were shown to be good precursors for ACC analogues. The requisite cyclisation of 2-(N-benzylidene)amino-4-chloro-3,3-dialkylnitriles 18 into cyclopropanes 19 was accomplished with potassium t-butoxide in tetrahydrofuran (room temperature or reflux) or by reaction of potassium cyanide in methanol (reflux). 1-(N-Benzylidene)-2,2-dialkylcyclopropanecarbonitriles 19 were obtained in nearly quantitative yield using either of the two cyclization reactions. Acidic hydrolysis of the cyclopropylimines 19 with 2N aqueous hydrogen chloride (10 equiv.) or aqueous oxalic acid afforded 1-aminocyclopropanecarbonitriles 20 ($R^1=R^2$=Me or Et) in 92-95% yield. These α-aminonitriles 20 were synthesized with overall yields of 65-75% (R^1=Me) or 60-68% (R^2=Et) from β-chloroaldehydes 5. α-Aminonitriles derived from cyclopropanones are rare compounds in the literature. Some derivatives were reported to result from the reaction of 1,1-bis(N,N-dialkyl)aminocyclopropanes or 1-(N,N-dialkyl)aminocyclopropanols with hydrogen cyanide,[18-20] and the



cyclisation of α-chloroketimines under the influence of cyanide.[17,21] 1-Amino-2,2-dialkylcyclopropanecarbonitriles 20 are good precursors to the corresponding 1-aminocyclopropanecarboxylic acids as exemplified by the conversion of 1-amino-2,2-dimethylcyclopropanecarbonitrile 20a with aqueous hydrogen chloride (2N; 10 equiv.; reflux 3d) into 1-amino-2,2-dimethylcyclopropanecarboxylic acid 11.[11,13,17,22]

Experimental Section

^{1}H NMR spectra were recorded with Varian T-60 (60 MHz), Jeol PMX60 (60 MHz) and Bruker WP-360 (360 MHz) NMR spectrometers, while ^{13}C NMR spectra were obtained on a Varian FT-80 NMR spectrometer. Infrared spectra were measured with a Perkin-Elmer model 1310 spectrofotometer. Mass spectra were recorded with a Varian MAT 112 mass spectrometer (70 eV) using the direct inlet system or a GC-MS coupling (capillary columns).
β-Chloroaldehydes 5 and β-chloroaldimines 6 were prepared as previously described.[15]

Synthesis of N-Substituted 2-amino-4-chloronitriles 7 by Addition of Acetone Cyanohydrin to β-Chloroaldimines

A 10% solution (w/v) of 0.01 mol of β-chloroaldimine 6 in dry acetone was treated with 0.02 mol of acetone cyanohydrin. The solution was stirred at room temperature for a time indicated in Table I. After the addition of 200 ml of pentane, dry hydrogen chloride was bubbled through the solution, which caused the precipitation of the hydrochloride of the N-substituted 2-amino-4-chloronitriles. The precipitate was filtered, washed with pentane and dried in vacuo. The solid hydrochloride was added to 100 ml of dry ether containing 0.02-0.05 mol of triethylamine. After stirring for 1h at room temperature, the solid triethylamine hydrochloride was filtered off and the solvent evaporated in vacuo to give pure N-substituted 2-amino-4-chloronitriles (^{1}H NMR, GC). These compounds 7 were immediately used in further experiments. Some derivatives were distilled in vacuo (Table I). It is recommended to store compounds 7 as their hydrochlorides.

Synthesis of N-Substituted or N-Unsubstituted 2-Amino-4-chloronitriles 7 by a Strecker-Type Synthesis

A solution of 0.2 mol of sodium bisulfite in 50 ml water was added dropwise to a stirred solution of 0.1 mol of β-chloroaldehyde 5 in 50 ml water. The mixture was stirred during two hours at room temperature after which 0.2 mol of the amine (primary amines, secondary amines and ammonia; the latter was used as an aqueous solution). The mixture was again stirred at room temperature for two hours and subsequently treated with 0.2 mol of potassium cyanide in 25 ml of water. After stirring one day at room temperature, the upper layer was taken up in 50 ml ether and the aqueous phase was extracted twice with 50 ml ether. The combined extracts were dried ($MgSO_4$), filtered and evaporated to leave pure 2-amino-4-chloronitriles 7 in most cases (^1H NMR, GC) (Table I). If the purity is not sufficient (< 92%) for further elaboration, the residue is dissolved in 100 ml of a 4:1 mixture of pentane-ether. Dry hydrogen chloride gas is bubbled in and the precipitated hydrochloride is isolated by filtration. The pure free base is regenerated by addition of triethylamine in ether as described in the previous experiment.

Spectrometric Data (IR, ^1H NMR, MS) of HCN Adducts of β-Chloroaldimines and Related Compounds

2-(N-t-Butyl)amino-4-chloro-3,3-dimethylbutanenitrile 7a

IR (KBr) : 3340 cm^{-1} (NH); 2225 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.07 (3H,s,CH_3); 1.18 (3H,s,CH_3); 1.19 (9H,s,$C(CH_3)_3$); 3.41 and 3.72 (2H,2xd,AB,J=10.4 Hz,CH_2); 3.56 (1H,s,br,CH); NH invisible. Mass spectrum m/z (%) : 202/200 (M^+; 1); 187/189(5); 160/162(9); 140(12); 120(6); 111(6); 84(14); 70(5); 67(3); 58(16); 57(100); 56(34); 55(8); 42(10); 41(27); 40(4); 39(7).

Elem. anal. : calcd. 13.82% N, 17.49% Cl; Found 13.95% N, 17.61% Cl.

2-(N-Phenyl)amino-4-chloro-3,3-dimethylbutanenitrile 7b

IR (KBr) : 3368 cm^{-1} (NH); 2240 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.22 (3H,s,CH_3); 1.29 (3H,s,CH_3); 3.49 and 3.73 (2H,2xd,AB,J=10.8Hz,CH_2); 4.41 (1H,s,CH); 6.70-7.50 (5H,m,C_6H_5); 3.80 (1H,s,br,N$\underline{H}$). Mass spectrum m/z (%) : 222/224 (M^+; 6); 197(6); 195(10); 161(7); 160(35); 158(7); 145(5); 144(11); 139 (8); 133(7); 132(10); 131(35); 130(11); 118(10); 105(11); 104(100); 91(5); 78(7); 77(74); 76(5); 65(5); 56(11); 55(10); 51(14); 43(6); 41(8); 40(10).

Elem. anal. : Calcd. 12.58% N; Found 12.71% N.

2-(N-Isopropyl)amino-4-chloro-3,3-dimethylbutanenitrile 7c

IR (KBr) : 3329 cm^{-1} (NH); 2225 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.07 (3H,s,CH_3); 1.15 (3H,s,C$\underline{H}_3$); 1.03 and 1.16 (6H,2xd,J=6Hz,CH(C$\underline{H}_3$)$_2$); 3.03 (1H, septet,J=6Hz,$CH(CH_3)_2$); 3.38 and 3.72 (2H,2xd,AB,J=10.4Hz,CH_2); 3.57 (1H,s,br,C$\underline{H}$); NH invisible. Mass spectrum m/z (%) 188/190 (M^+, 5); 175(4); 173 (10); 146(8); 127(4); 126(34); 112(4); 104(3); 98(17); 97(64); 84(8); 83 (19); 82(7); 71(8); 70(100); 69(3); 68(8); 67(5); 56(47); 55(39); 44(14); 43 (81); 42(11); 41(25).

Elem. anal. : Calcd. 14.85% N, 18.79% Cl; Found 14.72% N, 18.93% Cl.

2-[N-(α-Methylbenzyl)]amino-4-chloro-3,3-dimethylbutanenitrile 7d

IR (NaCl/CCl_4) : 3327 cm^{-1} (NH); 2226 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.11 (6H,s,$(CH_3)_2$); 1.41 (3H,d,J=6.2Hz,CH(C$\underline{H}_3$)); 3.44 and 3.62 (2H,2xd,AB,J=10.8 Hz,CH_2); 4.07 (1H,q,J=6.2Hz,C$\underline{H}$(CH_3)); 3.20 (1H,s,br,C$\underline{H}$); 7.36 (5H,s,C_6H_5); NH invisible. Mass spectrum m/z (%) 250/252 (M^+; 1); 235/237(4); 199(4); 198(14); 159(5); 140(2); 107(2); 106(19); 105(100); 104(9); 103(8); 91(3);

84(4); 79(9); 78(4); 77(11); 70(4); 56(4); 55(5); 51(3); 44(2); 43(4); 42 (2); 41(4); 40(8).
Elem. anal. : Calcd. 11.17% N, 14.09% Cl; Found 11.20% N, 14.01% Cl.

2-(N-Benzyl)amino-4-chloro-3,3-dimethylbutanenitrile 7e
IR (NaCl) : 3330 cm^{-1} (NH); 2228 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.08 (3H,s, CH_3); 1.12 (3H,s,CH_3); 1.78 (1H,s,br,NH); 3.34 and 3.60 (2H,2xd,AB,J=10.2Hz, $C\underline{H}_2$); 3.75 and 4.05 (2H,2xd,AB,J=12.4Hz,$C\underline{H}_2$-C_6H_5); 3.48 (1H,s,br,C$\underline{H}$); 7.32 (5H,s,$C_6\underline{H}_5$). Mass spectrum m/z (%) 236/238 (M^+; 4); 175(5); 174(18); 146 (4); 145(10); 126(4); 118(4); 92(18); 91(100); 83(5); 70(4); 65(8); 58(6); 57(5); 56(13); 55(8); 43(12); 42(5); 41(5); 39(5).
Elem. anal. : Calcd. 11.83% N, 14.98% Cl; Found 11.73% N, 15.10% Cl.

2-(N-Methyl)amino-4-chloro-3,3-dimethylbutanenitrile 7f
IR (NaCl) : 3356 cm^{-1} (NH); 2237 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.12 (3H,s, CH_3); 1.18 (3H,s,CH_3); 1.39 (1H,s,br,N$\underline{H}$); 2.58 (3H,s,CH_3N); 3.44 (1H,s, CHCN); 3.46 and 3.74 (2H,2xd,AB,J=10.8Hz,CH_2).
Elem. anal. : Calcd. 17.44% N; Found 17.30% N.

2-Amino-4-chloro-3,3-dimethylbutanenitrile 7g
IR (NaCl) : 3340 and 3400 cm^{-1} (NH); 2232 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 1.10 (3H,s,CH_3); 1.14 (3H,s,CH_3); 1.77 (2H,s,br,NH_2); 3.39 and 3.69 (2H,2xd, AB,J=10.8Hz,CH_2); 3.73 (1H,s,CH). Mass spectrum m/z (%) no M^+; 110(2); 97 (2); 91(3); 84(3); 82(7); 81(3); 70(2); 63(3); 58(3); 57(4); 56(100); 55 (25); 54(3); 53(4); 44(2); 43(3); 42(3); 41(9).
Elem. anal. : Calcd. 19.11% N, 24.19% Cl; Found 18.98% N, 24.08% Cl.

2-Amino-4-chloro-3,3-diethylbutanenitrile 7h
IR (NaCl) : 3340 and 3400 cm^{-1} (NH); 2235 cm^{-1} (C≡N), ^1H NMR ($CDCl_3$) : δ 0.6-2.2 (10H,m,($C\underline{H}_3C\underline{H}_2)_2$); 3.52 and 3.72 (2H,2xd,AB,J=11.2Hz,CH_2); 3.80 (1H, s,br,CH); NH_2 invisible. Mass spectrum m/z (%) no M^+; 151(1); 137(1); 125 (1); 121(1); 119(2); 112(3); 96(2); 95(2); 86(1); 85(2); 84(19); 83(15); 82 (4); 81(3); 77(2); 69(8); 68(2); 67(2); 57(7); 56(100); 55(36); 54(2); 53 (4); 43(12); 42(4); 41(17); 40(2).
Elem. anal. : Calcd. 16.04% N, 20.30% Cl; Found 16.19% N, 20.41% Cl.

2,4-Bis-(N,N-dimethylamino)-3,3-dimethylbutanenitrile 8
IR (NaCl) : 2222 cm^{-1} (C≡N). ^1H NMR ($CDCl_3$) : δ 0.98 (3H,s,CH_3); 1.00 (3H, s,CH_3); 2.13 and 2.33 (2H,2xd,AB,J=14Hz,CH_2); 2.31 (6H,s,N$(CH_3)_2$); 2.35 (6H,s,N$(CH_3)_2$); 3.74 (1H,s,CH). Mass spectrum m/z (%) 183 (M^+; 4); 125(2); 123(3); 100(9); 99(10); 98(3); 85(4); 84(10); 83(12); 70(2); 59(6); 58(100); 57(2); 56(4); 55(3); 45(2); 44(11); 43(5); 42(15); 41(4).

Table III : ^{13}C NMR Spectral Data (δ, $CDCl_3$) of Hydrogen Cyanide Adducts 7 and 8

Compound	C≡N (s)	CHCN (d)	CR^1R^2 (s)	CH_2Cl (t)	N-C	If R^1=Me $C(CH_3)_2$ (q)	Other carbons
7a	121.8	49.6	39.6	51.5	51.6(s)	22.5 20.7	29.4 (q, $C(CH_3)_3$)
7b	118.4	53.1	39.4	51.4	145.2(s)	22.6 21.2	129.6; 120.8 and 115.2 (3xd, Co, Cm and Cp)
7c	119.8	53.9	38.9	51.7	47.5(d)	23.7[a] 21.6[a]	20.8[a] and 22.9[a] (2xq, $CH(C_3)_2$)
7d	119.2	56.8[a]	38.8	51.6	54.9(d)[a]	22.9 21.2	25.0 (q, CH_3); 142.7 (s, Cq); 128.6; 127.1 and 127.7 (3xd; Co, Cm and Cp)
7e	119.0	56.1	39.0	51.7[a]	52.4(t)[a]	22.8 21.1	138.2 (s, Cq); 128.5; 128.3 and 127.6 (3xd, Co, Cm and Cp)
7f	119.0	59.1	39.0	51.9	35.4(q)	22.8 21.0	-
7g	120.8	49.3	39.3	51.5	-	22.4 20.4	-
7h	121.5	47.6	43.8	47.9	-	-	24.1 (t, CH_2); 8.2 and 7.6 (2xq, 2xCH_3)
8	116.1	64.7	40.8	67.3	44.8(q) 48.5(q)	24.5 22.7	-

a : or vice versa

Reaction of Hydrogen Cyanide Adducts with Various Bases

A mixture of 0.01 mol α-(N-alkyl)amino-γ-chloronitrile 7 and 0.02 mol base in the appropriate solvent (sodium methoxide in methanol; sodiumhydroxide or potassium hydroxide in ethanol; potassium t-butoxide in THF) was stirred at the given temperature and during the given period (see Table II). The reaction mixture was then poured into 100 ml water and extracted with ether. The combined extracts were dried ($MgSO_4$) and evaporated to leave an oil, which was investigated by ^1H NMR and preparative gas chromatography. The isolated compounds were identical with authentic samples (6a,c,e,[15], 10,[17] 13[14]) previously obtained.

Synthesis of 1-Amino-2,2-dimethylcyclopropanecarboxylic Acid 11 from 2-(N-t-Butyl)amino-4-chloro-3,3-dimethylbutanenitrile 7a

As described in the previous experiment, a mixture of 2-(N-t-butyl)amino-4-chloro-3,3-dimethylbutanenitrile 7a (5 mmol) and potassium t-butoxide (10 mmol) in 100 ml dry tetrahydrofuran was refluxed under stirring for 1h. The reaction mixture was poured into 500 ml water and extraction was performed with ether. The extract was dried ($MgSO_4$) and evaporated in vacuo to afford an oil consisting of 1-(N-t-butyl)amino-2,2-dimethylcyclopropanecarbonitrile 10 and N-(3-chloro-2,2-dimethyl-1-propylidene)t-butylamine 6a (^1H NMR, GC).

Distillation in vacuo over a short Vigreux column gave the aldimine 6a (bp. 50-56°C/11 mmHg) and the cyclopropanecarbonitrile 10 (bp. 86-89°C/11 mmHg). Compound 10 was identical in all aspects (^{1}H NMR, ^{13}C NMR, IR, MS) with the same compound previously obtained from the appropriate α-chloroketimine.[17] 1-(N-t-Butyl)amino-2,2-dimethylcyclopropanecarbonitrile 10 was converted into 1-amino-2,2-dimethylcyclopropanecarboxylic acid 11 by acidic hydrolysis under reflux as previously described.[11,17]

Conversion of HCN Adducts 7 into β-chloroimidoylcyanides 16

A stirred and cooled (ice-bath) solution of 0.01 mol of HCN adduct 7a,c in dry ether (10% solution; w/v) was treated dropwise with 0.02 mol of t-butyl-hypochlorite. The reaction mixture was stirred at room temperature for 1-2h (Table II) and subsequently treated with 0.05 mol of triethylamine. After stirring at room temperature for 3-5h, the mixture was poured into water and extraction was performed with ether. The combined ether extracts were dried ($MgSO_4$), filtered and evaporated to give a residual oil which was investigated by ^{1}H NMR and preparative GC. The resulting β-chloroaldimines 6a,c were identical with the previously reported substrates,[15] while the chlorinated imidoylcyanides 16 were fully characterized.

4-Chloro-2-(N-t-Butyl)imino-3,3-dimethylbutanenitrile 16a

IR (NaCl) : 1635 cm^{-1} (C=N) and 2218 cm^{-1} (C≡N). ^{1}H NMR ($CDCl_3$) : δ 1.28 (6H,s,Me_2); 1.38 (9H,s,t-Bu); 3.63 (2H,s,CH_2). ^{13}C NMR ($CDCl_3$) : δ 143.2 (s,C=N); 110.6 (s,C≡N); 58.2 (s,CMe_3); 52.0 (t,CH_2); 44.9 (s,CMe_2); 29.1 (q,Me_3); 23.3 (q,Me_2).

Elem. anal. : Calcd. 13.96% N, 17.66% Cl; Found 14.15% N, 17.78% Cl.

4-Chloro-2-(N-isopropyl)imino-3,3-dimethylbutanenitrile 16c

IR (NaCl) : 1634 cm^{-1} (C=N) and 2222 cm^{-1} (C≡N). ^{1}H NMR ($CDCl_3$) : δ 1.21 (6H,d,J=6Hz,$CHMe_2$); 1.30 (6H,s,Me_2); 3.67 (2H,s,CH_2); 4.02 (1H,septet,J=6Hz, NCH). ^{13}C NMR ($CDCl_3$) : δ 145.8 (s,C=N); 109.0 (s,C≡N); 59.3 (d,$CHMe_2$); 51.7 (t,CH_2); 43.6 (s,CMe_2); 23.3 (q,CMe_2 and $CHMe_2$; overlap).

Elem. anal. : Calcd. 15.00% N, 18.99% Cl; Found : 14.80% N, 19.16% Cl.

Synthesis of N-(Benzylidene)-3-chloro-1-cyano-2,2-dimethylpropylamine 18a from 2-(N-Benzyl)amino-4-chloro-3,3-dimethylbutanenitrile 7e

A solution of 0.01 mol of HCN adduct 7e in 25 ml dry ether was treated dropwise with 0.02 mol of t-butylhypochlorite at room temperature. After stirring 1.5h at room temperature, 0.1 mol of triethylamine was added and stirring was continued for 3h at ambient temperature. The triethylamine was filtered off and washed with dry ether. The filtrate was evaporated in vacuo. The last traces of t-butanol were removed under high vacuum (30°C). The residual liquid (86% yield from 7e) consisted of pure compound 18a (R^1=R^2=Me; R=H) (^{1}H NMR, tlc) and was used immediately in the next step. IR

(NaCl) : 2237 cm^{-1} (C≡N) and 1646 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$) : δ 1.12 (3H, s,CH_3); 1.23 (3H,s,CH_3); 3.51 and 3.71 (2H,2xd,AB,J=10.8Hz,CH_2); 4.67 (1H,d, J=1.4Hz,C<u>H</u>CN); 7.30-8.0 (5H,m,C_6H_5); 8.45 (1H,d,J=1.4Hz,CH=N). ^{13}C NMR ($CDCl_3$) : δ 21.4 and 22.7 (each q,Me_2); 40.1 (s,<u>C</u>Me_2); 51.9 (t,CH_2); 64.2 (d,<u>C</u>H-N); 116.5 (s,C≡N); 134.8 (s,$C_{quat.}$); 131.8 and 128.7 (each d,arom. CH; 2 signals are superimposed at 128.7); 164.0 (d,CH=N).
Elem. anal. : Calcd. 11.93% N, 15.10% Cl; Found : 11.81% N, 14.96% Cl.

<u>Synthesis of N-(Arylmethylidene)-3-chloro-1-cyano-2,2-dimethylpropylamine</u> <u>18</u> <u>from 2-Amino-4-chloro-3,3-dialkylbutanenitriles</u> <u>7g,h</u>
To a solution of 0.01 mol of HCN adduct <u>7g,h</u> in 20 ml dry ether was added 1 gram of anhydrous magnesium sulfate and 0.01 mol of benzaldehyde or 4-chlorobenzaldehyde. The mixture was stirred at ambient temperature during 1 day. The drying agent was removed by filtration and washed after which the filtrate was evaporated under vacuo. The residual liquid consisted of pure compound <u>18</u> (^{1}H NMR, tlc) and was used immediately further in the next step. Yields : <u>18a</u> (R^1=R^2=Me; R=H) : 97%; <u>18b</u> (R^1=R^2=Me; R=Cl) : 87%; <u>18c</u> (R^1=R^2= Et; R=Cl) : 83%.

<u>N-(4-Chlorophenylmethylidene)-3-chloro-1-cyano-2,2-dimethylpropylamine</u> <u>18b</u>
IR (NaCl) : 2232 cm^{-1} (C≡N) and 1645 cm^{-1} (C=N). ^{1}H NMR ($CDCl_3$) : δ 1.15 (3H,s,CH_3); 1.27 (3H,s,CH_3); 3.51 and 3.69 (2H,2xd,AB,J=11Hz,CH_2); 4.73 (1H, d,J=1.4Hz,C<u>H</u>CN); 7.40 and 7.80 (each 2H,each d,J=8.5Hz,o and m H's); 8.47 (1H,d,J=1.4Hz,C<u>H</u>=N). Mass spectrum m/z (%) : 268/270/272 (M^+; 6); 180(33); 179(29); 178(100); 177(56); 153(29); 152(22); 151(91); 150(24); 143(11); 142 (16); 141(24); 140(38); 139(44); 125(9); 113(13); 111(36); 100(20); 91(27); 89(18); 83(11); 82(56); 81(18); 77(13); 75(22); 74(9); 73(11); 72(24); 63 (15); 59(11); 58(44); 57(13); 56(42); 55(93); 54(11); 53(15); 51(15); 50 (16); 44(24); 43(29); 42(15); 41(33); 39(18). ^{13}C NMR ($CDCl_3$) : δ 21.4 and 22.8 (each q,Me_2); 40.2 (s,<u>C</u>Me_2); 51.9 (t,CH_2); 64.1 (d,<u>C</u>H-N); 116.3 (s, C≡N); 162.7 (d,<u>C</u>H=N); 130.0 and 129.1 (each s,C_o and C_m); 133.3 and 137.9 (each s,C_1 and C_p).
Elem. anal. : Calcd. 10.41% N, 26.34% Cl; Found 10.29% N, 26.21% Cl.

<u>N-(4-Chlorophenylmethylidene)-2-(chloromethyl)-1-cyano-2-ethylbutylamine</u> <u>18c</u>
Compound <u>18c</u> was only characterized as the crude product by ^{1}H NMR and used immediately in further experiments towards <u>20c</u> and <u>20b</u>.
^{1}H NMR ($CDCl_3$) : δ 0.97 (6H,t,J=7.5Hz,2Me); 1.4-2 (4H,m,2CH_2); 3.60 and 3.75 (2H,each d,AB,J=11Hz,CH_2Cl); 4.81 (1H,d,J=1.5Hz,C<u>H</u>CN); 7.48 and 7.78 (each 2H,each d,J=8.5Hz,o and m H's); 8.60 (1H,d,J=1.5Hz,CH=N).

Synthesis of 1-(N-arylmethylidene)amino-2,2-dialkylcyclopropanecarbonitriles 19

A solution of 0.01 mol of N-(arylmethylidene)-3-chloro-1-cyano-2,2-dimethylpropylamine 20 in 30 ml dry THF was treated with 0.02 mol of potassium t-butoxide. The mixture was refluxed under stirring during 3h (or 3 days at room temperature) after which the reaction mixture was poured into 150 ml water. After extraction with ether, the combined extracts were dried ($MgSO_4$) and evaporated to give compounds 19 in quantitative yield. Compound 19a (R^1=R^2=Me; R=H) was obtained analogously from compound 19a by using 2 molar equivalents potassium cyanide in methanol under reflux for 5h. Compounds 19 were used directly in the next hydrolysis step.

N-(benzylidene)-2,2-dimethylcyclopropanecarbonitrile 19

IR (NaCl) : 2220 cm^{-1} (C≡N) and 1640 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : δ 1.40 (3H,s,CH_3); 1.44 (3H,s,CH_3); 1.56 (2H,s,CH_2); 7.0-8.0 (5H,m,C_6H_5); 8.60 (1H, s,CH=N). Mass spectrum m/z (%) : 198 (M^+; 1); 183(1); 142(2); 123(9); 122 (82); 106(11); 105(100); 99(7); 94(5); 78(9); 77(73); 76(7); 75(5); 74(7); 66(5); 65(5); 55(5); 53(5); 52(9); 51(36); 50(18); 45(5); 43(9); 41(5); 40 (5); 39(14). ^{13}C NMR ($CDCl_3$) : δ 19.8 and 24.0 (each q,Me_2); 30.4 (s,<u>C</u>Me_2); 32.5 (t,CH_2); 45.4 (s,C-N); 117.5 (s,C≡N); 159.1 (s,C=N); 128.1, 128.6 and 130.9 (each d,C_o,C_m and C_p); 135.6 (s,$C_{quat.}$).
Elem. anal. : Calcd. 14.13% N; Found 14.31% N.

N-(4-Chlorophenylmethylidene)-2,2-dimethylcyclopropanecarbonitrile 19b

IR (NaCl) : 2226 cm^{-1} (C≡N) and 1640 cm^{-1} (C=N). ^1H NMR ($CDCl_3$) : δ 1.40 (3H,s,CH_3); 1.45 (3H,s,CH_3); 1.47 and 1.53 (2H,2xd,AB,J=5.2Hz,CH_2); 7.37 and 7.69 (each 2H,2xd,AB,J=8.5Hz,C_6H_4); 8.55 (1H,s,C<u>H</u>=N). Mass spectrum m/z (%) : 232/234 (M^+; 63); 231(32); 217/219(89); 176/178(100); 149(63); 141 (42); 139(32); 138(53); 125(26); 121(42); 100(37); 95(95); 94(95); 94(26); 89(84); 72(42); 58(63); 57(47); 56(32); 55(37); 53(32); 44(32); 43(68); 42 (21); 41(63); 40(21); 39(37). ^{13}C NMR ($CDCl_3$) : δ 19.8 and 23.9 (each q, Me_2); 30.7 (s,<u>C</u>Me_2); 32.6 (t,CH_2); 45.4 (s,<u>C</u>-N); 117.2 (s,C≡N); 157.8 (d, CH=N); 128.9 and 129.2 (each d,C_o and C_m); 134.0 and 136.9 (each s,=<u>C</u>Cl and C_1).
Elem. anal. : Calcd. 12.04% N, 15.23% Cl; Found 12.21% N, 15.38% Cl.

N-(4-Chlorophenylmethylidene)-2,2-diethylcyclopropanecarbonitrile 19c

Compound 20c was only characterized as the crude product by ^1H NMR and immediately used further in the next experiment towards 21b. ^1H NMR ($CDCl_3$) : δ 0.93 and 1.05 (each 3H,each t,J=7.5Hz,2Me); 1.5-2.1 (6H,m,3CH_2); 7.43 and 7.72 (each 2H,each d,J=8.5Hz,o and m H's).

Synthesis of 1-Amino-2,2-dialkylcyclopropanecarbonitriles 20

Compounds 19, obtained as described in the previous experiment, were directly treated under stirring with 5 molar equivalent of aqueous oxalic acid (about 10% w/v) during 2 days at ambient temperature. Similarly, the hydrolysis of the aldimine can be performed with aqueous hydrogen chloride (10 molar equiv.; 2N) at room temperature during 2 days. The aqueous solution was extracted with ether to remove the benzaldehyde(s). Afterwards, the reaction mixture was made alkaline with a concentrated sodium hydroxide solution and extraction was performed with dichloromethane. The extracts were dried ($MgSO_4$) and evaporated in vacuo to give almost pure α-aminonitriles 20 in 92-95% yield. Compound 20a was recrystallized from pentane, mp. 45°C.

1-Amino-2,2-dimethylcyclopropanecarbonitrile 20a

IR (KBr) : 2222 cm^{-1} (C≡N) and 3379 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : δ 0.81 and 1.05 (2H,2xd,AB,J=5.2Hz,CH_2); 1.23 (3H,s,CH_3); 1.28 (3H,s,CH_3); 1.90 (2H,s, br,NH_2). Mass spectrum m/z (%) : 110 (M^+; 3); 109(3); 95(100); 84(3); 83 (8); 82(4); 81(3); 78(11); 69(8); 68(44); 67(7); 66(6); 65(3); 58(8); 57(4); 56(8); 55(9); 54(9); 53(14); 52(4); 51(4); 45(4); 44(4); 43(19); 42(21); 41 (38); 40(7); 39(22). ^{13}C NMR spectrum ($CDCl_3$) : δ 18.5 and 23.6 (each q,Me_2); 25.8 and 31.3 (each s,$\underline{C}Me_2$ and $\underline{C}$-NH_2); 29.6 (t,CH_2); 122.9 (s,C≡N). Elem. anal. : Calcd. 25.43% N; Found 25.32% N.

1-Amino-2,2-diethylcyclopropanecarbonitrile 20b

IR (NaCl) : 2220 cm^{-1} (C≡N) and 3390 cm^{-1} (NH_2). ^1H NMR ($CDCl_3$) : δ 0.6-1.2 (8H,m,($C\underline{H}_3CH_2)_2$ and $C\underline{H}_2$); 1.2-1.8 (4H,m,($CH_3C\underline{H}_2)_2$); 2.03 (2H,s,br,NH_2). Mass spectrum m/z (%) : no M^+; 123(3; M^+-Me); 109(100); 95(4); 94(5); 91(6); 82(18); 81(15); 70(24); 69(16); 68(24); 67(5); 56(7); 55(58); 54(5); 53(9); 43(7); 42(33); 41(27); 39(9). ^{13}C NMR ($CDCl_3$) : δ 10.3 and 10.7 (each q,2Me); 20.6 and 26.3 (each t,2$\underline{C}H_2$Me); 31.8 and 35.8 (each s,$\underline{C}Et_2$ and $\underline{C}$-NH_2); 28.4 (t,CH_2); 123.1 (s,C≡N).
Elem. anal. : Calcd. 20.27% N; Found 20.1% N.

Synthesis of 1-Amino-2,2-dimethylcyclopropanecarboxylic Acid 11

A solution of 0.01 mol of 1-amino-2,2-dimethylcyclopropanecarbonitrile 20a was hydrolysed with 0.1 mol of aqueous hydrogen chloride (2N) under reflux during 3 days. The reaction mixture was evaporated to dryness in vacuo and the solid residue was treated with a cationic ion exchange resin (Dowex 50 X8-100, H^+ form, 15 gram) as previously described.[11,17] The yield of α-amino acid 11 varies from 35 to 60% according to this procedure.

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