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A NEW METHOD FOR THE PREPARATION OF β-(ALKYLAMINO)-CARBONYL COMPOUNDS BY REARRANGEMENT OF β-CHLOROIMINES VIA AZETIDINE INTERMEDIATES

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Abstract : The reaction of β-chloroimines with sodium methoxide in methanol gave rise to β-(alkylamino)- and β-(arylamino)-carbonyl compounds in high yield. The reaction mechanism for the generation of β-(alkylamino)- and β-(arylamino)-carbonyl compounds passes via an intermediate α-methoxyazetidine which is, after ringopening, transformed into a β-(alkylamino)- or β-(arylamino)-carbonyl compound. Only one 2-methoxyazetidine (2-methoxy-2,3,3-trimethyl-1-phenylazetidine) could be isolated under the given reaction conditions. β-Alkylaminocarbonyl compounds were also generated by reaction of β-chloroimines with potassium tert.-butoxide in tert.-butanol or tetrahydrofuran. The latter reaction is initiated by a deprotonation leading, after ring closure, to 2-methyleneazetidines, which are transformed into β-(alkylamino)-carbonyl compounds during the reaction or on workup.

Introduction

β-Aminoketones are a group of bifunctional compounds, which have already been described several times in review articles[1-5]. β-Aminoketones were mostly made accessible by the Mannich reaction, i.e. the reaction of a carbonyl compound, an aldehyde (usually formaldehyde) and an amine under acidic circumstances. Some β-aminoketones further described in this article were already prepared via this classical method[6-12]. Besides the classical procedure for performing the Mannich reaction, the literature also reveals novel versions of this reaction, e.g. the trimethylsilyl trifluoromethanesulphonate promoted addition of silyl enol ethers to imines[13]. Next to the Mannich reaction also other procedures are known for the preparation of β-aminoketones, e.g. the reduction of the imino function of β-iminoketones[14]. β-Aminoketones are important functionalized carbonyl compounds because they can be transformed into a variety of valuable compounds, among others α,β-unsaturated ketones, β-aminoalcohols and heterocyclic compounds. Some β-aminoketones (or their hydrochlorides) are also potentially biologically active com-

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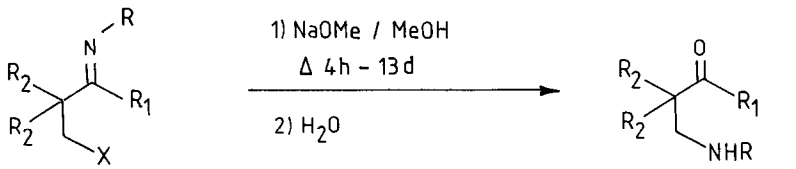
pounds, such as local anaesthetics[15-18], anticonvulsants[19], α-adrenoblocking agents[20-21], antibacterials[22-26], antitumor agents[23,27-32] and analgesics[32]. Herein we report a new method for the preparation of β-(alkylamino)- and β-(arylamino)-ketones by rearrangement of β-chloroimines with various nucleophilic bases.

Results and Discussion

Reaction of β-Chloroimines with Sodium Methoxide (Table I, entries 1-10)

The reaction of β-chloroimines 1 (X=Cl), prepared by condensation of β-chloroketones with primary amines[33], with two molar equivalents of sodium methoxide in methanol (2N), followed by aqueous workup, gave rise to β-(alkylamino)-carbonyl compounds 2 in good to high yields (Scheme I).



1 a,c,d,e,f,g,h,i,j (X = Cl)

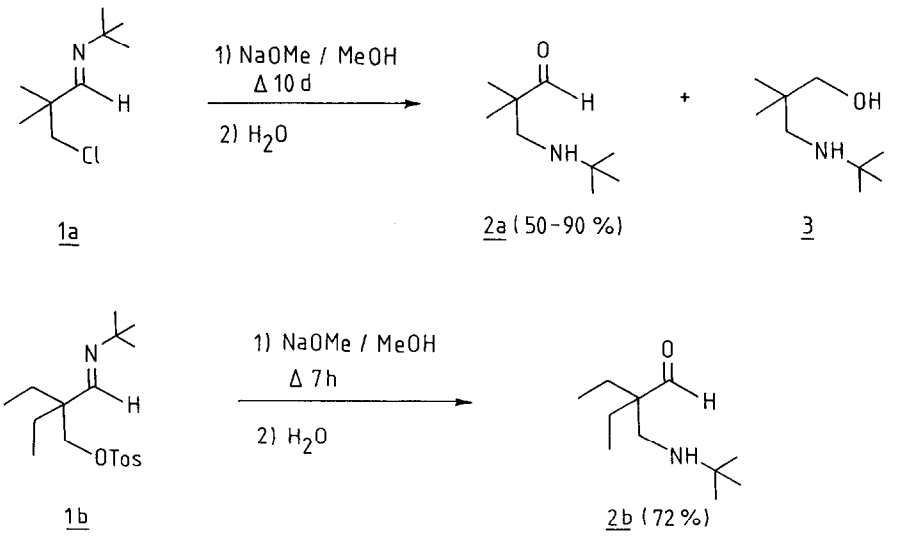
1 b (X = OTos)

2 (62 - 92 %)

SCHEME I

This reaction is fairly general because β-(alkylamino)-aldehydes 2 (R_1=H) as well as β-(alkylamino)-ketones 2 ($R_1 \neq H$) were accessible (Table I, entries 1-10). The reaction of β-chloroaldimine 1a (R=t-Bu, $R_2=CH_3$, R_1=H) with sodium methoxide in methanol (2 equiv./2N) was unexpectedly slow, probably due to the sterical hindrance in the starting material 1a. This reaction was also not very clean because, next to β-(alkylamino)-aldehyde 2a, variable amounts of aminoalcohol 3 were formed depending upon the reaction conditions (Table I, entry 1-3). On the other hand, the reaction of β-(tosyloxy)-aldimine 1b with sodium methoxide yielded only one reaction product, namely β-(alkylamino)-aldehyde 2b (R_1=H, R=t-Bu, R_2=Et; Table I, entry 4) (Scheme II).

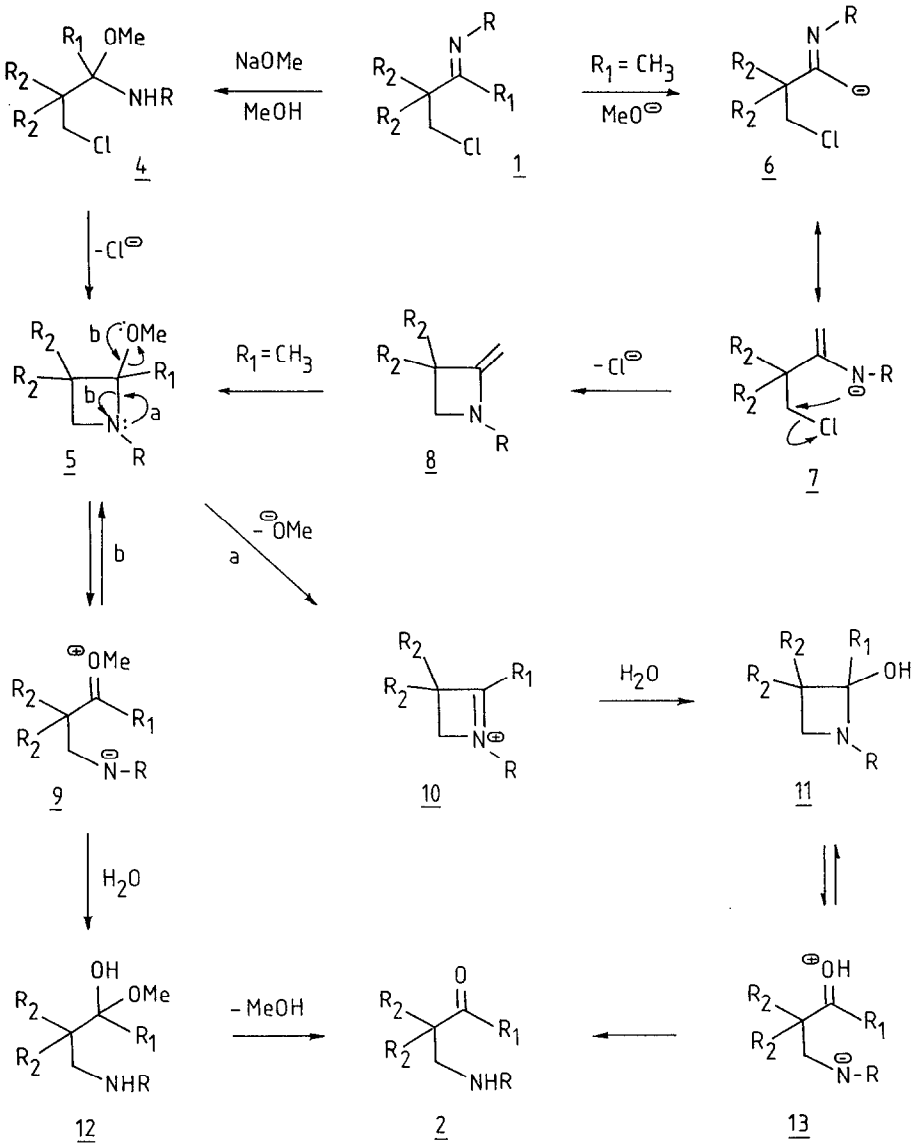
The reaction mechanism for the formation of β-(alkylamino)-carbonyl compounds 2 is presented in Scheme III and is interpreted via an intermediately formed 2-methoxyazetidine 5. In principle, 2-methoxyazetidine 5 can be formed via two possible pathways. The first possibility concerns the nucleophilic addition of methoxide across the imino function with the formation of adduct 4. α-Methoxyazetidine 5 is formed after intramolecular expulsion of a chloride anion from adduct 4. The second mechanistic route for the formation of 2-methoxyazetidine 5 entails the deprotonation of β-chloroimine 1 with sodium methoxide at the α'-position with the formation of mesomeric anions 6 and 7. In this case, sodium methoxide is acting as a base and not as a nucleophile. After ring closure with the expulsion of a chloride anion from intermediate 7, 2-methyleneazetidine 8 is produced, which is trapped by methoxide to give 2-methoxyazetidine 5. Both mechanistic pathways are plausible but the route via an initial nucleophilic addition of methoxide across the imino function deserves preference because β-chloroimine 1f ($R_1=C_6H_5$; R=i-Pr, $R_2=CH_3$) and β-chloroaldimine 1a (R=t-Bu, R_1=H; $R_2=CH_3$) gave, under the same reaction conditions, also rise to β-(alkylamino)-ketone 2f ($R_2=CH_3$, $R_1=C_6H_5$, R=i-Pr) and β-(alkylamino)-aldehyde 2a (R=t-Bu, R_1=H, $R_2=CH_3$), respectively. Both



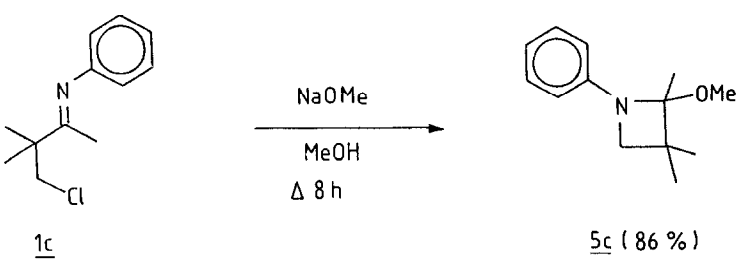
SCHEME II

substrates of the latter reactions do not have α'-hydrogens, making the mechanistic pathway via 2-methyleneazetidines 8 impossible. 2-Methoxyazetidines 5 are only isolable when the substituent on nitrogen is aromatic (Scheme IV). Accordingly and not unexpectedly, N-phenyl-β-chloroketimine 1c was converted into 2-methoxy-1-phenyl-2,3,3-trimethylazetidine 5c in 86% yield by reaction with sodium methoxide in methanol under reflux for 8 hours. By reaction with water, this azetidine 5c could be converted into β-(phenylamino)-ketone 2c (vide infra), which is indicative of the plausible intermediacy of α-methoxyazetidines in the transformation of β-chloroimines 1 into β-aminoketones 2.

In all the other cases 2-methoxyazetidines 5 are converted in situ or during workup into the corresponding β-(alkylamino)-carbonyl compounds 2. 2-Methoxyazetidine 5 might be viewed in equilibrium with the ring-opened intermediate 9, which can be trapped during aqueous workup with the formation of the hemiacetal 12. The observation that 9 is not trapped by methanol to produce the corresponding β-(alkylamino)-acetals lends support to the consideration that 2-methoxyazetidines 5 occur as such in the reaction mixture prior to aqueous workup. Attempts to isolate 1-alkyl-2-methoxyazetidines 5 under non-aqueous workup conditions failed. The most probable mechanism for the formation of β-(alkylamino)-carbonyl compounds 2 is the transformation of 2-methoxyazetidines 5 into azetinium salts 10 which, after aqueous workup, are rearranged into β-(alkylamino)-carbonyl compounds 2 via 2-hydroxyazetidines 11. It is reasonable to postulate azetinium salts 10 as intermediates in the reaction mechanism because they were already proposed in the literature as being transient products in the transformation of N-chlorocyclopropylamines into β-(alkylamino)-ketones[34]. Azetinium salts were also postulated as intermediates in the transformation of azetidine-2-carboxylic acids into β-lactams[35-37]. Thus, 2-methoxyazetidines 5 are the central intermediates in the reaction mechanism but they are only stable with aromatic substituents on nitrogen as has been shown by reaction of β-chloroimine 1c with sodium methoxide in methanol (Scheme IV). If the workup of this reaction mixture was performed carefully, α-methoxyazetidine 5c was isolated as the sole reaction product (Scheme IV). 2-Methoxyazetidine 5c is unstable at higher temperatures. Till now α-alkoxyazetidines have rarely been reported in the literature. They were already prepared by elec-



SCHEME III



SCHEME IV

Table I : Reaction of β-chloroimines 1 (X=Cl) and β-(tosyloxy)imines 1 (X=OTos) with bases and nucleophiles.

Entry	Starting Compound	R	R_1	R_2	X	Reaction Conditions[a]	Yield (%)	β-(alkylamino)-ketone 2 (%)
1	1a	t-Bu	H	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 50h	62	2a : 90[b]
2	1a	t-Bu	H	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 7d	70	2a : 70[c]
3	1a	t-Bu	H	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 13d	73	2a : 50[d]
4	1b	t-Bu	H	Et	OTs	NaOMe/MeOH (2E/2N) : Δ 7h	72	2b : 100
5	1c	C_6H_5	Me	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 8h	86	2c : 0[e]
6	1d	$CH_2C_6H_5$	Me	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 4h	85	2d : 100
7	1e	i-Pr	Me	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 4h	73	2e : 100
8	1f	i-Pr	C_6H_5	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 1d	90	2f : 100
9	1g	Me	Me	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 5h	92	2g : 100
10[f]	1h	$CH_2C_6H_5$	H	Me	Cl	NaOMe/MeOH (2E/2N) : Δ 8d	85	2h : 0[g]
11	1b	t-Bu	H	Et	OTs	t-Bu NH_2 (10%) : Δ 2d	0	2b : 0
12	1e	i-Pr	Me	Me	Cl	t-Bu NH_2/ether (5E/10%) : RT 20h	0	2e : 0
13	1e	i-Pr	Me	Me	Cl	i-Pr NH_2/ether (5E/10%) : Δ 7d	0	2e : 0
14	1e	i-Pr	Me	Me	Cl	i-Pr NH_2/ether/K_2CO_3 (5E/10%) : RT 8d	0	2e : 0
15	1e	i-Pr	Me	Me	Cl	NaOH/H_2O(5E/10%) : RT 2d	90	2e : 63[h]
16	1e	i-Pr	Me	Me	Cl	KOH/DMSO(5E/10%) : RT 6d	93	2e : 100
17	1e	i-Pr	Me	Me	Cl	KSCN/CH_3CN(2E/10%) : Δ 0.5h	80-95	2e : 100
18	1e	i-Pr	Me	Me	Cl	KCN/CH_3CN(2E/10%) : Δ 1.5h	75	2e : 100
19	1e	i-Pr	Me	Me	Cl	NaSi-Pr/MeOH(2E/10%) : Δ 2h	90	2e : 70[i]
20	1i	4-ClC_6H_4	Me	Me	Cl	t-BuLi/THF(2E/10%) : 0° 10h	72	2i : 100
21	1e	i-Pr	Me	Me	Cl	KOt-Bu/THF(2E/10%) : Δ 16h	85	2e : 100
22	1e	i-Pr	Me	Me	Cl	KOt-Bu/ether(2E/10%) : Δ 40h	0	2e : 0[j]
23	1a	t-Bu	H	Me	Cl	KOt-Bu/THF(2E/10%) : Δ 8d	0	2a : 0[j]

a : E= equivalents; N= normal; Δ= reflux; h= hours; d= days; 10%= 10 % solution (w/v); RT= room temperature.

b : 10% unidentified products.

c : 30% 2,2-dimethyl-3-tert-butylamino-1-propanol 3.

d : 50% 3.

e : 2-Methoxy-2,3,3-trimethyl-1-phenylazetidine 5c, exclusively.

f : Compound 1h is a β,β,β-trichlorocompound,i.e. N-(3,3,3-trichloro-2,2-dimethyl-1-propylidene)-benzylamine.

g : Imine 25, exclusively.

h : 37% 4-chloro-3,3-dimethyl-2-butanone 30.

i : 30% starting material.

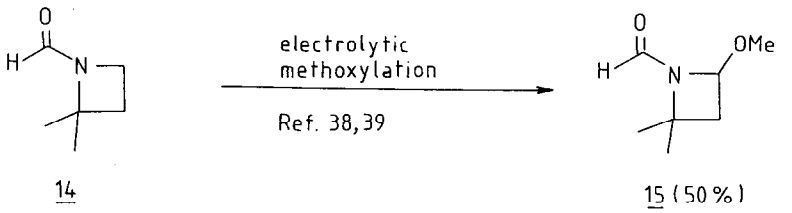
j : No reaction observed. The starting material was totally recovered.

Elemental analyses of β-(alkylamino)carbonyl compounds 2 :

2c ($C_{12}H_{17}NO$) : 7.20% N found, 7.32% N calcd.. 2d ($C_{13}H_{19}NO$) : 6.98% N found, 6.82% N calcd..

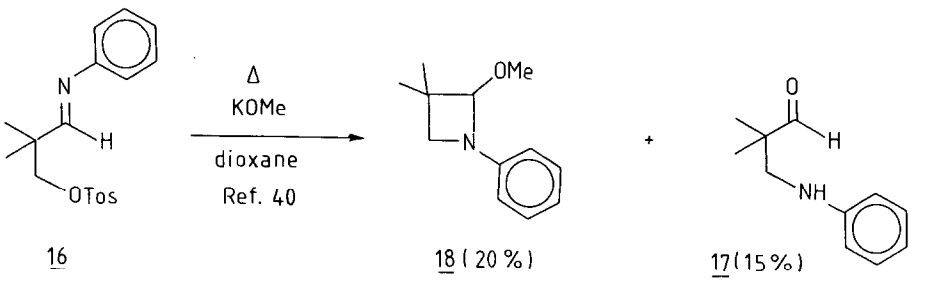
2e ($C_9H_{19}NO$) : 8.96% N found, 8.91% N calcd.. 2f ($C_{14}H_{21}NO$) : 6.28% N found, 6.39% N calcd..

2g ($C_7H_{15}NO$) : 10.75% N found, 10.84% N calcd.. 2i ($C_{12}H_{16}ClNO$) : 6.35% N found, 6.21% N calcd..



14 15 (50 %)

SCHEME V



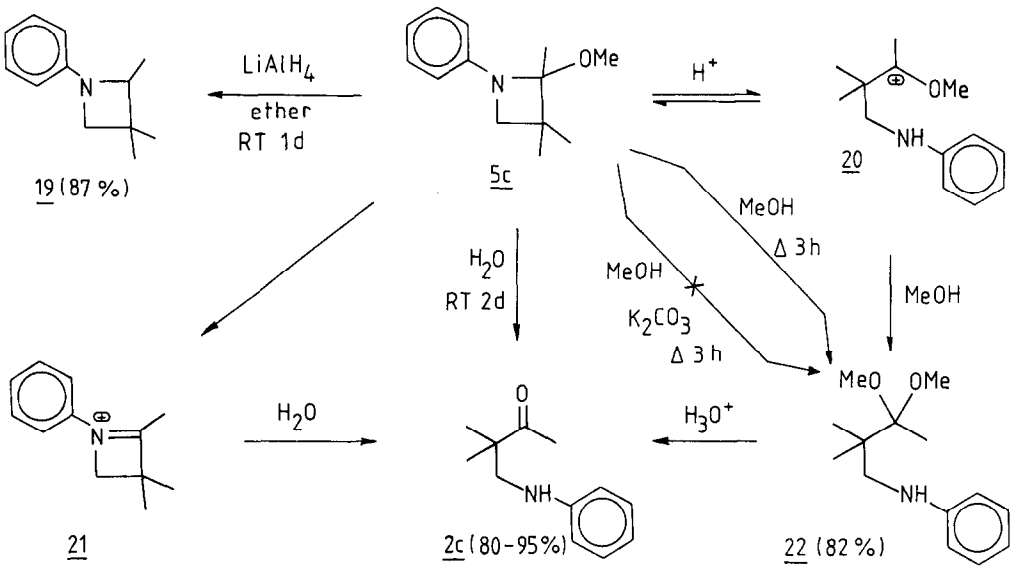
16 18 (20 %) 17 (15 %)

SCHEME VI

trolytic alkoxylation of 1-formylazetidine 14 in the presence of tetramethylammonium tetrafluoroborate[38,39] (Scheme V), by cyclisation of β-(tosyloxy)aldimine 16 with potassium methoxide in dioxane[40] (Scheme VI) or by reaction of ethoxyethene with N-(1,1,1,3,3,3-hexafluoro-2-propylidene)tosylamine[41]. A recent communication reported on some bicyclic α-oxygenated azetidines, the stability of which could be ascribed to some extent to the N-phenyl substituent.[42]

Because 2-methoxyazetidine 5c could be isolated from the reaction of β-chloroimine 1c with sodium methoxide in methanol, some experiments were performed in order to gain insight in the synthetic potential of these heterocycles. If 2-methoxyazetidine 5c was brought into reaction with lithium aluminium hydride at room temperature, azetidine 19 was produced in 87% yield. On reaction of 2-methoxyazetidine 5c with methanol under reflux β-(phenylamino)-acetal 22 was formed (82% yield), while on reaction with water β-(phenylamino)-ketone 2c was obtained (80-95% yield) (Scheme VII). The transformation of 2-methoxyazetidine 5a into β-(phenylamino)-acetal 22 via intermediate 20 only proceeds if a trace of acid is present in the alcoholic medium (i.e. commercial dry methanol which had not been treated with a basic substance prior to use in these reactions). If potassium carbonate is added to the methanol, 2-methoxyazetidine 5c was recovered unchanged after reflux during three hours, indicative of an acid-catalyzed transformation of azetidine 5c into acetal 22. Azetidines such as 19 were already prepared by reaction of β-chloroimines 1 with lithium aluminium hydride in dry ether,[43] proving the synthetic potential of β-chloroimines for the synthesis of four-membered heterocycles.

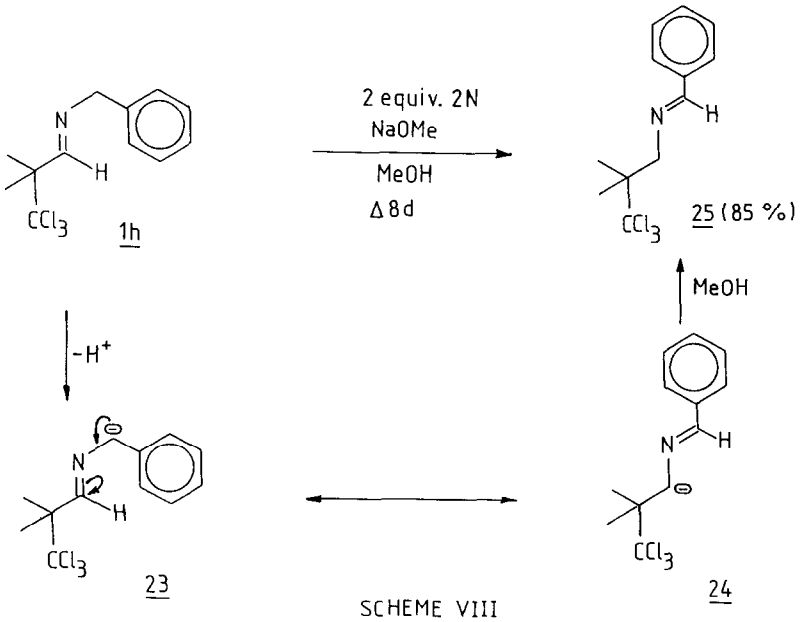
The reaction of β-chloroimines 1 with sodium methoxide in methanol did not always lead to the formation of β-(alkylamino)-carbonyl compounds 2, exclusively. If, next to β-(alkylamino)-carbonyl compounds 2, also other compounds were present in the reaction medium they could easily be separated by treatment with aqueous acid (removal of all the side products without amino functions) followed by basic extractive workup (N-containing compounds such as β-(alkylamino)-carbonyl compounds 2). As reported already above, the reaction of β-chloroaldimine 1a with



SCHEME VII

sodium methoxide in methanol (Table I, entry 1-3) was surprisingly slow and gave rise to the expected β-(alkylamino)-aldehyde 2a next to the unexpected alcohol 3 (Scheme II). Aminoalcohol 3 results probably from the reaction of β-(alkylamino)-aldehyde 2a with methoxide, by which the latter acted as hydride donor during the reaction. The reduction of the carbonyl function only happened when reflux was performed during several days (needed for completion of the reaction). The longer the reaction time under reflux, the more of alcohol 3 was present in the reaction mixture.

The reaction of β,β,β-trichloroaldimine 1h with sodium methoxide in methanol did not give rise to the corresponding β-(alkylamino)-ketone or 2-methoxyazetidi-

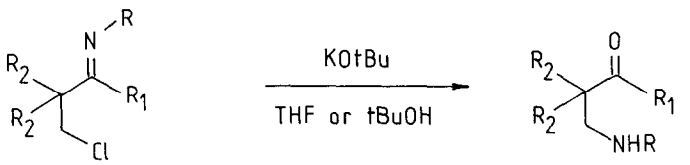


SCHEME VIII

ne. Instead, benzylidenamine 25 was formed exclusively, the formation of which originated from deprotonation of 1h at the benzylic position with the generation of the mesomeric anions 23 and 24. After proton uptake from the solvent, the more stable N-(benzylidene)-3,3,3-trichloro-2,2-dimethylpropylamine 25 was formed (Scheme VIII).

Reaction of β-Chloroimines with Potassium Tert.-Butoxide (Table I, entries 21-23)

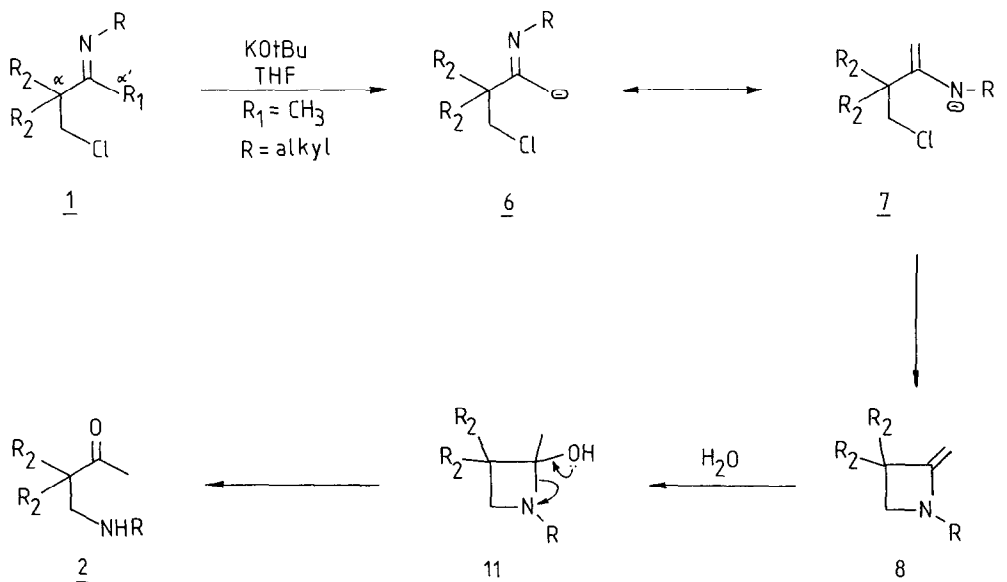
The reaction of β-chloroketimines 1 ($R_1 \neq H$) with potassium tert.-butoxide in tetrahydrofuran (THF) or tert-butanol also gave rise to β-(alkylamino)-ketones 2 (Scheme IX). This reaction proceeds well in tetrahydrofuran or tert-butanol but fails in ether. The reaction of β-chloroimines 1 with potassium tert-butoxide in THF or t-BuOH only yielded β-(alkylamino)ketones if there are hydrogen atoms present at the α'-position (e.g. $R_1 = CH_3$). This can be explained by the fact that the first step in the reaction mechanism is the deprotonation of ketimine 1 ($R_1 = CH_3$) at the α'-position by the non-nucleophilic strong base, leading to the mesomeric



1 2

SCHEME IX

anions 6 and 7 (Scheme X). After ring closure of anion 7, 2-methyleneazetidines 8 are formed, which are trapped by water during aqueous workup with the formation of

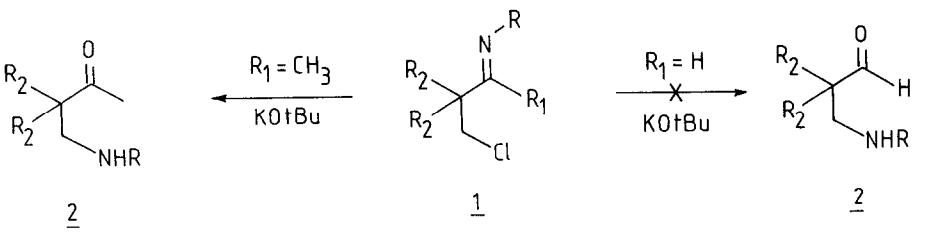


1 6 7

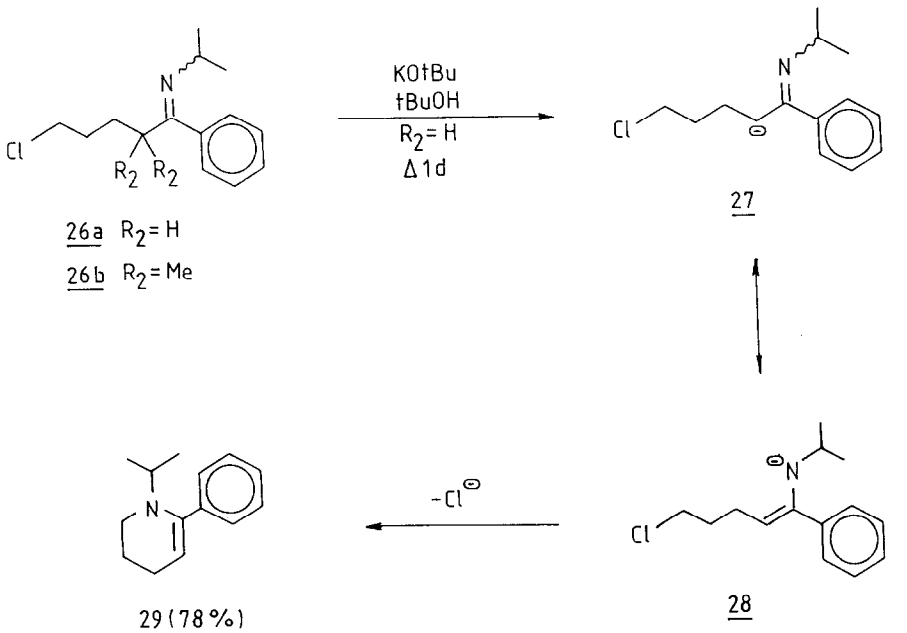
2 11 8

SCHEME X

2-hydroxyazetidines 11. After ring opening the unstable 2-hydroxyazetidines 11 are converted into β-(alkylamino)-ketones 2. Accordingly, the reaction mechanism for



SCHEME XI



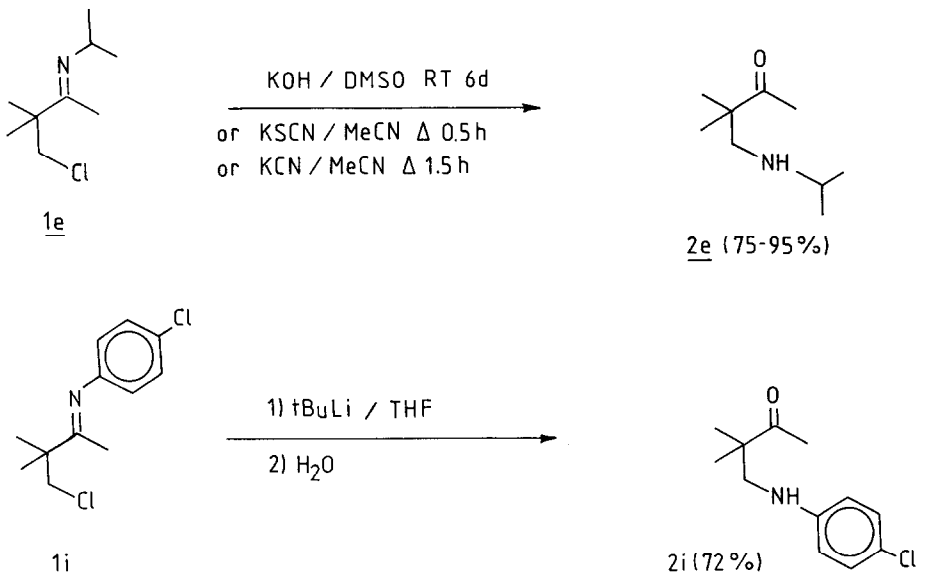
SCHEME XII

the generation of β-(alkylamino)-ketones 2 from β-chloroimines is different if the base is potassium tert-butoxide with respect to sodium methoxide as base, although the starting materials and the end products are identical. The reaction of β-chloroimines 1 with sodium methoxide starts with an initial nucleophilic addition across the imino function, while an initial deprotonation occurs on reaction of 1 with potassium tert-butoxide. If no hydrogen atoms are present at the α'-position (R_1=H), it is acceptable that the formation of carbonyl compounds 2 does not occur on reaction of aldimines 1 with potassium tert-butoxide (Table I, entry 23) (Scheme XI). It must be noticed that if no α'-hydrogen atoms are present in the molecule the deprotonation can also occur at the α-position if R_2=H. This is the case when ketimine 26a, although not being a β- but a δ-chloroketimine, was reacted with KOt-Bu in tert-butanol. This reaction did not lead to the formation of the corresponding δ-(alkylamino)-ketone. Instead, the deprotonation occurred at

the α-position leading to the mesomeric anions 27 and 28. After ring closure of 28, the cyclic enamine 29 was obtained in 78% yield. This result is in accordance with earlier findings of Evans[44]. On the other hand, δ-chloro-α,α-dimethylketimine 26b did not show any conversion on treatment with potassium tert-butoxide in ether under reflux.

Reaction of β-Chloroimines with Other Bases or Nucleophiles (Table I, entries 11-20)

In most cases, the reaction of β-chloroimines 1 with various other bases led to β-(alkylamino)-ketones 2. Thus, the reaction of N-(4-chloro-3,3-dimethyl-2-butylidene)isopropylamine 1e or β-chloroimine 1i with potassium hydroxide in dimethylsulfoxide, with potassium thiocyanate in acetonitrile, with tert-butyllithium in tetrahydrofuran and with potassium cyanide in acetonitrile, followed by aqueous workup, gave rise to the corresponding β-(alkylamino)-ketones 2e or 2i (Scheme XIII).

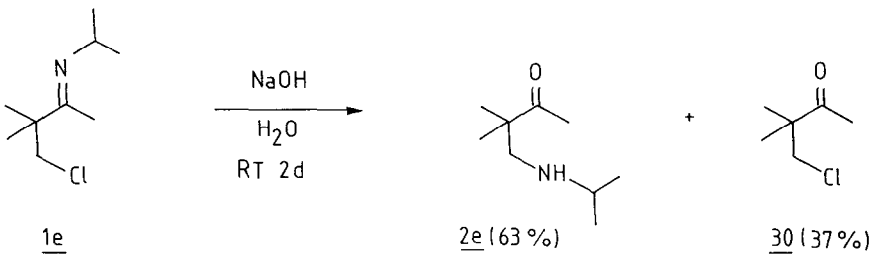


SCHEME XIII

By reaction of β-chloroimine 1c with an aqueous sodium hydroxide solution the expected β-(alkylamino)-ketone 2e next to β-chloroketone 30 (hydrolysis of the imino function of β-chloroimine 1e) were isolated. The reaction of the same imine 1e with sodium isopropylthiolate in methanol was not totally complete. After reflux during two hours, next to β-(alkylamino)-ketone 2e, also 30% of starting material was isolated from the reaction mixture. In contrast with these reactions, the reaction of β-chloroimine 1e, with amines did not yield the corresponding β-(alkylamino)-ketone 2e at all, but yielded only recovered starting material.

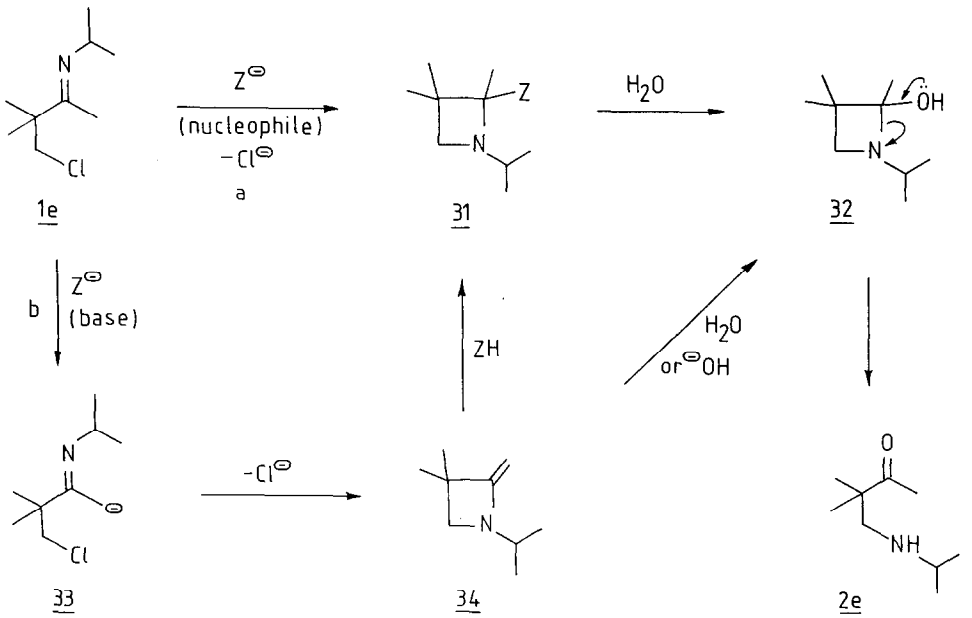
The reaction mechanism for the formation of β-(alkylamino)-ketones 2 from β-chloroimines 1 on reaction with different bases can be explained via a reaction-pathway analogous to that of the reaction of β-chloroimines 1 with sodium methoxide in methanol. The reagent can act as a nucleophile or as a base. In the first case adduct 31 is formed while in the second case anion 33 is produced which, af-

ter ring closure, and addition of the nucleophile is transformed into azetidine 31. After aqueous workup of the reaction mixture, β-(alkylamino)-ketone 2e is isolated. The nature of the reagent determines whether path a or b is followed. With



SCHEME XIV

tert-butyllithium the first step in the reaction mechanism is the deprotonation of imine 1e at the α'-position, while on reaction of 1e with potassium thiocyanate the first step is probably the nucleophilic addition.



SCHEME XV

In conclusion, a useful synthetic method for the preparation of β-(alkylamino)-carbonyl compounds was developed starting from β-chloroimines, by which functionalized azetidines intervene as intermediates during this rearrangement.

Table II : Spectral Data (IR, ^{1}H-NMR, MS) of β-(Alkylamino)-ketones 2.

	IR (NaCl) $\nu_{C=O}$ cm^{-1}	IR (NaCl) ν_{NH} cm^{-1}	^{1}H - NMR (60 MHz, δ)	Mass Spectrum (70ev) m/e (%)
2a	1730	3330	($CDCl_3$) : 1.05 (6H,s,(CH_3)$_2$); 1.05 (9H,s,C(CH_3)$_3$); 2.67 (2H,s,CH_2); 9.23 (1H, s,CH=O); NH invisible	-
2b	1728	3330	($CDCl_3$) : 0.76 (6H,t,J=7.2 Hz, (CH_3CH_2)$_2$); 1.02 (9H,s, C(CH_3)$_3$); 1.30-1.80 (4H,m, (CH_2CH_3)$_2$); 2.63 (2H,s,CH_2 N); 9.33 (1H,s,CHO); NH invisible	-
2c	1708	3440	($CDCl_3$) : 1.23 (6H,s,(CH_3)$_2$ C); 2.15 (3H,s,CH_3C=O); 3.21 (2H,s,CH_2N); 3.60-4.00 (1H,s,br,NH; 6.40-7.40 (5H,m,C_6H_5).	191 (M^+,7); 107(8); 106(97); 105 (9); 104(7); 91(20); 77(15); 44 (7); 43(16); 41(8); 40(100).
2d	1710	3342	($CDCl_3$); 1.10 (6H,s,(CH_3)$_2$); 1.52 (1H,s,br,NH); 2.09 (3H,s,CH_3C=O); 2.65 (2H,s,CH_2); 3.75 (2H,s, $CH_2C_6H_5$); 7.28 (5H,s,C_6H_5).	205 (M^+,3); 121(6); 120(42); 119 (5); 106(6); 92(10); 91(100); 88 (5); 86(27); 84(39); 65(9); 49(9); 47(8); 43(15); 40(12).
2e	1713	3340	($CDCl_3$) : 0.99 (6H,d,J=6.2 Hz,CH(CH_3)$_2$); 1.10 (6H,s, (CH_3)$_2$); 2.12 (3H,s,CH_3 C=O); 2.63 (2H,s,CH_2); 2.62 (1H,septet,J=6.2 Hz CH(CH_3)$_2$); NH invisible	157 (M^+,1); 142(2); 73(2); 72(26); 71(2); 70(3); 58(2); 57(1); 56(8); 55(3); 44(14); 43(10); 42(3); 41 (6); 40(100); 39(2).
2f	1678	3340	(CCl_4) : 0.95 (6H,d,J=6.2 Hz,(CH_3)$_2$CH); 1.27 (6H,s, (CH_3)$_2$); 2.63 (1H,septet, J=6.2 Hz,CH(CH_3)$_2$); 2.73 (2H,s,CH_2); 7.00-7.80 (5H, m,C_6H_5); NH invisible	219 (M^+,2); 204(2), 148(3); 106(2); 105(18); 77(13); 73(6); 72(100); 70(3); 58(2); 57(2); 56(13); 55 (6); 51(3); 44(4); 43(7); 42(3); (41(7).
2g	1710	3342	($CDCl_3$) : 1.13 (6H,s,(CH_3)$_2$); 2.10 (3H,s,CH_3C=O); 2.37 (3H,s,CH_3NH); 2.60 (2H,s,CH_2); 1.42 (1H,s, br,NH).	129 (M^+,2); 100(2); 89(2); 86(4); 85(2); 84(2); 72(2); 71(7); 70(6); 58(2); 57(2); 56(3); 55(6); 45(5); 44(100); 43(16); 42(11); 41(7); 40(2); 39(3).

Table II continued

2i	1705	3385	($CDCl_3$) : 1.23 (6H,s,(CH_3)$_2$); 2.18 (3H,s,CH_3C=O), 3.22 (2H,s,CH_2); 3.90 (1H, s,br,NH); 6.62 and 7.18 (4H,2xd,AB,J=8.8Hz,C_6H_4).	225/227(M+,10); 142(33); 141(10); 140(100); 139(5); 138(5); 111(6); 105(9); 86(9); 77 (8); 75(5); 71(6); 43(18); 41(6); 40(8).

Table III : ^{13}C-NMR Spectral Data (δ,20MHz,$CDCl_3$) of β-(Alkylamino)-ketones 2

	C=O (s)	$C(R_2)_2$ (s)	CH_2N (t)	R_2=CH_3 (CH_3)$_2$C (q)	CH_2NC	R=CH_3 CH_3C=O (q)	Other signals
2a	206.3	46.4	49.3	20.0	50.0(s)	-	29.0 (q,C(CH_3)$_3$).
2b	207.2	52.8	43.7	-	50.1(s)	-	29.0 (q,C(CH_3)$_3$); 22.4 (t,(CH_2CH_3)$_2$); 7.7 (q,(CH_2CH_3)$_2$).
2c	213.2	48.6	52.0	22.8	148.5(s)	25.2	129.1; 117.3 and 112.8 (3xd; Co, Cm and Cp).
2d	213.5	48.6	54.4	23.0	57.7(t)	25.2	140.3 (s,Cq); 128.3; 128.0 and 126.9 (3xd; Co, Cm and Cp).
2e[a]	211.2	48.4	56.4	23.1	49.4(d)	25.0	23.1 (q,CH(CH_3)$_2$).
2f	209.3	48.7	56.8	24.4	49.2(d)	-	22.9 (q,CH(CH_3)$_2$); 139.6 (s,Cq); 128.0; 127.8 and 127.3 (3xd; Co, Cm and Cp).
2g	213.1	48.5	61.0	23.0	37.3(q)	25.1	-
2i	213.4	48.7	52.0	22.9	147.1(s)	25.3	129.0 and 113.9 (2xd; Co and Cm); 121.7 (s,Cp).

a ^{13}C-NMR Spectral Data in C_6D_6

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 or GC-MS; 70 eV).

Preparation of β-Chloroimines 1 (X=Cl or OTos)

β-Chloro- and β-(tosyloxy)imines 1 (X=Cl, OTos) were synthesized according to our previously published method involving condensation of β-haloketones, β-halo aldehydes or β-(tosyloxy)-aldehydes with primary amines.[33] Via the same method, δ-chloroimines 26a,b were prepared in 85-91% yield, respectively. Physical and spectral data of most of the β-chloroimines 1 have been described in our previous paper[33]. The spectral data of the remaining new imines 1 are compiled below.

N-[2-ethyl-2-(tosyloxymethyl)-1-butylidene]t.-butylamine 1b

M.p. 83°C. IR (KBr) $\nu_{N=C}$: 1662 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) : δ 0.66 (6H,t,J= 7.2 Hz, 2 x $C\underline{H}_3CH_2$); 1.09 (9H,s,$(C\underline{H}_3)_3C$); 1.10-1.80 (4H,m, 2 x $C\underline{H}_2CH_3$); 2.44 (3H, s, $C\underline{H}_3C_6H_4$); 4.12; (2H,s,$C\underline{H}_2O$); 7.23 (1H,s,$C\underline{H}$=N); 7.28 and 7.78 (4H, 2 x d, AB, J=8 Hz, $C_6\underline{H}_4$). Mass Spectrum (70 eV) m/e (%) : no M^+; 324(8); 310(10); 184(4); 169(5); 168(25); 167(5); 155(6); 152(7); 141(11); 140(100); 139(4); 128(4); 124(6); 112(20); 110(6); 100(14); 99(43); 98(6); 96(5); 95(5); 91(21); 85(5); 84(50); 83(6); 82(8); 70(7); 69(21); 65(5); 58(12); 57(58); 56(12); 55(17); 43(14); 42(8); 41(26); 39(5). ^{13}C-NMR (20 MHz,$CDCl_3$) : δ 160.2 (d,$\underline{C}$H=N); 144.5 (s,$\underline{C}$q); 133.3 (s,$\underline{C}$p); 129.8 and 127.9 (2 x d, $\underline{C}$o and $\underline{C}$m); 71.0 (t,$\underline{C}H_2$); 56.9 (s,$\underline{C}(CH_3)_3$); 45.4 (s,$\underline{C}(Et)_2$); 29.6 (q,$(\underline{C}H_3)_3$); 21.6 (q,$\underline{C}H_3C_6H_4$); 26.5 (t,$CH_3\underline{C}H_2$); 7.6 (q,$\underline{C}H_3CH_2$).

N-(4-chloro-3,3-dimethyl-2-butylidene)-4-chlorophenylamine 1i

IR (NaCl) $\nu_{C=N}$: 1665 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.26 (6H,s,$C(C\underline{H}_3)_2$); 1.75 (3H,s,$C\underline{H}_3C$=N); 3.70 (2H,s,$C\underline{H}_2$); 6.61 and 7.25 (4H, 2 x d, AB, J=8.6 Hz, $C_6\underline{H}_4$). Mass Spectrum (70 eV) m/e (%) : 243 (M^+,12); 210(12); 209(9); 208(30); 162(21); 160(27); 154(42); 153(15); 152(100); 151(8); 138(9); 129(23); 127(70); 113(12); 111(30); 100(9); 99(9); 92(15); 91(9); 90(9); 75(12); 65(15); 64(9); 63(9); 56(24); 55(12); 43(12); 41(21); 40(9); 39(9). ^{13}C-NMR (20 MHz, $CDCl_3$) : 174.8 (s,$\underline{C}$=N); 128.9 and 120.3 (2 x d, $\underline{C}$o and $\underline{C}$m); 128.1 (s,$\underline{C}$p); 150.0 (s,$\underline{C}$q); 53.6 (t,$\underline{C}H_2$); 44.9 (s,$\underline{C}(CH_3)_2$); 23.9 (q,$C(\underline{C}H_3)_2$); 15.7 (q,$\underline{C}H_3C$=N).
$C_{12}H_{15}NCl_2$: 5.88% N found, 5.74% N calcd.

N-(5-chloro-1-phenyl-1-pentylidene)isopropylamine 26a (E/Z)

IR (NaCl) $\nu_{C=N}$ = 1632 cm^{-1}. ^{1}H-NMR (60 MHz, C_6D_6) : δ 1.10 and 1.25 (6H, 2 x d, J=6 Hz, $CH(C\underline{H}_3)_2$ (E/Z)); 0.80-2.00 (4H,m,-$(C\underline{H}_2)_2CH_2Cl$); 2.00-2.70 (2H,m,$C\underline{H}_2$-C=N); 2.80-4.00 (3H,m,$C\underline{H}_2Cl$ and $(CH_3)_2C\underline{H}$ (E/Z)); 6.80-8.00 (5H,m,$C_6\underline{H}_5$). ^{13}C-NMR (20 MHz, $CDCl_3$) : δ 163.7 (s,$\underline{C}$=N); 140.4 and 139.8 (2 x s, $\underline{C}$q (E/Z)); 130.1-126.3 ($\underline{C}$o, $\underline{C}$m and $\underline{C}$p (E/Z)); 52.4 and 51.0 (2 x d, $\underline{C}$-N=C (E/Z); 44.7 and 44.1 (t,$\underline{C}H_2Cl$ (E/Z)); 40.9; 32.6; 32.4; 26.9; 25.1 and 23.9 (6 x t $(\underline{C}H_2)_3$ (E/Z)); 24.3 and 24.4 (2 x q, $CH(\underline{C}H_3)_2$), (E/Z)).

N-(5-chloro-2,2-dimethyl-1-phenyl-1-pentylidene)isopropylamine 26b

IR (NaCl) $\nu_{C=N}$ = 1669 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) : δ 1.03 (6H,s,$C(C\underline{H}_3)_2$; 1.12 (6H,d,J=6.2 Hz,$CH(C\underline{H}_3)_2$); 1.40-1.80 (4H,m,-$(C\underline{H}_2)_2CH_2Cl$); 3.28 (1H,septet, J=6.2 Hz, $C\underline{H}(CH_3)_2$); 3.50 (2H,t,J=6 Hz, $C\underline{H}_2Cl$); 7.48 (1H,s,$C\underline{H}$=N). Mass Spectrum (70 eV) m/e (%) : no M^+, 176(2); 174(7); 155(7); 154(42); 138(3); 133(2); 132(4); 126(11); 114(5); 113(55); 112(10); 110(2); 99(3); 98(30); 96(3); 95(3); 84(7); 83(11); 82(4); 71(4); 70(65); 69(6); 68(4); 67(3); 57(4); 56(10); 55(24); 54(3); 53(3); 44(10); 43(100); 42(11); 41(32); 39(8). ^{13}C-NMR (20 MHz, $CDCl_3$) : δ 166.6 (d, $\underline{C}$=N); 61.4 (d, C=N-$\underline{C}$); 45.3 (t,$\underline{C}H_2Cl$); 38.2 (s,$(CH_3)_2\underline{C}$); 37.5 and 28.1 (t,$(\underline{C}H_2)_2Cl$); 25.0 and 24.5 (2xq,$(\underline{C}H_3)_2CH$ and $(\underline{C}H_3)_2C$).

Reaction of β-Chloroimines 1 (X=Cl, OTs) with Sodium Methoxide in Methanol (General Procedure)

0.01 Mol of β-chloroimine 1 (X=Cl) or β-(tosyloxy)imine 1 (X=OTs) was reacted with 10 ml 2N sodium methoxide in methanol at reflux temperature during several hours as mentioned in table I. Afterwards, the reaction mixture was cooled and poured into 100 ml water. The aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$), the drying agent was remo-

ved and the solvent was evaporated. Normally only β-(alkylamino)-ketones 2 were present in the residual reaction mixture thus obtained. The spectral data of β-(alkylamino)-ketones 2 are compiled in tables II and III.

Reaction of β-Chloroaldimine 1a with Sodium Methoxide in Methanol

The reaction of β-chloroaldimine 1a with sodium methoxide in methanol (2 equiv./2N) was carried out in the same way as the general method described above (Table 1, entry 1-3). This reaction gave rise to β-(alkylamino)-aldehyde 2a next to 2,2-dimethyl-3-t-butylamino-1-propanol 3. Compound 3 is a solid material and could easily be separated from aldehyde 2a by crystallisation.

2,2-dimethyl-3-t-butylamino-1-propanol 3

^{1}H-NMR (60 MHz,$CDCl_3$) : δ 0.95 (6H,s,$(C\underline{H}_3)_2$); 1.13 (9H,s,$C(C\underline{H}_3)_3$); 2.63 (2H,s,br, $C\underline{H}_2$); 3.55 (2H,s,br,$C\underline{H}_2$); 3.43 (2H,s,br,N<u>H</u> and O<u>H</u>). IR (KBr) ν_{NH} = 3285 cm^{-1}; ν_{OH} = 2160 cm^{-1} (broad). ^{13}C-NMR (20 MHz,$CDCl_3$); 23.2 (q,$(\underline{C}H_3)_2$); 28.7 (q, $(\underline{C}H_3)_3$); 34.5 (s,$\underline{C}(CH_3)_2$); 50.5 (s,$\underline{C}(CH_3)_3$); 54.5 (t,$\underline{C}H_2$); 74.7 (t,$\underline{C}H_2$).

Reaction of β-Chloroimine 1c with Sodium Methoxide in Methanol

The reaction of β-chloroimine 1c with sodium methoxide in methanol (2 molar equiv./2N) was performed as described in the general procedure. This reaction gave rise to 2-methoxy-2,3,3-trimethyl-1-phenylazetidine 5c in 86% yield (purity 95%). The workup of the reaction mixture must be carried out carefully, which means that the aqueous workup must be done very quickly with ice water and the solvent must be evaporated at room temperature, because 2-methoxyazetidine 5c is unstable at higher temperatures.

2-Methoxy-2,3,3-trimethyl-1-phenylazetidine 5c

^{1}H-NMR (60 MHz,$CDCl_3$) : 1.12 (3H,s,$C\underline{H}_3$); 1.30 (6H,s,2x$C\underline{H}_3$); 3.00 and 3.20 (2H,2xd, AB,J=6 Hz,$C\underline{H}_2$); 3.33 (3H,s,$C\underline{H}_3O$); 6.20-7.20 (5H,m,$C_6\underline{H}_5$). ^{13}C-NMR (20 MHz, $CDCl_3$) : 147.0 (s,<u>C</u>q); 128.7; 118.4; 114.1 (3xd,<u>C</u>o,<u>C</u>m and <u>C</u>p); 97.4 (s,<u>C</u>-OCH_3); 56.5 (t,$\underline{C}H_2$); 51.8 (q,$O\underline{C}H_3$); 41.2 (s,$\underline{C}(CH_3)_2$); 23.4 (q,$\underline{C}H_3$); 23.2 (q,$\underline{C}H_3$); 16.00 (q,$\underline{C}H_3$).
No specific IR-absorptions; no mass spectrum was recorded because the purity of α-methoxyazetidine 5c was only 95% (α-methoxyazetidine 5c is very unstable).

Reaction of β-Chloroimine 1h with Sodium Methoxide in Methanol

The reaction of β,β,β-trichloroimine 1h with sodium methoxide in methanol (2 molar equiv. 2N) according to the general method gave rise to the rearranged imine 25 (m.p. : 45°C; Yield 85%).

N-(benzylidene)-3,3,3-trichloro-2,2-dimethylpropylamine 25

^{1}H-NMR (60 MHz,$CDCl_3$) : δ 1.42 (6H,s,$(C\underline{H}_3)_2$); 3.90 (2H,d,J=1.2 Hz,$C\underline{H}_2$); 7.10-7.80 (5H,m,$C_6\underline{H}_5$); 8.30 (1H,t,J=1.2 Hz,C<u>H</u>=N). IR (KBr) $\nu_{C=N}$: 1652 cm^{-1}. ^{13}C-NMR (20 MHz,$CDCl_3$) : δ 162.4 (d,<u>C</u>H=N); 136.1 (s,<u>C</u>q); 130.8; 128.6 and 128.2 (3xd,<u>C</u>o,<u>C</u>m and <u>C</u>p); 110.4 (s,$\underline{C}Cl_3$); 66.7 (t,$\underline{C}H_2$); 53.7 (s,$\underline{C}(CH_3)_2$); 22.1 (q,$\underline{C}H_3$). Mass Spectrum (70 eV) m/e (%) : no M^+; 242(3); 161(2); 160(10); 118(100); 117(6); 103(4); 92(5); 91(63); 90(8); 89(10); 87(2); 77(7); 65(10); 64(2); 63(5); 55(7); 53(5); 51(8); 50(2); 44(5); 43(3); 42(2); 41(10); 40(46); 39(8).

Reaction of β-Chloroimines 1 with various bases (Table 1, entries 11-19, 21-23)

The reaction of β-chloroimines 1 with amines (entry 11-14), with sodium hydroxide in water (entry 15), with sodium hydroxide in DMSO (entry 16), with potassium thiocyanate in acetonitrile (entry 17), with potassium cyanide in acetonitrile (entry 18), with sodium isopropylthiolate in methanol (entry 19) and with potassium tert-butoxide in several solvents (entry 21-23) was performed in the same way as the reaction of β-chloroimines 1 with sodium methoxide in methanol. If more than one product was present in the reaction mixture after workup (entry 15, 19) the products were separated by preparative gas chromatography. The spectral data of the isolated β-(alkylamino)-ketones 2 are compiled in tables II and III.

Reaction of β-chloroimine 1i with tert-butyllithium in tetrahydrofuran

0.01 Mol of β-chloroimine 1i was reacted with 0.02 mol of t.-butyllithium (1.07M solution in pentane) in tetrahydrofuran (10% solution) for 10 hours at 0°C under a nitrogen atmosphere (Table I, entry 20). Afterwards the reaction mixture was poured into 100 ml of water. The aqueous phase was extracted with dichloromethane (3 x 50 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent was evaporated. The reaction mixture consited of pure β-(alkylamino)-ketone 2i (72% yield).

Reaction of δ-Chloroimine 26a with Potassium t.-Butoxide in t.-Butanol

A solution of 0.01 mol of δ-chloroimine 26a in t.-butanol was reacted with 0.02 mol of potassium t.-butoxide. After reflux for one day the reaction mixture was cooled and poured into 100 ml of water. After extraction, drying of the extracts and evaporation of the solvent, cyclic enamine 29 was isolated from the reaction mixture by preparative gas chromatography. Compound 29 was isolated in 78% yield but some unidentified side products mounted to 22%.

1-Isopropyl-2-phenyl-1,4,5,6-tetrahydropyridine 29

^{1}H-NMR (60 MHz,$CDCl_3$) : δ 0.94 (6H,d,J=6.4 Hz,$CH(C\underline{H}_3)_2$); 0.80-2.40 (4H,m,N-$C\underline{H}_2$-$C\underline{H}_2$); 2.95-3.20 (2H,m,$C\underline{H}_2$C=); 3.40 (1H,septet,J=6.4 Hz,$C\underline{H}(CH_3)_2$); 4.77 (1H,m,$C\underline{H}$=); 7.00-7.50 (5H,m,$C_6\underline{H}_5$). ^{13}C-NMR (20 MHz,$CDCl_3$) : δ 141.0 and 146.8 (2xs,$\underline{C}$=CH and $\underline{C}$q); 127.9; 127.5 and 127.0 (3xd,$\underline{C}$o,$\underline{C}$m and $\underline{C}$p); 104.3 (d,C=$\underline{C}$H); 49.1 (d,$\underline{C}H(CH_3)_2$); 41.3 (t,$\underline{C}H_2$); 23.7 (t,$\underline{C}H_2$); 22.8 (t,$\underline{C}H_2$); 19.9 (q,$\underline{C}H_3$). IR (NaCl) $\nu_{C=C}$: 1628 cm^{-1}. Mass Spectrum (70 eV) m/e (%) : 201 (M^+,55); 200(26); 186(100); 179(35); 171(21); 158(35); 156(21); 155(21); 149(19); 140(38); 135(38); 128(28); 127(40); 126(20); 117(30); 115(28); 113(20); 112(76); 105(32); 104(26); 102(33); 99(49); 98(25); 97(19); 91(24); 84(20); 83(24); 78(29); 71(28); 70(54); 69(35); 58(54); 57(68); 56(32); 55(47); 46(22); 45(22); 44(46); 43(28); 42(46); 41(64); 40(94); 39(40).

Reaction of 2-Methoxyazetidine 5c with Lithium Aluminium Hydride

A solution of 0.01 mol of 2-methoxyazetidine 5c in freshly distilled dry ether (20 ml) was treated with 0.02 mol of lithium aluminium hydride. The reaction was stirred under reflux during one hour. Afterwards the reaction mixture was poured into 200 ml of water and extracted with ether (3 x 30 ml). The combined extracts were dried ($MgSO_4$), the drying agent was removed and the solvent evaporated. The residue was analyzed by ^{1}H-NMR and preparative gas chromatography, revealing only one compound i.e. azetidine 19.

2,3,3-Trimethyl-1-phenylazetidine 19

^{1}H-NMR (60 MHz,$CDCl_3$) : δ 1.07 (3H,s,$C\underline{H}_3$); 1.18 (3H,s,$C\underline{H}_3$); 1.24 (3H,d,J=6.4 Hz, $C\underline{H}_3CH$); 3.25 and 3.55 (2H,2xd,AB,J=6.4 Hz,$C\underline{H}_2$); 3.64 (1H,q,J=6.4 Hz,$C\underline{H}CH_3$); 6.30-7.40 (5H,m,$C_6\underline{H}_5$). Mass Spectrum (70 eV) m/e (%) : 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). ^{13}C-NMR (20 MHz,$CDCl_3$) : δ 152.5 (s,N-$\underline{C}$); 128.8; 117.5 and 112.1 (3xd,$\underline{C}$o,$\underline{C}$m and $\underline{C}$p); 68.3 (d,$\underline{C}HCH_3$); 63.7 (t,$\underline{C}H_2$); 34.3 (s, $\underline{C}(CH_3)_2$); 27.3 and 22.3 (q,$C(\underline{C}H_3)_2$); 16.6 (q,$CH\underline{C}H_3$).
$C_{12}H_{17}N$: 7.80% N found, 7.99% N calcd.

Reaction of 2-Methoxyazetidine 5c with Water

A mixture of 0.01 mol 2-methoxyazetidine 5c and 25 ml of water was stirred during two days at room temperature. The reaction mixture was then extracted with dichloromethane (3 x 30 ml). The combined extracts were dried ($MgSO_4$) for 1 hour and the solvent was evaporated in vacuo to leave β-(alkylamino)-ketone 2c in high yield. The spectral data of compound 2c are compiled in table II and III.

Reaction of 2-Methoxyazetidine 5c with Methanol

A solution of 0.01 mol 2-methoxyazetidine 5c in anhydrous methanol (15 ml) was refluxed during three hours, after which it was concentrated in vacuo to 1/3 of its volume. The reaction mixture was then poured into 0.5N aqueous sodium hydroxide (20 ml) and extracted with dichloromethane (3 x 20 ml). After drying of the extracts (K_2CO_3) for 2 hour and evaporation of the solvent acetal 22 was isolated in 82% yield.

Spectral data of acetal 22

No specific IR-absorptions. ^{1}H-NMR (60 MHz,$CDCl_3$) : δ 1.05 (6H,s,$(C\underline{H}_3)_2$); 1.27 (3H,s,$C\underline{H}_3$); 2.93 (2H,s,$C\underline{H}_2$); 3.34 (6H,s,$(OC\underline{H}_3)_2$); 4.57 (1H,s,br,$N\underline{H}$); 6.30-7.30 (5H,s,$C_6\underline{H}_5$). Mass Spectrum (70 eV) m/e (%) : no M^+; 219(5); 195(3); 187(4); 121(5); 120(38); 119(5); 118(4); 106(6); 101(4); 100(36); 92(13); 91(100); 89(16); 85(13); 67(4); 65(11); 45(4); 43(13); 42(4); 41(13); 40(4); 39(7).

References

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1. G.A. Gevorgyan, A.G. Agababyan and O.L. Mndzhoyan, Russian Chem. Rev., 53, 561 (1984) and references cited therein.
2. G.A. Gevorgyan, A.G. Agababyan and O.L. Mndzhoyan, Russian Chem. Rev., 54, 495 (1985) and references cited therein.
3. M. Tramontini, Synthesis, 705 (1973).
4. B. Reichert, "Die Mannich Reaktion", Springer-Verlag, Berlin (1959).
5. H. Hellman and G. Opitz in "α-Aminoalkylierung", Verlag-Chemie, Weinheim (1960).
6. J.R. Granados, C.J. Bosch, A.M. Rubiralta, R.C. Martinez and P.F. Rabadan, Span. 471,168 (Cl. C07D), 16 Jan. 1979, Appl. 27 Jun. 1978; Chem. Abstr., 92 6423m (1980).
7. A. Abdul-Baki, F. Rotter, T. Schrauth and H.J. Roth, Arch. Pharm., 311, 341 (1978); Chem. Abstr., 89, 23896y (1978).
8. J.R. Granados, C.J. Bosch, A.M. Rubiralta, R.C. Martinez and P.F. Rabadan, Span. 474,907 (Cl. C07D), 01 Apr. 1979, Appl. 08 Nov. 1978; Chem. Abstr., 92,

9. H. Piotrowska and H. Prejzner, Bull. Acad. Pol. Sci., Ser. Sci. Chim., 28, 181 (1980); Chem. Abstr., 95, 132802j (1981).
10. H. Gnichtel and B.P. Gau, Justus Liebigs Ann. Chem., 2223 (1982).
11. G. Chen, X. Xu and L. Liu, Gaodeng Xuesciao Huascue Xuebao, 83 (1982); Chem. Abstr., 99, 5288d (1983).
12. J. Bosch and M. Rubiralta, An. Quim., Ser C., 79, 27 (1983); Chem. Abstr., 100, 6286c (1984).
13. R.A. Pilli and D. Russowsky, J. Chem. Soc. Chem. Commun., 1053 (1987).
14. D. Armesto, R. Pérez-Ossorio, J. Plumet and A. Ramos, J. Chem. Res. (S), 80 (1987).
15. A.N. Kudrin and V.G. Vorob'ev in "Aminoketony" (Aminoketones), Izd. Meditsina, Moscow (1970).
16. E. Profft in "Die Falikaine, ihre Chemie, Pharmakologie, Sowie Anwendung in der Medizin", Berlin (1954).
17. B.E. Abreu, A.B. Richards, L.C. Weaver, G.R. Burch, C.A. Bunde, E.R. Bockstahler and D.L. Wright, J. Pharm. Exp. Ther., 155, 419 (1955); Chem. Abstr., 50, 3631a (1956).
18. H.J. Florestano and M.E. Bahler, J. Am. Pharm. Assoc., 45, 320 (1956); Chem. Abstr., 50, 10187c (1956).
19. J. Porszasz, K. Nador, K. Gibiszer-Porszasz and T. Barankay, Acta Physiol. Sci. Hung., 18, 149 (1960); Chem. Abstr., 55, 13637a (1961).
20. O.M. Avakyan in "Veschchestva Deistvuyuschchie na Simpato-Adrenalovuyu Sistemu" (Substances Acting on the Sympathetic-Adrenal System), Izd. Akad. Nauk Arm. SSR, Erevan, 129 (1980).
21. S.S. Krylov and N.T. Starykh, Farmakol. Toksikol., 36, 396 (1973); Chem. Abstr., 80, 22628q (1974).
22. H. Schönenberger, T. Bastug, L. Bindl, A. Adam, D. Adam, A. Petter and W. Zwez, Pharm. Acta Helv., 44, 691 (1969); Chem. Abstr., 72, 65748f (1970).
23. J.R. Dimmock, C.B. Nyathi and P.J. Smith, J. Pharm. Sci., 67, 1543 (1978).
24. H. Schönenberger and T. Bastug., Arzneimittel-Forsch., 20, 386 (1970); Chem. Abstr., 72, 129593m (1970).
25. H. Schönenberger and T. Bastug, Arzneimittel-Forsch., 21, 68 (1971); Chem. Abstr., 74, 64349 (1971).
26. H. Schönenberger and P. Lippert, Pharmazie, 25, 617 (1970); Chem. Abstr., 74, 20718w (1971).
27. W. Werner, W. Jungstand and W. Gutsche, Arzneimittel-Forsch., 20, 246 (1970); Chem. Abstr., 72, 109349k (1970).
28. W. Jungstand, W. Gutsche and K. Wohlrabe, Arzneimittel-Forsch., 21, 404 (1971); Chem. Abstr., 74, 139132r (1971).
29. C.B. Nyathi, V.S. Gupta and J.R. Dimmock, J. Pharm. Sci., 68, 1383 (1979); Chem. Abstr., 92, 69355n (1980).
30. W. Werner, W. Jungstand, W. Gutsche and K. Wohlrabe, Pharmazie, 32, 341 (1977); Chem. Abstr., 87, 145546p (1977).
31. J.R. Dimmock and W.G. Taylor, J. Pharm. Sci., 64, 241 (1975); Chem. Abstr., 82, 119010m (1975).
32. E.V. Vlasenko, Z.S. Mkrtchyan and A.S. Edilyan, Biol. Zhur. Armenii, 25, 125 (1972).
33. P. Sulmon, N. De Kimpe, R. Verhé, L. De Buyck and N. Schamp, Synthesis, 192 (1986).
34. P.G. Gassman and A. Carrasquillo, J. Chem. Soc., Chem. Commun., 495 (1969).
35. H.H. Wasserman and A.W. Tremper, Tetrahedron Lett., 1449 (1977).
36. H.H. Wasserman, A.W. Tremper and J.S. Wu, Tetrahedron Lett., 1089 (1979).

37. H.H. Wasserman, W.T. Han, J.M. Schaus and J.W. Faller, Tetrahedron Lett., 3111 (1984).
38. M. Mitzlaff, K. Warning and H. Jensen, Justus Liebigs Ann. Chem., 1713 (1978).
39. M. Mitzlaff, K. Warning and H. Jensen, Ger. Offen. 2,539,777 (1977); Chem. Abstr., 87, 5820y (1977).
40. F. Nerdel, P. Weyerstahl and K. Zabel, Chem. Ber., 102, 1606 (1969).
41. Y.V. Zeifman, N.P. Gambaryan, L.A. Simonyan, R.B. Minasyan and I.L. Knunyants, Zh. Obshch. Khim., 37, 2476 (1967); Chem. Abstr., 69, 2919e (1968).
42. J. Cabral, P. Laszlo, M.T. Montaufier, Tetrahedron Lett., 29, 547 (1988).
43. P. Sulmon, N. De Kimpe, N. Schamp, B. Tinant, J.-P. Declercq, Tetrahedron, 44, 3653 (1988).
44. D.A. Evans, J. Am. Chem. Soc., 92, 7593 (1970).