Tetrahedron Vol. 44, No. 12, pp. 3653 to 3670, 1988
Printed in Great Britain.

0040-4020/88 $3.00 + .00

SYNTHESIS OF AZETIDINES FROM β-CHLORO IMINES

PAUL SULMON[¶], NORBERT DE KIMPE* AND NICEAS SCHAMP

Laboratory of Organic Chemistry, Faculty of Agricultural Sciences,
State University of Gent, Coupure Links 653, B-9000 Gent, Belgium

BERNARD TINANT AND JEAN-PAUL DECLERCQ

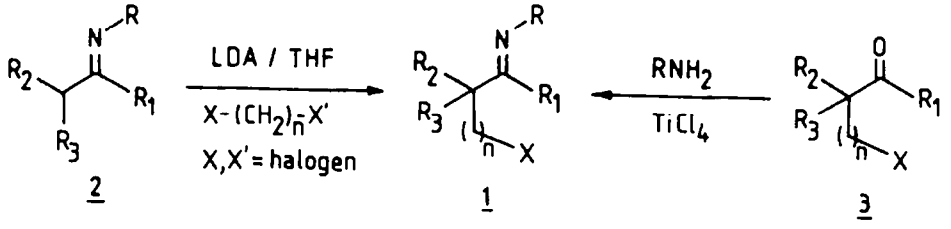
Laboratoire de Chimie Physique et de Cristallographie, Bâtiment Lavoisier,
1, Place Louis Pasteur, B-1348 Louvain-la-Neuve, Belgium

(*Received in UK 29 February* 1988)

Abstract - The reaction of β-chloro imines 4 with potassium cyanide in methanol or with lithium aluminium hydride in dry ether gave rise to 2-cyanoazetidines 5 and azetidines 21. The reaction proceeded by nucleophilic addition of cyanide or hydride across the carbon-nitrogen double bond, followed by ringclosure. The corresponding β-chloro tosylhydrazones, which could either give rise to a four- or five-membered heterocycle on treatment with potassium cyanide in methanol, were shown to afford N-tosylamino 2-cyanoazetidines, exclusively.

Introduction :

ω-Halo imines 1 are a class of bifunctional compounds, the synthesis of which was recently described by us[1,2]. These compounds were prepared from the corresponding carbonyl compounds 3 i.e. ω-halo ketones and ω-halo aldehydes, by reaction with a primary amine[1] or from imines 2 by a base-induced α-alkylation with a α,ω-dihaloalkane[2] (Scheme I). ω-Haloimines are quite versatile reagents for the synthesis of heterocyclic compounds. In this article, the reactivity of β-chloro imines 1 towards nucleophiles, such as potassium cyanide and complex metal hydrides, leading to azetidines will be described.



2 1 3

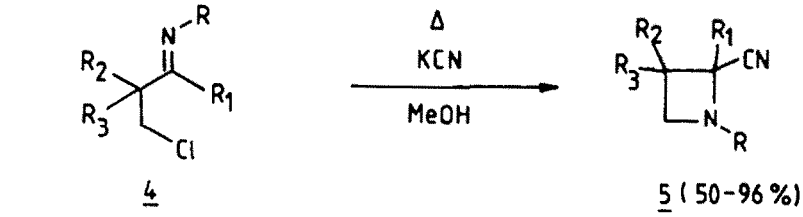
SCHEME I

¶ Present address : Laboratory of Chemical Products, DSM Limburg b.v., 6160 MB Geleen, The Netherlands.

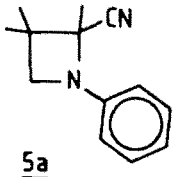
Results and discussion :

Reactivity of β-Chloro Imines towards Potassium Cyanide : Synthesis of 2-Cyano-azetidines

In general, azetidines are an important class of heterocyclic compounds which have received considerable attention in the literature[3-5]. 2-Cyanoazetidines[6-10] have only been prepared by hydrogen cyanide addition to 1-azetines[6], by reaction of triphenylphosphine dibromide with azetidine-2-carboxamides[7] or by cyclization of α,γ-dibromonitriles with amines[8]. In a preliminary report[11] we described some examples of the novel synthesis of 2-cyano-3,3-dimethylazetidines 5 by reaction of β-chloro imines 4 with potassium cyanide in methanol (Scheme II). In this article the preparation of 2-cyanoazetidines 5 from β-chloroimines 4 will be described in



4 5 (50-96 %)



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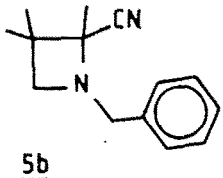

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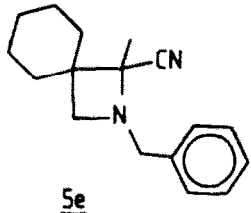

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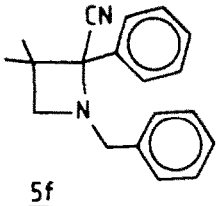

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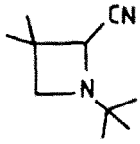

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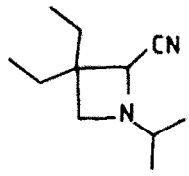

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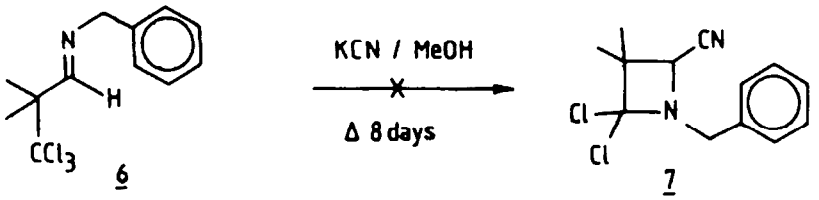
SCHEME II

detail (Table I). Normally the reaction of β-chloroimines 4 with potassium cyanide in methanol, affording α-cyanoazetidines 5, was complete within several hours (Table I), but for sterically hindered β-chloro imines 4 (Table I, entry 5,9 and 10) even after 50 hours or more the starting material was not totally consumed. In order to test the possibility to prepare β-lactams from β-halo imines, the reaction of β,β,β-trichloroaldimine 6, prepared from 3,3,3-trichloro-2,2-dimethyl-propanal[1,12], with potassium cyanide was investigated. Unfortunately,aldimine 6



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SCHEME III

Table I : Synthesis of Azetidines 5 and 21.

Entry	Starting Material	R	R_1	R_2	R_3	Reaction conditions[a]	Yield[b]
1	4a	C_6H_5	Me	Me	Me	2E KCN/MeOH Δ 20h	5a : 76[c]
2	4b	$CH_2C_6H_5$	Me	Me	Me	2E KCN/MeOH Δ 1h	5b : 93
3	4c	i-Pr	Me	Me	Me	2E KCN/MeOH Δ 2,5h	5c : 96/82[d,e]
4	13	$NHSO_2C_6H_4$ -4-CH_3	Me	Me	Me	2E KCN/MeOH Δ 6h	5d : 87/92[d,f]
5	4d	$CH_2C_6H_5$	Me	$-(CH_2)_5-$		2E KCN/MeOH Δ 3d	5e : 84
6	4e	$CH_2C_6H_5$	C_6H_5	Me	Me	2E KCN/MeOH Δ 6h	5f : 93
7	4f	i-Pr	C_6H_5	Me	Me	2E KCN/MeOH Δ 12h	5g : 89
8	4g	$CH_2C_6H_5$	H	Me	Me	2E KCN/MeOH Δ 6d	5h : 88
9	4h	t-Bu	H	Me	Me	2E KCN/MeOH Δ 50h	5i : 83[g]
10	4i	i-Pr	H	Et	Et	2E KCN/MeOH Δ 24h	5j : 50[g]
11	4g	$CH_2C_6H_5$	H	Me	Me	8E LAH/ether Δ 2h	21a : 94
12	4h	t-Bu	H	Me	Me	8E LAH/ether Δ 2h	21b : 85
13	4i	i-Pr	H	Et	Et	8E LAH/ether Δ 1d	21c : 65[g]
14	4c	i-Pr	Me	Me	Me	8E LAH/ether Δ 3h	21d : 92
15	4a	C_6H_5	Me	Me	Me	8E LAH/ether Δ 1h	21e : 95
16	4b	$CH_2C_6H_5$	Me	Me	Me	8E LAH/ether Δ 2h	21f : 88
17	4j	C_6H_5	Me	$-(CH_2)_5-$		8E LAH/ether Δ 15d	21g : 90
18	4e	$CH_2C_6H_5$	C_6H_5	Me	Me	8E LAH/ether Δ 20h	21h : 0[g]
19	4f	i-Pr	C_6H_5	Me	Me	8E LAH/ether Δ 2h	21i : 87

a : Reaction conditions (10% w/v solution); KCN = potassium cyanide; LAH = lithium aluminium hydride; Δ = reflux; E = equivalents; h = hour(s); d = day(s); The reactions were normally performed on a 0.01 mol scale except otherwise indicated. All compounds gave satisfactory microanalyses : C ± 0.15; H ± 0.20; N ± 0.20%.

b : Yields refer to isolated yields (distillation, crystallisation), other yields refer to glc analyses. Reaction mixtures were isolated in nearly quantitative yield.

c : Mp 59°C d : 0.1 molar scale e : Bp 82-85°C/14mmHg f : Mp 130°C

g : the rest is starting material.

Table II : Spectral Data (IR, ^{1}H-NMR, MS) of Azetidines 5 and 21.

Compound	IR(NaCl) $\nu_{C\equiv N}$ cm^{-1}	^{1}H-NMR (δ, $CDCl_3$)	Mass Spectrum (70eV) m/e (%)
5a	2228	1.34 (3H,s,C<u>H</u>$_3$); 1.53 (3H,s, C<u>H</u>$_3$); 1.71 (3H,s,C<u>H</u>$_3$); 3.57 (2H,s,C<u>H</u>$_2$); 6.60-7.60 (5H,m, C_6<u>H</u>$_5$).	200(M$^+$,14); 145(9); 144(52); 143(9); 129(10); 118(14); 106 (9); 105(25); 104(12); 77(38); 51(16); 44(15); 43(5); 42(6); 41(14); 40(100); 39(10).
5b	2221	1.19 (3H,s,C<u>H</u>$_3$); 1.25 (6H,2xs, C(C<u>H</u>$_3$)$_2$); 2.84 and 3.00 (2H, 2xd,AB,J=6.4Hz,C<u>H</u>$_2$ ring); 4.79 and 4.64 (2H,2xd,AB,J=13.2Hz, C<u>H</u>$_2$C$_6$H$_5$); 7.33 (5H,s,C_6<u>H</u>$_5$).	214(M$^+$,6); 123(8); 92(10); 91 (100); 82(5); 65(9); 56(9); 42 (5); 41(8); 39(5).
5c	2221	0.93 and 1.02 (6H,2xd,J=6Hz, CH(C<u>H</u>$_3$)$_2$); 1.23 (6H,2xs,2xC<u>H</u>$_3$); 1.43 (3H,s,C<u>H</u>$_3$); 2.72 (1H,sep-tet,J=6Hz,C<u>H</u>(CH$_3$)$_2$); 2.72 and 3.03 (2H,2xd,AB,J=6.4Hz,C<u>H</u>$_2$).	166(M$^+$,6); 151(13); 139(6); 111 (13); 95(6); 83(9); 82(6); 72 (20); 70(69); 69(20); 57(6); 56 (60); 55(15); 44(9); 43(39); 42 (28); 41(48); 40(100); 39(11).
5d	2222 3191 (ν_{NH})	1.17 (3H,s,C<u>H</u>$_3$); 1.23 (6H,s,2x C<u>H</u>$_3$); 2.45 (3H,s,C<u>H</u>$_3$); 3.01 and 3.11 (2H,2xd,AB,J=6.6Hz,C<u>H</u>$_2$); 6.30 (1H,s,*br*,N<u>H</u>); 7.38 and 7.88 (4H,2xd,AB,J=8Hz,C_6<u>H</u>$_4$).	no M$^+$; 155(11); 139(15); 138 (100); 111(16); 96(22); 95(13); 94(12); 92(12); 91(33); 83(22); 69(9); 68(9); 67(11); 65(19); 57(33); 56(10); 55(58); 45(15); 43(32); 42(8); 41(33); 39(8).
5e	2222	1.23 (3H,s,C<u>H</u>$_3$); 0.60-2.20 (10H,m,C_6<u>H</u>$_{10}$); 2.74 and 3.10 (4H,2xd,AB,J=6.4Hz,ring C<u>H</u>$_2$); 3.60 and 3.78 (2H,2xd,AB,J=12.4 Hz,C<u>H</u>$_2$C$_6$H$_5$); 7.28 (5H,s,C_6<u>H</u>$_5$).	
5f	2222	0.83 (3H,s,C<u>H</u>$_3$); 1.37 (3H,s, C<u>H</u>$_3$); 2.93 and 2.97 (2H,2xd,AB, J=6.8Hz,ring C<u>H</u>$_2$); 3.64 and 3.90 (2H,2xd,AB,J=12.8Hz,C<u>H</u>$_2$C$_6$ H$_5$); 7.10-7.70 (10H,m,2xC$_6$<u>H</u>$_5$).	276(M$^+$,5); 250(6); 194(8); 185 (6); 107(9); 105(20); 104(10); 91(100); 77(10); 65(9); 57(6); 56(24); 55(7); 51(6); 44(7); 43 (5); 41(13); 40(67); 39(6).
5g	2223	0.74 (3H,s,C<u>H</u>$_3$); 0.81 and 1.02 (6H,2xd,J=6.2Hz,CH(C<u>H</u>$_3$)$_2$); 1.28 (3H,s,C<u>H</u>$_3$); 2.82 (1H,septet,J= 6.2Hz,C<u>H</u>(CH$_3$)$_2$); 3.10 and 2.82 (2H,2xd,AB,J=6.5Hz,C<u>H</u>$_2$); 7.00-7.70 (5H,m,C_6<u>H</u>$_5$).	228(M$^+$,36); 227(8); 213(10); 185(34); 173(19); 172(10); 158 (15); 157(85); 146(8); 131(25); 130(17); 116(8); 115(13); 107 (15); 105(15); 104(100); 103 (15); 91(10); 82(8); 77(17); 70 (10); 56(68); 55(15); 43(27); 41(27); 39(8).
5h	2222	1.25 (3H,s,C<u>H</u>$_3$); 1.44 (3H,s, C<u>H</u>$_3$); 2.87 and 3.13 (2H,2xd, AB,J=6.4Hz,C<u>H</u>$_2$ ring); 3.63 (1H,s,C<u>H</u>CN); 3.71 and 3.74 (2H, 2xd,AB,J=13Hz,C<u>H</u>$_2$C$_6$H$_5$); 7.37 (5H,s,C_6<u>H</u>$_5$).	200(M$^+$,6); 155(7); 114(7); 92 (12); 91(100); 65(12); 56(19); 55(5); 41(15); 40(22); 39(7).

Table II : continued

Compound	IR(NaCl) $\nu_{C\equiv N}$ (cm^{-1})	^{1}H-NMR (δ, $CDCl_3$)	Mass Spectrum (70eV) m/e (%)
5i	2239	0.98 (9H,s,t-Bu); 1.11 (3H,s, CH_3); 1.45 (3H,s,CH_3); 2.88 (2H,s,CH_2); 3.62 (1H,s,CH).	166(M^+,4); 152(11); 151(82); 97 (5); 95(7); 82(16); 70(23); 68 (9); 58(18); 57(100); 56(39); 55(16); 54(5); 53(7); 43(4); 42 (18); 41(77); 40(7); 39(25).
5j	2239	0.92 and 1.02 (6H,2xd,J=6Hz, $CH(CH_3)_2$); 0.60-2.02 (10H,m, $2xCH_2CH_3$); 2.50 (1H,septet,J= 6Hz,$CH(CH_3)_2$); 2.65 and 3.15 (2H,2xd,AB,J=6.6Hz,CH_2 ring); 3.52 (1H,s,CHCN).	
21a	-	1.22 (6H,s,$(CH_3)_2C$); 2.99 (4H, s,ring CH_2 (2x)); 3.57 and 3.63 (2H,2xd,AB-system,J=12Hz,CH_2C_6 C_5). 7.28 (5H,s,C_6H_5).	175(M^+,5); 174(4); 120(6); 119 (3); 118(4); 98(4); 92(13); 91 (100); 65(11); 57(2); 56(6); 55 (4); 42(8); 42(8); 41(15); 40 (6); 39(9).
21b	-	0.91 (9H,s,$C(CH_3)_3$); 1.17 (6H, s,$(CH_3)_2$); 2.91 (4H,s,ring CH_2 (2x)).	
21c	-	0.89 (6H,d,J=6Hz,$CH(CH_3)_2$); 0.77 (6H,t,J=7Hz,$(CH_3CH_2)_2$); 1.58 (4H,q,J=7Hz,$(CH_3CH_2)_2$); 2.29 (1H,septet,J=6Hz,$CH(CH_3)_2$); 2.90 (6H,s,ring CH_2(2x)).	
21d	-	0.90 and 0.98 (6H,2xd,J=6,0Hz, $CH(CH_3)_2$); 1.01 (3H,s,CH_3); 1.12 (3H,s,CH_3); 1.07 (3H,d,J= 6.4Hz,$CHCH_3$); 2.35 (1H,septet, J=6Hz,$CH(CH_3)_2$); 2.82 (1H,q,J= 6.4Hz,$CHCH_3$); 2.52 and 3.16 (2H,2xd,AB,J=6.8Hz,CH_2).	141(M^+,12); 126(15); 115(5); 97 (6); 87(9); 86(73); 85(20); 84 (18); 83(5); 73(5); 72(58); 71 (11); 70(100); 69(9); 60(14); 58(14); 57(18); 56(43); 55(33); 53(4); 45(10); 44(93); 43(40); 42(40); 41(44); 40(12); 39(13).
21e	-	1.07 (3H,s,CH_3); 1.18 (3H,s, CH_3); 1.24 (3H,d,J=6.4Hz,CH_3 CH); 3.25 and 3.55 (2H,2xd,AB, J=6.4Hz,CH_2); 3.64 (1H,q,J= 6.4Hz,$CHCH_3$); 6.30-7.40 (5H,m, C_6H_5).	175(M^+,22); 120(19); 119(100); 118(13); 106(10); 105(41); 104 (85); 91(5); 78(7); 77(50); 55 (11); 51(15); 43(6); 42(6); 41 (16); 40(21); 39(10).
21f	-	(CCl_4); 0.85 (3H,d,J=6.2Hz, CH_3CH); 1.00 (3H,s,CH_3); 1.11 (3H,s,CH_3); 2.48 and 3.02 (2H, 2xd,AB,J=6.2Hz,CH_2); 2.82 (1H, q,J=6.2Hz,CH_3CH); 3.42 and 3.66 (2H,2xd,AB,J=12.4Hz,CH_2); 7.22 (5H,s,C_6H_5).	189(M^+,7); 188(4); 176(4); 174 (4); 134(7); 133(4); 132(7); 120(8); 118(5); 106(8); 105(4); 93(4); 92(34); 91(100); 89(4); 77(4); 70(8); 65(13); 57(4); 56 (7); 55(15); 51(4); 43(4); 42 (8); 41(13); 40(7); 39(6).

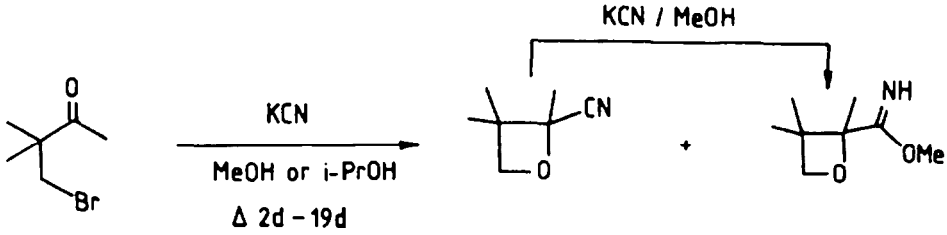
Table II : continued

Compound	IR(NaCl) $\nu_{C\equiv N}$ (cm^{-1})	^{1}H-NMR (δ, $CDCl_3$)	Mass Spectrum (70eV) m/e (%)
21g	–	0.60-2.00 (10H,m,$C_5\underline{H}_{10}$); 1.37 (3H,d,J=6.6Hz,$C\underline{H}_3CH$); 3.31 and 3.75 (2H,2xd,AB,J=6.5Hz,$C\underline{H}_2$); 3.71 (1H,q,J=6.6Hz,$CH_3C\underline{H}$); 6.30-7.50 (5H,m,$C_6\underline{H}_5$).	215(M^+,12); 120(16); 119(100); 118(5); 106(11); 105(20); 104(28); 81(6); 77(15); 67(4); 55(4); 51(4); 41(7); 40(16).
21i	–	0.76 and 0.98 (6H,2xd,J=6Hz, $CH(C\underline{H}_3)_2$); 0.78 (3H,s,$C\underline{H}_3$); 1.16 (3H,s,$C\underline{H}_3$); 2.45 (1H,septet,J=6Hz,$C\underline{H}(CH_3)_2$); 2.66 and 3.20 (2H,2xd,AB,J=6.4Hz,$C\underline{H}_2$); 3.81 (1H,s,$C\underline{H}C_6H_5$); 7.00-7.50 (5H,m,$C_6\underline{H}_5$).	203(M^+,10); 202(3); 188(5); 148 (12); 147(27); 146(11); 133(12); 132(100); 131(5); 118(4); 117 (16); 115(4); 113(3); 106(6); 105(14); 104(14); 103(3); 91 (12); 90(3); 84(4); 79(4); 78 (4); 77(6); 70(6); 56(13); 55 (6); 43(11); 42(3); 41(10); 39 (4).

did not react over a period of 8 days with potassium cyanide in methanol to form the desired 2-cyano-4,4-dichloroazetidine 7 (Scheme III) but resulted in complete recovery of the starting material. This functionalized α-cyanoazetidine 7 would have been a suitable precursor for the preparation of β-lactams.

The synthesis and the spectral data of α-cyanoazetidines are given in Tables I, II and III. Several β-chloro imines were not previously described, not even in our previous article on the synthesis of these compounds. All new β-chloro imines 4 and β-chloro tosylhydrazone 13,which were used in the synthesis of azetidines,are described in Tables IV (IR, ^{1}H-NMR, MS) and V (^{13}C-NMR).

For comparative reasons β-bromoketone 8 was reacted under the same reaction conditions as the β-halo imines with potassium cyanide in methanol leading to the



8 9 10

KCN / MeOH Δ 2d.	33 %	67 %
KCN / i-PrOH Δ 19 d.	100 %	-

SCHEME IV

Table III : ^{13}C-NMR Spectral Data (δ, $CDCl_3$) of Azetidines 5 and 21.

Compound	C≡N (s)	$\underline{C}R_1$	$\underline{C}R_2R_3$ (s)	CH_2 (t)	$R_1=\underline{C}H_3$ (q)	$R_2=R_3=CH_3$ $C(\underline{C}H_3)_2$(q)	N-$\underline{C}$	$\underline{C}$o (d)	$\underline{C}$m (d)	$\underline{C}$p	if N-C ≠ $\underline{C}$q $\underline{C}$q (s)	Other signals
5a	119.3	66.5 (s)	38.3	60.6	20.3	25.3;22.3	146.8 (s)	129.1;	119.5 (3xd)	and 113.3		-
5b	119.3	68.5 (s)	38.2	63.5	19.8	24.2;22.4	56.7 (t)	128.9;	128.2 (3xd)	and 127.2	137.3	-
5c	119.3	66.9 (s)	36.5	62.5	19.9	24.6;22.7	53.5 (d)	-	-	-	-	22.1 and 21.4 (2xq,$CH(\underline{C}H_3)_2$
5d	118.5	74.0 (s)	36.4	68.0	18.2	24.1;21.9	-	135.6[a]; (2xd,	129.5 1xs)	and 128.2	144.2[a]	21.6 (q,$\underline{C}H_3C_6H_4$)
5e	119.0	68.8 (s)	42.1	61.0	19.6	-	56.8 (t)	128.9;	128.2 (3xd)	and 127.2	137.4	34.5; 31.1; 25.6; 22.9 and 22.8 (5xt;-$(\underline{C}H_2)_5$-)
5f	118.4	75.1 (s)	41.8	62.3	-	24.2;23.4	56.7 (t)	128.8 128.6	128.5 128.4 (6xd)	127.3 125.8	136.9 135.8	-
5g	118.1	74.5 (s)	39.7	62.0	-	24.5;24.0	54.3 (d)	128.3;	128.0 (3xd)	and 126.4	137.3	21.6 and 19.7 (2xq,$CH(\underline{C}H_3)_2$)
5h	117.4	62.0 (d)	35.9	64.4	-	26.7;24.4	60.8 (t)	128.7;	128.4 (3xd)	and 127.5	136.5	-
5i	119.5	55.3 (d)	33.4	57.3	-	26.5;24.9	52.6 (s)		-		-	24.3 (q,$(\underline{C}H_3)_3$)
5j	118.7	59.3 (d)	40.9	60.3	-	-	57.4 (d)		-		-	29.1 and 26.0 (2x t,2x$CH_3\underline{C}H_2$); 19.7 and 19.6 (2xq, $CH(\underline{C}H_3)_2$); 7.9 and 7.8 (2xq, 2x$CH_2\underline{C}H_3$)
21a	-	66.7 (t)	31.5	66.7	-	27.4	63.7 (t)	128.2;	128.1 (3xd)	and 126.6	138.7	-
21b	-	58.7 (t)	28.7	58.7	-	27.4	51.4 (s)		-		-	24.1 (q,$C(\underline{C}H_3)_3$)
21c	-	62.5 (t)	36.7	62.5	-	-	58.7 (d)		-		-	28.9 (t,2x$\underline{C}H_2CH_3$); 19.6 (q,$CH(\underline{C}H_3)_2$); 8.2 (q,2x$CH_2\underline{C}H_3$)
21d	-	69.3 (d)	32.4	64.6	17.5	28.1;22.3[a]	59.4 (d)		-		-	21.4[a] and 20.2[a] (2xq,$CH(\underline{C}H_3)_2$)
21e	-	68.3 (d)	34.3	63.7	16.6	27.3;22.3	152.5 (s)	128.8;	117.5 (3xd)	and 112.1	-	-
21f	-	70.3 (d)	34.5	65.5	15.0	27.4;21.9	62.4 (t)	128.7;	128.0 (3xd)	and 126.7	139.0	-
21g	-	68.6 (d)	38.8	61.5	16.1	-	152.4 (s)	128.9;	117.3 (3xd)	and 111.9	-	37.7; 31.5; 26.0; 23.2 and 22.9 (5xt,-$(\underline{C}H_2)_5$-)
21i	-	77.3 (d)	35.1	63.5	-	27.9;21.6[a]	59.4 (d)	127.6;	126.9 (3xd)	and 126.5	141.7	23.3[a] and 20.1[a]; (2xq,$CH(\underline{C}H_3)$)

a : or vice versa.

Table IV : Spectral Data (IR, ^{1}H-NMR, MS) of β-Chloro imines 4 and 13[a].

Compound	IR(NaCl) $\nu_{C=N}$ (cm^{-1})	^{1}H-NMR ($CDCl_3$, 60MHz) δ(ppm)	Mass Spectrum (70eV) m/e (rel. intensity %)
13	1600[b] 3242[b] (ν_{NH})	1.10 (6H,s,$(C\underline{H}_3)_2C$); 1.78 (3H, s,$C\underline{H}_3$-C=N); 2.42 (3H,s,$C\underline{H}_3C_6H_4$); 3.51 (2H,s,$C\underline{H}_2Cl$); 7.32 and 7.88 (4H,2xd,AB-system,J=8.4Hz, $C_6\underline{H}_4$); 8.10 (1H,s,br,N$\underline{H}$).	302(M^+,2); 267(11); 157(9); 149 (6); 148(4); 147(17); 146(6); 139(4); 117(4); 111(6); 97(8); 92(6); 91(25); 89(6); 86(8); 84 (13); 83(100); 82(8); 81(11); 71(6); 70(6); 69(8); 67(9); 65 (15); 57(23); 56(42); 55(53); 53(8); 51(9); 49(25); 43(43); 42(15); 41(64); 39(15).
4d	1654	1.20-2.40 (10H,m,$C_6\underline{H}_{10}$); 1.84 (3H,s,$C\underline{H}_3$C=N); 3.64 (2H,s, $C\underline{H}_2Cl$); 4.57 (2H,s,$C\underline{H}_2C_6H_5$); 7.00-7.70 (5H,s,$C_6\underline{H}_5$).	263(M^+,1); 229(9); 228(46); 200 (31); 149(8); 147(8); 132(6); 106(8); 104(9); 96(12); 95(10); 93(6); 92(11); 91(100); 81(18); 79(8); 77(15); 67(10); 65(14); 55(13); 51(6); 43(10); 42(6); 41(15); 40(34); 39(9).
4e	1645	(CCl_4) : 1.24 (6H,s,$C(C\underline{H}_3)_2$); 3.72 (2H,s,$C\underline{H}_2Cl$); 4.22 (2H,s, $C\underline{H}_2C_6H_5$); 7.19 (5H,s,$CH_2C_6\underline{H}_5$); 6.9-7.4 (5H,m,$C_6\underline{H}_5$).	no M^+; 250(4); 195(4); 194(5); 162(3); 107(10); 106(3); 105 (28); 104(3); 92(5); 91(40); 79 (3); 78(3); 77(12); 65(5); 58 (31); 57(3); 56(14); 55(4); 51 (6); 44(10); 43(100); 42(8); 41 (9); 40(84); 39(8).
4f	1641	0.98 (6H,d,J=6.4Hz,$CH(C\underline{H}_3)_2$); 1.14 (6H,s,$C(C\underline{H}_3)_2$); 3.14 (1H, septet,J=6.4Hz,$C\underline{H}(CH_3)_2$); 3.69 (2H,s,$C\underline{H}_2$); 6.80-7.50 (5H,m, $C_6\underline{H}_5$).	no M^+; 188(7); 147(10); 146(25); 132(24); 105(16); 104(100); 91 (8); 84(12); 77(12); 74(20); 59 (30); 58(5); 56(11); 55(7); 45 (30); 44(10); 43(26); 42(34); 41 (26); 40(20); 39(6).
4i	1665	0.79 (6H,t,J=7.3Hz,$2xC\underline{H}_3CH_2$); 1.15 (6H,d,J=6.2Hz,$CH(C\underline{H}_3)_2$); 1.00-2.00 (4H,m,$2xC\underline{H}_2CH_3$); 3.32 (1H,septet,J=6.2Hz,$C\underline{H}(CH_3)_2$); 3.70 (2N,s,$C\underline{H}_2Cl$); 7.46 (1H,s, C$\underline{H}$=N).	-
4j	1660	1.20-2.40 (10H,m,$C_6\underline{H}_{10}$); 1.77 (3H,s,$C\underline{H}_3$C=N); 3.68 (2H,s,$C\underline{H}_2$); 6.50-7.50 (5H,m,$C_6\underline{H}_5$).	249(M^+,7); 215(13); 214(69); 143 (7); 133(7); 119(11); 118(100); 104(7); 95(4); 93(7); 91(12); 81 (4); 79(4); 78(8); 77(76); 68 (8); 66(7); 57(9); 55(11); 53 (8); 51(13); 43(9); 42(8); 41 (26); 39(9).

a : All other β-chloro imines were reported in ref. 1.

b : IR taken in KBr.

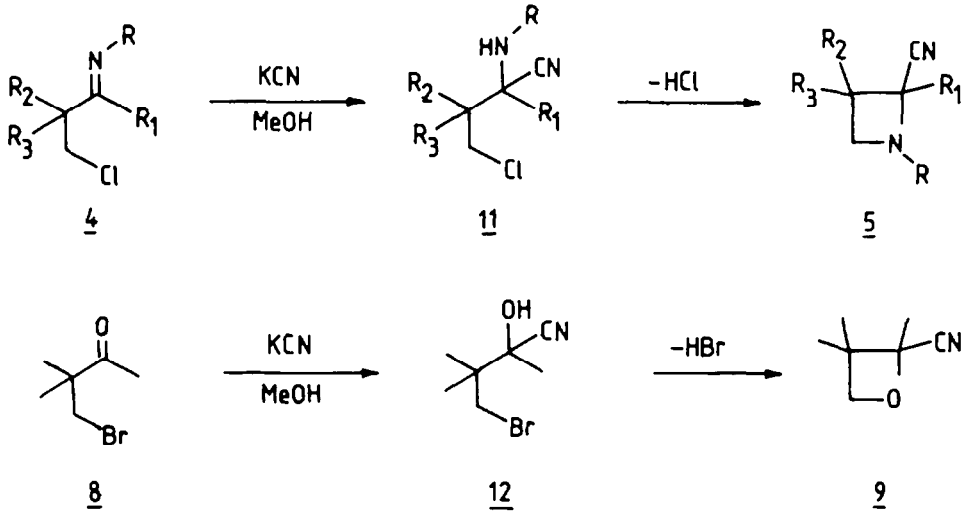
Table V : ^{13}C-NMR Spectral Data (δ, $CDCl_3$) of β-chloro imines 4 and 13[a].

Compound	C=N	CR_2R_3 (s)	CH_2Cl (t)	if R_2=R_3=CH_3 $C(CH_3)_2$ (q)	N-C	if R_1=CH_3 CH_3-C=N (q)	Other signals
13	159.9 (s)	43.5	52.9	23.5	-	12.1	143.9 (s,Cq); 135.3 (s,Cp); 129.4 and 128.0 (2xd,Co and Cm); 21.5 (q,$CH_3C_6H_4$).
4d	171.4 (s)	48.4	54.7[b]	-	52.1 (t)[b]	14.0	140.8 (s,Cq); 128.2; 127.4 and 126.2 (3xd,Co,Cm and Cp); 32.2; 26.0 and 22.5 (3xt, 5xCH_2).
4e	175.7 (s)	45.0	53.9[b]	24.7	56.7 (t)[b]	-	136.6 and 140.5 (2xs,2xCq); 128.3;128.1; 127.9; 127.3; 126.7 and 126.3 (6xd,2x(Co, Cm and Cp)).
4f	171.0 (s)	44.1	54.3	23.6[b]	52.4 (d)	-	137.1 (s,Cq); 128.0; 127.5 and 126.8 (3xd,Co,Cm and Cp); 24.7 (q,$(CH_3)_2C$)[b].
4i	165.0 (d)	46.3	47.5	-	62.0 (d)	-	7.2 (q,CH_3CH_2); 26.9 (t, CH_3CH_2); 24.3 (q,$C(CH_3)_2$).
4j	172.4 (s)	47.9	52.1	-	152.0 (s)	16.0	129.0; 122.8 and 118.7 (3xd, Co,Cm and Cp); 32.4; 26.1 and 22.5 (3xt,5xCH_2).

a : All other β-chloro imines were reported in ref. 1.
b : or vice versa.

formation of 2-cyanooxetane 9 (Scheme IV). It was unexpected that this reaction was slower than the reaction of β-chloro imines 4 with potassium cyanide in methanol. The solvent also had an important influence on the reaction. If the reaction was performed in methanol, oxetane 9 and 10 were present in the reaction mixture while in isopropanol only oxetane 9 could be observed. Oxetane 10 is formed from oxetane 9 by addition of the solvent (methanol) to the nitrile function.
In contrast to 2-cyanoazetidines, 2-cyanooxetanes are better known in the literature[13-25]. They were already prepared by photochemical or thermal cycloaddition of an alkenenitrile to a carbonyl compound[14-23] or by reaction of β-chloroketones or β-tosyloxyketones with potassium cyanide in different solvents[13,24,25].

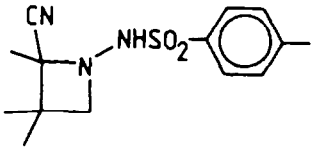
The reaction mechanism for the formation of 2-cyanoazetidines 5 and for the formation of 2-cyanooxetane 9 can be explained as originating from a nucleophilic addition of cyanide across the double bond (imino function, carbonyl function) with the formation of intermediate 11 or 12, followed by intramolecular nucleophilic substitution and expulsion of a halide anion (Scheme V). Via this reaction, several 2-cyanoazetidines 5 were prepared, among others 2-benzyl-1-cyano-1-methyl-2-azaspiro[3,5]nonane 5e and 2-cyano-1-(4-methylphenylsulphonyl)amino-2,3,3,-trimethylazetidine 5d. By reaction of β-chlorohydrazone 13 with potassium cyanide in methanol, the structure of the solid reaction product was not immediately clear.



4 11 5

8 12 9

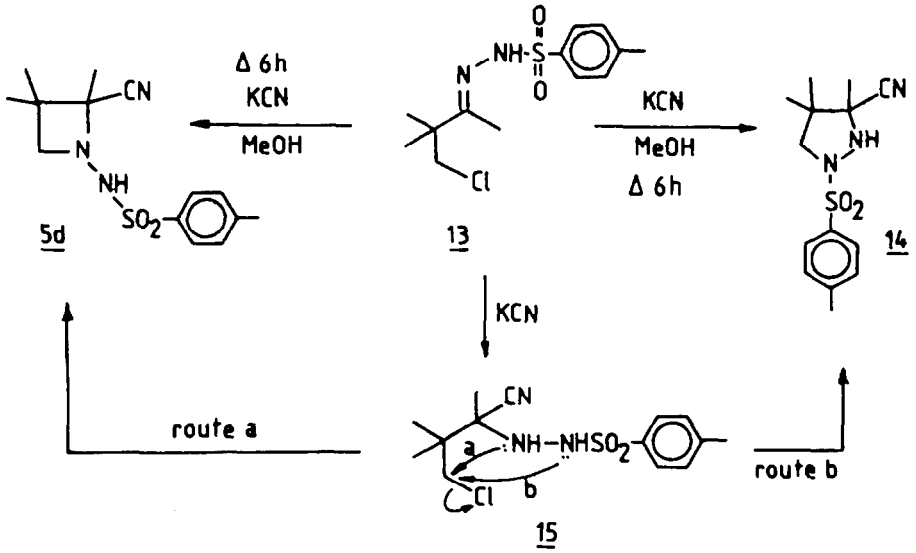
SCHEME V



5d

SCHEME VI

Either 2-cyanoazetidine 5d or 3-cyanopyrazolidine 14 could be expected as the reaction product (Scheme VII). These two possible compounds (5d and 14) would result from cyanide adduct 15, formed by addition of cyanide across the imino



5d 13 14

15

SCHEME VII

function. Intermediate 15 can either give rise to 2-cyanoazetidine 5d by expulsion of a chloride anion (route a), but it is also possible that adduct 15 would give a ring closure to 3-cyanopyrazolidine 14 (route b). It was not clear from the spectral data (IR, MS, ^{1}H-NMR, ^{13}C-NMR) to distinguish between a four-membered or a five-membered heterocyclic structure. Therefore, an X-ray crystallographic analysis of the reaction product was performed, revealing that azetidine 5d was formed from β-chlorohydrazone 13 on reaction with cyanide. The principal crystallographic parameters of azetidine 5d are as follows : Mr = 293.39, triclinic, P-1, a = 7.108 (2), b = 15.129 (3), c = 7.404 (2) Å, α = 87.99 (2), β = 75.98 (2), γ = 85.66 (2)°, V = 770.2 (3) Å^3 Z = 2, Dx = 1.27 g. cm^{-3}, CuK_α, λ = 1.54178 Å, μ = 18.71 cm^{-1}, F(000) = 312, R = 0.065 for 2276 observed reflections. Figure 1 gives a stereoscopic view of the structure of azetidine 5d. More details about the X-ray analysis are given in Tables VI-IX.

Table VI : Atomic coordinates (X10^4) and equivalent temperature factors (Å^2).

$$Beq=(8/3)\pi^2\Sigma_i\Sigma_j U_{ij}a^*_i a^*_j a_i a_j$$

	x/a	y/b	z/c	Beq
N1	11269(3)	1934(2)	3406(3)	4.45(4)
C2	12040(4)	1292(2)	1881(4)	4.34(5)
C3	14081(4)	1370(2)	2349(4)	5.18(6)
C4	12907(5)	1697(3)	4274(4)	5.14(6)
N5	9336(3)	1874(2)	4443(3)	4.65(4)
S6	8162(1)	2856(1)	4927(1)	4.79(1)
O7	8094(4)	3285(2)	3202(3)	6.27(5)
O8	6409(3)	2659(2)	6243(3)	6.19(5)
C9	9595(4)	3454(2)	6006(4)	4.53(5)
C10	11109(6)	3899(2)	4932(5)	5.86(6)
C11	12349(6)	4294(2)	5782(5)	6.21(7)
C12	12079(5)	4266(2)	7692(4)	5.22(6)
C13	10542(5)	3851(2)	8741(5)	5.51(6)
C14	9266(5)	3449(2)	7919(4)	5.21(6)
C15	13486(7)	4675(3)	8581(7)	6.94(9)
C16	11336(4)	402(2)	2376(4)	4.77(5)
N17	10824(5)	-295(2)	2724(4)	6.48(6)
C18	11667(6)	1578(3)	16(5)	5.68(7)
C19	15188(7)	2092(4)	1177(7)	7.58(9)
C20	15370(6)	523(4)	2335(6)	7.37(9)

Table VII : Bond distances (Å).

C2 -N1	1.488(3)	C4 -N1	1.476(4)
N5 -N1	1.410(3)	C3 -C2	1.585(4)
C16 -C2	1.474(4)	C18 -C2	1.511(4)
C4 -C3	1.544(4)	C19 -C3	1.517(5)
C20 -C3	1.517(5)	S6 -N5	1.655(2)
O7 -S6	1.422(2)	O8 -S6	1.428(2)
C9 -S6	1.755(3)	C10 -C9	1.378(4)
C14 -C9	1.378(4)	C11 -C10	1.381(5)
C12 -C11	1.380(4)	C13 -C12	1.375(4)
C15 -C12	1.503(5)	C14 -C13	1.383(5)
N17 -C16	1.142(4)		

Table VIII : Bond angles (°)

C4	-N1	-C2	92.1(2)	N5	-N1	-C2	117.8(2)
N5	-N1	-C4	120.4(2)	C3	-C2	-N1	85.6(2)
C16	-C2	-N1	112.1(2)	C16	-C2	-C3	111.0(2)
C18	-C2	-N1	115.0(2)	C18	-C2	-C3	122.2(3)
C18	-C2	-C16	109.2(3)	C4	-C3	-C2	86.0(2)
C19	-C3	-C2	111.2(3)	C19	-C3	-C4	112.7(3)
C20	-C3	-C2	117.2(3)	C20	-C3	-C4	116.5(3)
C20	-C3	-C19	111.1(4)	C3	-C4	-N1	87.5(2)
S6	-N5	-N1	112.7(2)	O7	-S6	-N5	107.2(1)
O8	-S6	-N5	103.9(1)	O8	-S6	-O7	120.4(2)
C9	-S6	-N5	106.4(1)	C9	-S6	-O7	108.3(1)
C9	-S6	-O8	109.8(1)	C10	-C9	-S6	119.7(2)
C14	-C9	-S6	119.9(2)	C14	-C9	-C10	120.3(3)
C11	-C10	-C9	119.5(3)	C12	-C11	-C10	121.1(3)
C13	-C12	-C11	118.4(3)	C15	-C12	-C11	120.2(3)
C15	-C12	-C13	121.4(3)	C14	-C13	-C12	121.5(3)
C13	-C14	-C9	119.2(3)	N17	-C16	-C2	173.3(3)

Table IX : Torsion angles (°) (σ=1).

C4	-N1	-C2	-C3	-22
C4	-N1	-C2	-C16	88
C4	-N1	-C2	-C18	-146
N5	-N1	-C2	-C3	-149
N5	-N1	-C2	-C16	-38
N5	-N1	-C2	-C18	88
C2	-N1	-C4	-C3	23
N5	-N1	-C4	-C3	147
C2	-N1	-N5	-S6	-140
C4	-N1	-N5	-S6	109
N1	-C2	-C3	-C4	21
N1	-C2	-C3	-C19	-91
N1	-C2	-C3	-C20	139
C16	-C2	-C3	-C4	-91
C16	-C2	-C3	-C19	156
C16	-C2	-C3	-C20	27
C18	-C2	-C3	-C4	138
C18	-C2	-C3	-C19	25
C18	-C2	-C3	-C20	-104
N1	-C2	-C16	-N17	-166
C3	-C2	-C16	-N17	-72
C18	-C2	-C16	-N17	65
C2	-C3	-C4	-N1	-21
C19	-C3	-C4	-N1	90
C20	-C3	-C4	-N1	-140
N1	-N5	-S6	-O7	62
N1	-N5	-S6	-O8	-170
N1	-N5	-S6	-C9	-54
N5	-S6	-C9	-C10	84
N5	-S6	-C9	-C14	-93
O7	-S6	-C9	-C10	-31
O7	-S6	-C9	-C14	152
O8	-S6	-C9	-C10	-164
O8	-S6	-C9	-C14	19
S6	-C9	-C10	-C11	-174
C14	-C9	-C10	-C11	3
S6	-C9	-C14	-C13	174
C10	-C9	-C14	-C13	-2
C9	-C10	-C11	-C12	-1
C10	-C11	-C12	-C13	-1
C10	-C11	-C12	-C15	178
C11	-C12	-C13	-C14	2
C15	-C12	-C13	-C14	-177
C12	-C13	-C14	-C9	0

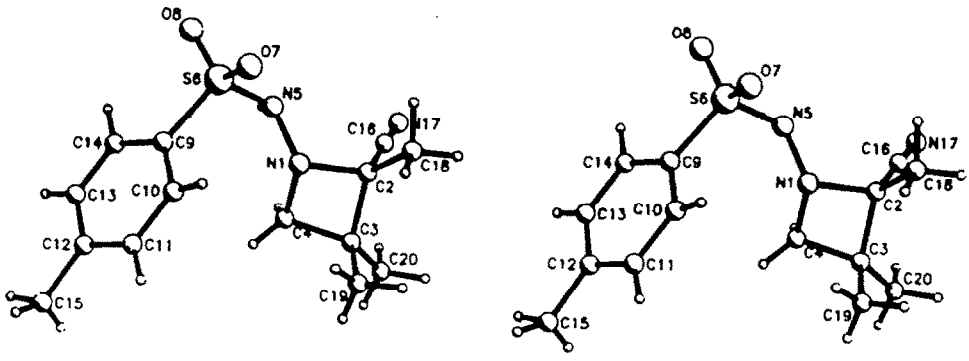
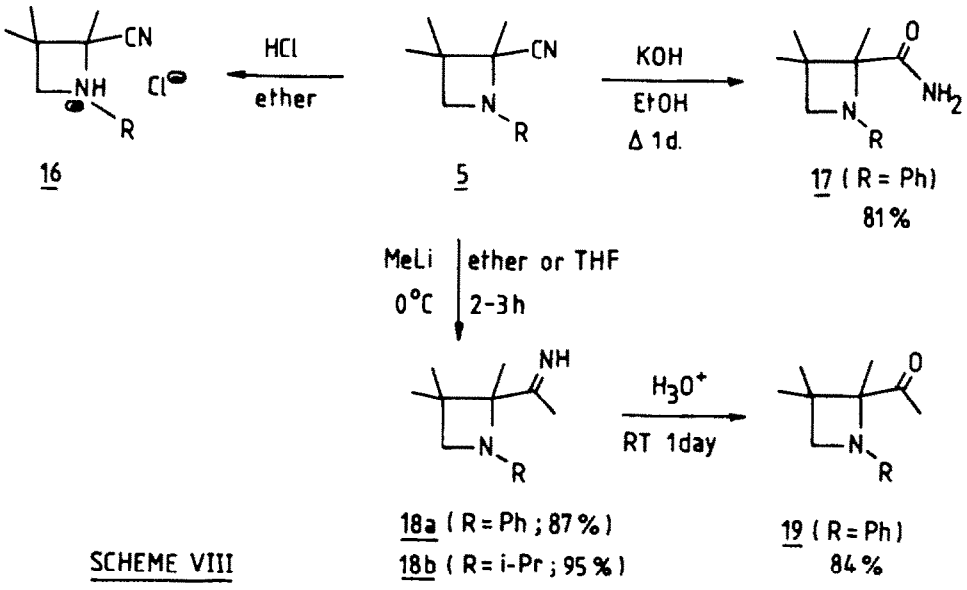


Figure 1 : Stereoscopic view of 3-cyano-1-(4-methylbenzenesulphonyl)amino-2,3,3-trimethylazetidine 5d.

The spectral data of 2-cyanoazetidines 5 are compiled in Tables II and III. In the ^{1}H-NMR spectrum the CH_2-group of the azetidine ring mostly shows an AB-system (J = 6.4-6.8Hz). If the substituent on nitrogen is a benzyl group, also the CH_2-group of the substituent on nitrogen shows an AB-system in the ^{1}H-NMR spectrum. The coupling constant (J) of the CH_2-group on the nitrogen substituent is quite different (J = 12.4-13.2Hz) in such a way that both signals can easily be distinguished in the ^{1}H-NMR spectrum.

The stable azetidines 5 were easily converted into the corresponding hydrochlorides 16 with dry hydrogen chloride in ether (Scheme VIII). Recrystallisation of the hydrochlorides was performed in a mixture of acetone and ether (1/1). By



SCHEME VIII

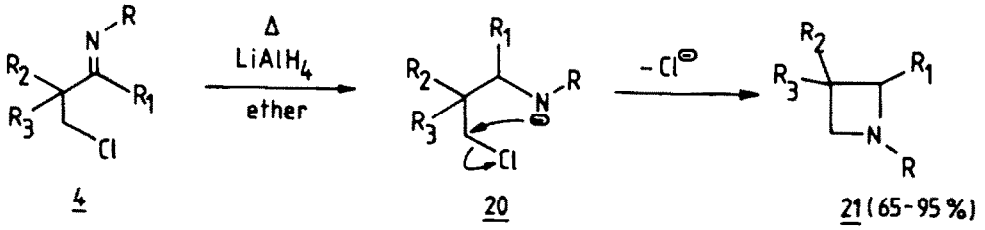
reaction of azetidines 5 with methyllithium in diethylether the corresponding 2-acetimidoylazetidines 18 were formed. The latter were hydrolyzed with an aqueous hydrogen chloride solution to give the corresponding acetylazetidines 19 in high yield (Scheme VIII). On reaction with potassium hydroxide in absolute ethanol, 2-cyanoazetidine 5a (R=C_6H_5) was transformed into the corresponding azetidine-2-carboxamide 17 (Scheme VIII). The synthesis and spectral data of 2-imidoylazetidines 18, 2-acetylazetidine 19 and 2-carbamoylazetidine 17 are given in the expe-

rimental section.

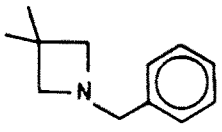
This high yield synthesis of 2-cyanoazetidines 5 provides a new approach to this class of small-ring heterocycles. According to the literature, some 2-cyanoazetidines could be converted into useful medicinal products, such as appetite depressants and products which can control obesity[8]. In addition, a number of related compounds, such as azetidine-2-carboxylic acids, received already a lot of attention in the literature because of their occurrence in the amino acid fraction of plants.

Reaction of β-Chloro Imines with Lithium Aluminium Hydride : Synthesis of Azetidines

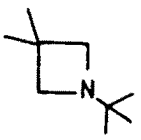
The reaction of β-chloro imines 4 with lithium aluminium hydride (LAH) in dry ether proceeds practically in an identical way as the reaction of β-chloroimines 4 with potassium cyanide in methanol (Scheme IX). After nucleophilic addition of



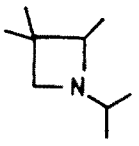
4 20 21 (65-95 %)



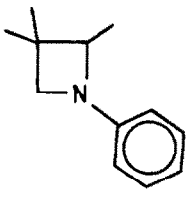
21a



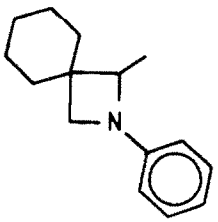
21b



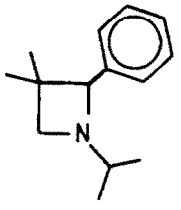
21d



21e



21g



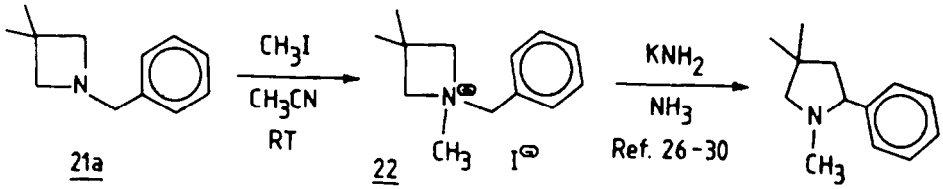
21i

SCHEME IX

hydride across the imino function of imine 4, adduct 20 is formed, which undergoes ring closure with the expulsion of a chloride anion and the formation of azetidines 21 in high yields (65-95%). Via this way a lot of azetidines 21 were prepared but the reaction of β-chloro ketimine 4 (R_1=C_6H_5; R_2=R_3=CH_3; R=$CH_2C_6H_5$) with LAH in dry ether never gave rise to the corresponding azetidine. Even after a reflux period of 20 hours no azetidine was observed in the reaction mixture (Table I, entry 18), but the starting material was totally recovered. The syn-

thesis of azetidines 21 is given in Table I while the spectral data of compounds 21 are compiled in Tables II and III.

1-Benzyl-3,3-dimethylazetidine 21a, obtained as described above, reacts with methyl iodide in acetonitrile with the formation of the azetidinium salt 22. It is known from the literature, that this azetidinium iodide can be transformed into 1,4,4-trimethyl-2-phenylpyrrolidine 23 on reaction with potassium amide in liquid ammonia (Stevens rearrangement)[26-30]. Accordingly, the conversion of β-chloroimines 4 into azetidines 21 provides an additional entry into pyrrolidines via this rearrangement.



21a 22 23

SCHEME X

As already pointed out above, azetidines were already described in the literature in a number of publications[3-5]. Some azetidines prepared via this novel method described in this article, have already been prepared by ring closure of N-alkylamines having a good leaving group in the γ-position[29,30] or by reduction of some azetidinones[31,32].

In conclusion, the reaction of β-chloro imines with cyanide or hydride opens a new and attractive way for the generation of 2-cyanoazetidines 5 and azetidines 21.

Experimental section :

Infrared spectra were recorded with a Perkin Elmer model 1310 spectrophotometer while ^{1}H NMR spectra were measured with Varian T-60 (60 MHz) or Bruker WH-360 FT (360 MHz) spectrometers. ^{13}C NMR spectra were taken on Varian FT 80 (20 MHz) or Bruker WH-360 FT (50 MHz) spectrometers. Mass spectra were obtained from a Varian MAT 112 mass spectrometer (direct inlet system; 70 eV).

Preparation of β-chloro imines 4, 6 and 13

β-Chloro imines 4, 6 and 13 were synthesized according to our previously published method involving condensation of β-halo ketones or β-haloaldehydes with primary amines in ether (or benzene) with or without the presence of titanium(IV) chloride[1]. For the preparation of aldimines (4g, 4h, 4i), the corresponding aldehyde anhydrous magnesium sulphate and the primary amine were stirred in ether during several hours at room temperature (5h-1d). After stirring, the reaction mixture was filtered and the solvent was evaporated in vacuo and afterwards, the residual product was distilled.

For the preparation of β-chloroketimines (4a, 4b, 4c, 4d, 4e, 4f, 4j) and β-chloroaldehyde 6 titanium(IV) chloride in pentane was added to a cooled ethereal solution of the β-chloro ketone or β-chloroaldehyde and the primary amine (benzene was used as solvent for β-chloro imine 4d and 4j). The reactions were run over several hours at ambient temperature (6 : 4 hours) or at reflux temperature (4d and 4j : 1 day; 4e : 3 days; 4f; 4a; 4b; 4c : 1-5 hours). Regular sampling of the reaction is advisable in order to determine the degree of conversion (1N NaOH (ether; test tube;GLC analysis or preferably NMR monitoring). Workup of all reaction mixtures was done with an aqueous sodium hydroxide solution as described previously[1] except in the case of less volatile amines (e.g. benzylamine) where the filtration method was used Hydrazone 13 was prepared by reaction of 4-chloro-3,3-dimethyl-2-butanone with 0.9 equivalents of tosylhydrazine in dichloromethane at reflux temperature (2-3 days) in the presence of a catalytic amount of para-toluenesulphonic acid (the normal hydrazone formation). Hydrazone 13 is a crystalline compound isolated in high yield (95%). Physical and spectral

data of all new compounds (13, 4d, 4e, 4f, 4i and 4j) are compiled in Table IV and V. The remaining β-chloro imines have been described in a previous paper[1]. All β-chloro imines used in this paper gave a halogen analysis in agreement with the proposed structure. All compounds in this paper are obtainable in a purity of at least 97% (GLC, spectrometric methods).

Synthesis of 2-cyanoazetidines 5 (General Procedure) :

A solution of 0.01 mol of β-chloro imine 4 in dry methanol (10% solution W/V) was treated with 0.02 mol of potassium cyanide. After stirring (magnetic bar) under reflux during several hours as mentioned in Table I, the reaction mixture was cooled and afterwards poured into water (200 ml). Extraction of the organic components was performed with ether or dichloromethane (3x : 100 ml), the combined extracts were dried ($MgSO_4$) and after removal of the drying agent the solvent was evaporated to leave a clear oil which was distilled and analyzed by gas chromatography. The spectroscopic data of 2-cyanoazetidines 5 are given in Tables II and III.

Synthesis of Oxetanes 9 and 10 :

Oxetanes 9 and 10 were prepared according to the procedure described above, namely by reaction of 4-bromo-3,3-dimethyl-2-butanone 8 with potassium cyanide in methanol or isopropanol. After reflux during several hours the reaction mixtures were analysed by preparative gas chromatography. Via this method products 9 and 10, present in the reaction mixture when the reaction was performed in methanol, could easily be separated.

2-Cyano-2,3,3-trimethyloxetaan 9 (Yield 33-100%)

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.30 (3H,s,CH_3); 1.49 (3H,s,CH_3); 1.67 (3H,s,CH_3); 4.43 and 4.21 (2H,2xd,AB-system,J=5.6Hz,CH_2).
IR (NaCl) $\nu_{C\equiv N}$: 2237 cm^{-1}.
Mass Spectrum (70 eV) m/e (%) : no M^+; 95(12); 94(2); 83(2); 80(3); 73(8); 72(7); 71(2); 70(4); 69(2); 68(8); 67(3); 64(2); 59(2); 58(33); 57(3); 56(21); 55(14); 54(2); 53(5); 44(12); 43(100); 42(10); 41(28); 40(88).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 119.7 (s,C≡N); 83.4 (s,C-CN); 80.9 (t,CH_2); 41.5 (s,CMe_2); 25.0 (q,CH_3); 22.3 (q,CH_3); 21.4 (q,CH_3).

Compound 10 (Yield 0-67%)

^{1}H-NMR (60 MHz; CCl_4) : δ 1.06 (3H,s,CH_3); 1.21 (3H,s,CH_3); 1.37 (3H,s,CH_3); 3.70 (3H,s,OCH_3); 4.02 and 4.19 (2H,2xd,AB-system,J=5.6Hz,CH_2); NH invisible.
IR (NaCl) ν_{NH} : 3300 cm^{-1}; $\nu_{C=N}$: 1662 cm^{-1}.

Synthesis of azetidinium chloride 16 :

Dry hydrogen chloride was bubbled during half an hour through a solution of 0.01 mol of α-cyanoazetidine 5c in ether (10% solution W/V). The azetidinium chloride 16 precipitated and was isolated by filtration. Recrystallisation was performed in a mixture of acetone and ether (1/1).

Azetidinium chloride 16 :

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.41 and 1.57 (6H,2xd,J=6.4Hz,$(CH_3)_2CH$); 1.48 (3H,s,CH_3); 1.63 (3H,s,CH_3); 2.07 (3H,s,CH_3); 3.69 and 3.91 (2H,2xd,AB-system,J=9.6Hz,CH_2); NH invisible $CH(CH_3)_2$ under AB-system of CH_2.
IR (KBr) $\nu_{C\equiv N}$: 2215 cm^{-1}
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 114.9 (s,C≡N); 71.6 (s,C-C≡N); 61.4 (t,CH_2); 57.9 (d,CH); 38.4 (s,$C(CH_3)_2$); 25.2 (q,CH_3); 21.1 (q,CH_3); 19.5 (q,CH_3); 18.0 (q,CH_3); 16.7 (q,CH_3).

Reaction of α-cyanoazetidines 5 with methyllithium :

A solution of 0.01 mol of α-cyanoazetidine 5a or 5c in ether or tetrahydrofuran was cooled in an ice bath and treated dropwise under nitrogen with a solution of methyllithium in ether (1.5 molar equivalents). After stirring during 2-3 hours at room temperature, the reaction mixture was poured into water. The organic layer was separated and the aqueous phase was extracted twice with ether. The combined ethereal extracts were dried ($MgSO_4$) and the solvent was evaporated to afford pure azetidines 18.

Azetidine 18a (R=C_6H_5; yield 87%)

IR (NaCl) : $\nu_{C=N}$: 1647 cm^{-1}; ν_{NH} : 3210 cm^{-1}
^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.13 (6H,s,$(CH_3)_2$); 1.33 (3H,s,CH_3); 1.92 (3H,s,CH_3C=N) 3.30 (2H,s,CH_2); 6.20-7.30 (5H,m,C_6H_5).
Mass Spectrum (70 eV) m/e (%) : 216 (M^+;7); 175(6); 174(42); 124(11); 118(9); 106(10); 105(6); 77(17); 72(18); 56(8); 44(6); 43(13); 42(12); 41(22); 40(100).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 179.2 (s,C=N); 147.8 (s,Cq); 128.8, 118.5 and 114.3 (3xd,Co,Cm and Cp); 77.8 (s,CC≡N), 59.3 (t,CH_2); 36.8 (s,$C(CH_3)_2$); 24.9; 21.6 and 21.7 (3xq,3xCH_3); 14.7 (q,CH_3CC≡N)

Azetidine 18b (R=i-Pr; yield 95%)

IR (NaCl) : $\nu_{C=N}$: 1652 cm^{-1}; ν_{NH} : 3200 cm^{-1}
^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.80 and 0.94 (6H,2xd,J=6.1Hz,CH(CH_3)$_2$); 0.98 (3H,s,CH_3); 1.03 (3H,s,CH_3); 1.26 (3H,s,CH_3); 1.84 (3H,s,CH_3C=N); 2.43 (1H,septet,J=6.1 Hz,CH(CH_3)$_2$); 2.60 and 2.88 (2H,2xd,AB-system,J=6.2Hz,CH_2).
Mass Spectrum (70 eV) m/e (%) : no M^+; 141(12); 140(100); 112(22); 111(6); 98(71); 95(5); 84(8); 72(6); 70(8); 69(12); 57(9); 56(20); 55(11); 53(6); 44(7); 43(21); 42(68); 41(39); 40(19).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 180.6 (s,C=N); 73.0 (s,CC=N); 60.6 (t,CH_2); 49.7 (d, NCH); 35.3 (s,C(CH_3)$_2$); 24.9; 22.8; 22.0; 21.7 and 20.0 (5xq,C(CH_3)$_2$ and 3xCH_3); 11.6 (q,CH_3CC=X).

Hydrolysis of 2-acetimidoylazetidine 18a :

Stirring a solution of azetidine 18a in an aqueous hydrogen chloride solution (10E/2N) at room temperature during one day resulted in the quantitative formation of 2-acetylazetidine 19, which was isolated after extraction of the organic compounds with dichloromethane, drying of the combined extracts ($MgSO_4$) and evaporation of the solvent. Compound 19 was isolated in pure form with a yield of 84%.

2,3,3-trimethyl-2-(1-oxoethyl)-1-phenylazetidine

IR (NaCl) : $\nu_{C=O}$ = 1720 cm^{-1}
^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.21 (3H,s,CH_3); 1.28 (3H,s,CH_3); 1.43 (3H,s,CH_3); 2.23 (3H,s,CH_3C=O); 3.43 and 3.51 (2H,2xd,AB-system,J=6.6Hz,CH_2); 6.20-7.40 (5H,m,C_6H_5).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 211.1 (s,C=O); 147.5 (s,Cq); 128.8; 117.9 and 113.5 (3xd; Co,Cm and Cp); 79.1 (s,CC=O); 59.5 (t,CH_2); 38.2 (s,C(CH_3)$_2$); 27.6; 24.7 and 22.3 (3xq,3xCH_3); 15.1 (q,H_3C CC=O).

Reaction of 2-cyanoazetidine 5a with potassium hydroxide in ethanol :

To a solution of 0.01 mol of α-cyanoazetidine 5a in dry ethanol 0.05 mol potassium hydroxide was added and then the reaction mixture was refluxed during one day. Afterwards most of the ethanol was evaporated and the residu was poured into 100 ml of water. The aqueous layer was extracted with dichloromethane (3x20 ml) and the combined extracts were dried ($MgSO_4$). After filtration, the solvent was evaporated to leave a solid residuewhich consisted of pure amide 17 (yield : 81%; melting point 150°C).

Azetidine 17 :

IR (NaCl) : $\nu_{C=O}$: 1677 cm^{-1}; ν_{NH_2} = 3459 cm^{-1}
^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.17 (3H,s,CH_3); 1.40 (3H,s,CH_3); 1.43 (3H,s,CH_3); 3.41 and 3.45 (2H,2xd,AB-system,J=7.8Hz,CH_2); 6.40-7.40 (5H,m,C_6H_5).
Mass Spectrum (70 eV) m/e (%) : 218 (M^+,15); 175(17); 174(100); 159(8); 158(9); 145(7); 144(11); 132(11); 118(21); 106(41); 105(10); 104(9); 103(8); 77(32); 75(6); 51(7); 41(24); 40(14).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 176.7 (s,C=O); 147.1 (s,Cq); 129.0; 118.8 and 114.2 (3xd;Co,Cm and Cp); 74.5 (s,CC=O); 59.8 (t,CH_2); 37.4 (s,C(CH_3)$_2$); 24.9 and 22.1 (2xq;C(CH_3)$_2$); 14.3 (q,CH_3-C-C=N).

Synthesis of azetidines 21 (General Procedure)

A solution of 0.01 mol of β-halo imine 4 in freshly distilled dry ether was treated with 0.02 mol of lithium aluminium hydride. The reaction was stirred under reflux during several hours as indicated in Table I. Afterwards the reaction mixture was poured into 200 ml of water and extracted with ether (3x30 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent evaporated. The residue was analyzed by preparative gas chromatography, revealing only one compound i.e. azetidine 21. The spectral data of azetidines 21 are compiled in Tables II and III.

Synthesis of azetidinium iodide 22

To a solution of 0.01 mol of 1-benzyl-3,3-dimethylazetidine 21a in acetonitrile was added 0.05 mol of methyl iodide and the reaction mixture was stirred at room temperature during 12 hours. The solvent and the excess methyl iodide were evaporated and the residual azetidinium iodide 22 was isolated as a solid material.

Azetidinium iodide 22

^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.98 (3H,s,CH_3); 1.43 (3H,s,CH_3); 3.64 (3H,s,CH_3-N); 4.24 and 4.60 (4H,2xd,AB-system,J=11.4Hz,ring CH_2); 5.07 (2H,s,$CH_2C_6H_5$); 7.20-8.00 (5H,m,C_6H_5).
^{13}C-NMR (20 MHz, $CDCl_3$) : δ 132.9 (s,Cq); 130.9; 129.4 and 128.6 (3xd,Co,Cm and Cp); 73.7 (t,ring CH_2); 67.0 (t,$CH_2C_6H_5$); 54.0 (q,CH_3N); 28.7 (s,C(CH_3)$_2$); 28.4 and 26.6 (2xq,C(CH_3)$_2$).

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* N. De Kimpe, to whom correspondance should be addressed, "Senior Research Associate" (Onderzoeksleider) of the Belgian "National Fund for Scientific Research" (Nationaal Fonds voor Wetenschappelijk Onderzoek);

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