Synthesis of Perhydro-1,3-diazine-2-thiones from β-Chloro Imines

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The reaction of β-chloro imines with methanol gave rise to β-alkylamino acetals via intermediate 2-methoxyazetidines. If an aromatic β-chloro imine was used under these conditions, 1-methoxy-2-methyl-1-phenyl-1-propene was also formed. The reaction of β-chloro imines with potassium thiocyanate in methanol gave rise to perhydro-1,3-diazine-2-thiones in 10–55% yield in addition to β-alkylamino acetals, again via methoxyazetidines.

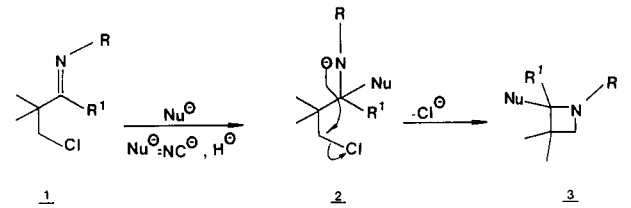
Introduction

β-Chloro imines **1** are a class of bifunctional compounds that have been recently described by us.[1] They are accessible from appropriate β-chloro ketones on reaction with primary amines in the presence of titanium(IV) chloride. The latter β-chloro ketones were synthesized by hydroxymethylation (CH_2O/TFA) of ketones and subsequent tosylation (TosCl/pyridine) and chloride substitution (LiCl/DMF).[1] Other entries into the field of β-chloro ketones[2] involve the reaction of cyclopropanols and allylic alcohols with hypohalides.[3-6] Less sterically hindered substrates, e.g. β-chloro aldehydes, could be condensed with primary amines without the use of strong dehydrating reagents.[1] β-Chloro imines **1** have been shown to be a useful group of compounds in organic synthesis. For instance, on reaction with nucleophiles (such as hydride and cyanide), they give rise to functionalized azetidines **3** (Scheme I).[7,8] We now report on the rearrangement of β-chloro imines **1** in alcoholic medium and with potassium thiocyanate leading to β-alkylamino acetals **4** and perhydro-1,3-diazine-2-thiones **6**.

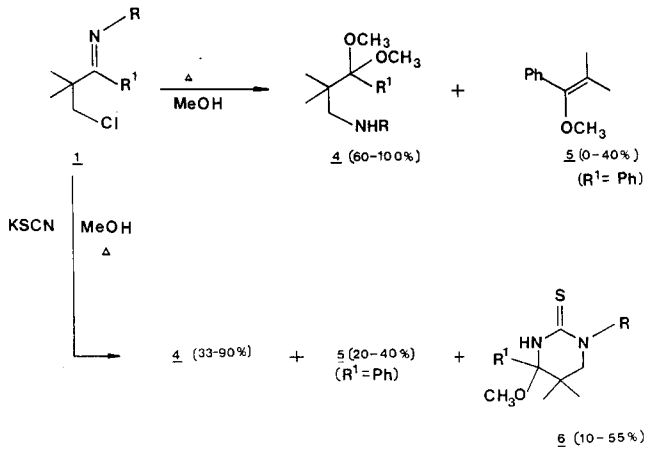
Results and Discussion

Reaction of β-Chloro Imines with Methanol (Table I, entries 1–6). The reaction of β-chloro imines **1** with methanol (10% solution w/v) under reflux gave rise to β-alkylamino acetals **4** in good to nearly quantitative yield (Scheme II, Table I). β-Alkylamino acetals **4** are interesting products as they are considered as a protected form of β-alkylamino ketones. β-Amino ketones have already been described several times in review articles.[9-13] They are usually prepared via the Mannich reaction, namely by reaction of a carbonyl compound, an amine, and formaldehyde. The synthesis of β-amino acetals and ketones from β-chloro imines provides an alternative to the Mannich reaction. This methodology utilizes β-chloro imines as key substrates, which are accessible from the corresponding β-chloro ketones (vide supra).[2] The reaction mechanism for the formation of β-alkylamino acetals **4** is given in Scheme III. The rearrangement of β-chloro imines **1** into β-alkylamino acetals **4** is initiated by a nucleophilic addition of methanol across the imino function. The intermediate adduct **7** undergoes immediately an intramolecular nucleophilic substitution with the formation of 2-methoxyazetidines **8**. In this acidic medium (HCl is liberated during the reaction) 2-methoxyazetidines **8** are not stable and are quickly converted into the corresponding β-alkylamino acetals **4** via **10**. By evaporation of the solvent, these acetals **4** are isolated as crystalline hydro-

Scheme I



Scheme II



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(1) Sulmon, P.; De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Synthesis* **1986**, 192.
(2) Sulmon, P.; De Kimpe, N.; Schamp, N. *Org. Prep. Proced. Int.*, in press.
(3) De Puy, C. H.; Arney, W. C., Jr.; Gibson, D. M. *J. Am. Chem. Soc.* **1968**, *90*, 1830.
(4) Wilt, J. W.; Hill, J. W. *J. Org. Chem.* **1961**, *26*, 3523.
(5) Johnson, C. R.; Herr, R. W. *J. Org. Chem.* **1973**, *38*, 3153.
(6) Johnson, C. R.; Cheer, C. J.; Goldschmith, D. J. *J. Org. Chem.* **1964**, *29*, 3320.
(7) Preliminary communication: Sulmon, P.; De Kimpe, N.; Schamp, N. *J. Chem. Soc., Chem. Commun.* **1985**, 715.
(8) Sulmon, P.; De Kimpe, N.; Schamp, N.; Tinant, B.; Declercq, J.-P. *Tetrahedron* **1988**, *44*, 3653.
(9) Gevorgyan, G. A.; Agababyan, A. G.; Mndzhoyan, O. L. *Russian Chem. Rev.* **1984**, *53*, 561 and references cited therein.
(10) Gevorgyan, G. A.; Agababyan, A. G.; Mndzhoyan, O. L. *Russian Chem. Rev.* **1985**, *54*, 495 and references cited therein.
(11) Tramontini, M. *Synthesis* **1973**, 705.
(12) Reichert, B. In *Die* Mannich *Reaktion*; Springer-Verlag: Berlin, 1959.
(13) Hellman, H.; Opitz, G. In *α-Aminoalkylierung*; Verlag-Chemie: Weinheim, 1960.

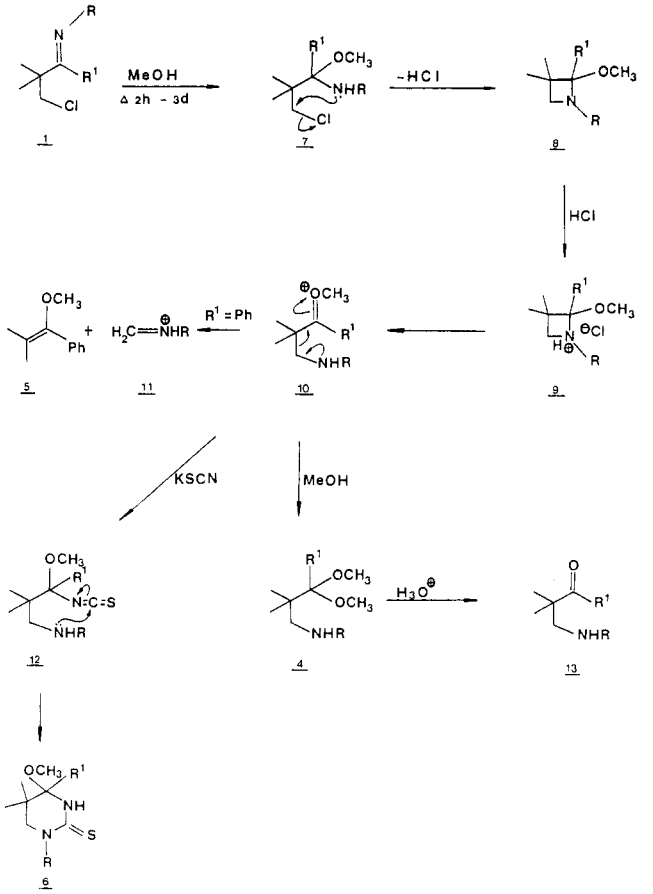
0022-3263/89/1954-2587$01.50/0

Table I. Synthesis of β-Alkylamino Acetals 4 and Perhydro-1,3-diazine-2-thiones 6

entry	starting compd	R	R^1	reaction conditions[a] (10% solution)	% yield reaction mixture	reaction products: acetal 4	reaction products: heterocycle 6	reaction products: enol ether 5	mp, °C, of heterocycle 6
1	**1a**	*t*-Bu	H	MeOH Δ 3–8 days	88	**4a**: 100	0	0	
2	**1b**	$CH_2C_6H_5$	Me	MeOH Δ 2 h	87	**4b**: 100	0	0	
3	**1c**	*i*-Pr	Me	MeOH Δ 2 h	86[b]	**4c**: 100	0	0	
4	**1c**	*i*-Pr	Me	MeOH Δ 4 h	91	**4c**: 100	0	0	
5	**1d**	*i*-Pr	C_6H_5	MeOH Δ 6 h	90	**4d**: 60–70	0	30–40	
6	**1e**	$CH_2C_6H_5$	C_6H_5	MeOH Δ 4 h	91	**4e**: 75	0	25	
7	**1f**	$CH_2C_6H_5$	H	KSCN (2 E)/MeOH Δ 3 days	83	**4f**: 70	**6f**: 30	0	**6f**: 159
8	**1c**	*i*-Pr	Me	KSCN (2 E)/MeOH Δ 4 h	89–95	**4c**: 87–90	**6c**: 10–13	0	**6c**: 140
9	**1b**	$CH_2C_6H_5$	Me	KSCN (2 E)/MeOH Δ 2 h	87	**4b**: 45	**6b**: 55	0	**6b**: 134
10	**1g**	$CH(CH_3)C_6H_5$	Me	KSCN (2 E)/MeOH Δ 6 h	77[c]	**4g**: 69	**6g**: 31	0	**6g**: 128
11	**1e**	$CH_2C_6H_5$	C_6H_5	KSCN (2 E)/MeOH Δ 20 h	83	**4e**: 33	**6e**: 47	20	**6e**: 130
12	**1d**	*i*-Pr	C_6H_5	KSCN (2 E)/MeOH Δ 6 h	78	**4d**: 36–37	**6d**: 20–23	34–40	**6d**: 190

[a] Δ = reflux; E = molar equivalents; satisfactory analytical data for compounds **4b–d**, **6b–f** (±0.2% for N) were obtained. [b] Acetal **4c** was initially isolated as the hydrochloride. After workup (aqueous sodium hydroxide) acetal **4c** was liberated. [c] After isolation of the heterocycle **6d**, the reaction mixture was hydrolyzed.

Scheme III



chlorides, while by workup with an aqueous sodium hydroxide solution the acetal hydrochlorides are transformed into the corresponding acetals **4**. Amino acetals **4** or their hydrochlorides are cleanly hydrolyzed by an aqueous hydrogen chloride solution at room temperature to yield the corresponding β-alkylamino ketones **13**.

The reaction of β-chloro imines **1** with methanol did not always lead to one reaction product. If aromatic β-chloro imines **1** were used, i.e. if $R^1 = C_6H_5$ (**1d** and **1e**), the reaction with methanol under reflux furnished not only β-alkylamino acetals **4d** and **4e** ($R^1 = C_6H_5$) but also enol ether **5** in amounts varying from 25 to 40% (Scheme II, Table I). The formation of enol ether **5** is explained by a Grob fragmentation by which intermediate **10** is transformed into enol ether **5** and formaldiminium ion **11**. Thus, by reaction of β-chloro imine **1** ($R^1 = C_6H_5$) with methanol, α-methoxyazetidine **8** is initially formed, but this intermediate might be viewed in equilibrium with the ring-opened form **10**. This intermediate resonance-stabilized form can give rise to β-alkylamino acetal **4** by trapping with methanol or to enol ether **5** by a Grob-type splitting. The latter process only occurs in cases when the phenyl substituent has a major directing influence (cf. stabilization of the charge in **10**). The determination of the ratio of acetal **4** (R^1 = Ph) and enol ether **5** (R^1 = Ph) was performed by gas chromatography and ^1H NMR analysis, or after hydrolysis. In the latter case, compounds **13** (R^1 = Ph) and isobutyrophenone were separated by acid (isobutyrophenone) followed by basic (β-alkylamino ketone **13**) extractive workup. The structure of enol ether **5** was established via synthesis of the authentic product. For this purpose, isobutyrophenone was treated with sodium amide in toluene at reflux temperature after which the sodio enolate was reacted with dimethyl sulfate. After 2 h of reflux the reaction mixture revealed 28% enol ether **5** (methylation on oxygen) and 72% of 2,2-dimethyl-1-phenyl-1-propanone (methylation on carbon).

The synthesis of β-alkylamino acetals **4** is given in Table I, while the spectral data are compiled in Tables II and III (supplementary material).

It should be stressed that 2-alkoxyazetidines (e.g. **8**) are very rare in the literature and that they are only accessible in special cases.[14]

The spectral data of most of the corresponding β-alkylamino ketones have been reported in a previous paper.[14]

Reaction of β-Chloro Imines with Potassium Thiocyanate in Methanol (Table I, entries 6–12). When the reaction of β-chloro imines **1** with methanol was performed in the presence of potassium thiocyanate, perhydro-1,3-diazine-2-thiones **6** and enol ether **5** ($R^1 = C_6H_5$) were isolated, in addition to β-alkylamino acetals **4** (Scheme II). After removal of the solid perhydro-1,3-diazine-2-thiones **6** (10–55%), only β-alkylamino acetals **4** and enol ether **5** were present in the residual reaction mixture. Both compounds **4** and **5** could easily be separated by preparative gas chromatography or after hydrolysis as described above. The reaction mechanisms for the formation of perhydro-1,3-diazine-2-thiones **6** is included in Scheme III. As discussed before, 2-methoxyazetidines **8** are formed from β-chloro imines **1** but the ring-opened form **10** not only undergoes interception of methanol (to form acetals **4**) and Grob fragmentation (to form enol ether **5**), but it also suffers reaction with the ambident nucleophile thiocyanate. The adduct **12** then gives an intramolecular nucleophilic

(14) Sulmon, P.; De Kimpe, N.; Schamp, N. *Tetrahedron*, in press.

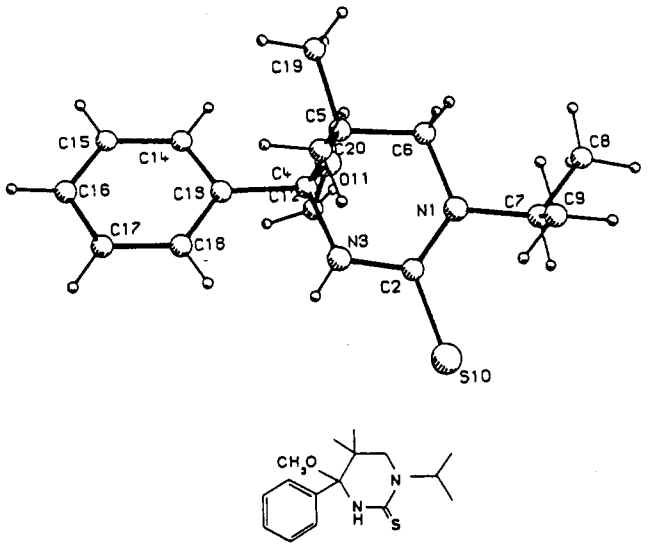
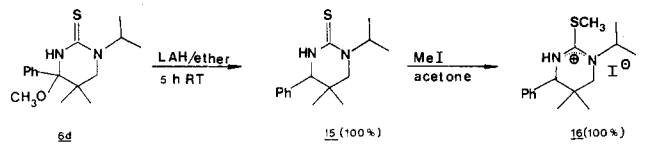
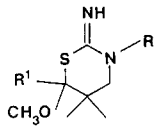


Figure 1. Stereochemical view of 1-isopropyl-4-methoxy-4-phenyl-5,5-dimethylperhydro-1,3-diazine-2-thione (**6d**).

Scheme IV



addition of the amino moiety across the cumulenic system to provide the perhydro-1,3-diazine-2-thiones **6**. Via the spectral data (^{1}H NMR, IR, ^{13}C NMR, MS), it is not easy to make an unambigous distinction between the isomeric heterocyclic compounds **6** and **14**. Only the ^{1}H NMR



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spectrum of compound **6f** (R^1 = H) gave an indication about the exact structure of the crystalline product, because a coupling constant of 4.5 Hz between N*H* and C*H*OCH$_3$ was observed. X-ray crystallographic analysis undoubtedly established the exact structure of the solid reaction products, being perhydro-1,3-diazine-2-thiones **6** as exemplified for compound **6d** (R^1 = Ph; R = *i*-Pr). The stereochemical view of the molecule is given in Figure 1. A supplementary proof for the structure of perhydro-1,3-diazine-2-thiones **6** was obtained by reaction of perhydro-1,3-diazine-2-thione **6d** (R = *i*-Pr; R^1 = C_6H_5) with lithium aluminium hydride in ether at room temperature whereby demethoxylated compound **15** was formed by nucleophilic substitution of the methoxy group by hydride (neighboring group participation of the adjacent amino group). On reaction with 2 equiv of methyl iodide in acetone, compound **15** was transformed into the salt **16** (Scheme IV). The synthesis of the new perhydro-1,3-diazine-2-thiones **6** is compiled in Table I, while the spectral data of these heterocyclic compounds are presented in Tables IV and V (supplementary material). Some related 4-alkoxyperhydro-1,3-diazine-2-thiones were already reported in the literature.[15-20] The latter were prepared by reaction of thiourea with 4-phenyl-3-butene-2-one, by methanolysis of 4-amino-4,6,6-trimethyltetrahydropyrimidine-2-thiones, by reaction of 4-isothiocyanato-2-butanone with alcoholic ammonia, or by addition of alcohols across 1,4-dihydropyrimidine-2(3*H*)-thiones.[18,19] On the contrary, 4-hydroxyperhydro-1,3-diazine-2-thiones are better known in the literature.[21-26] For instance, they have been prepared by reaction of β-isothiocyanato ketones with amines.

In conclusion, the reaction of β-chloro imines with methanol leads to a novel and highly useful synthesis of β-alkylamino acetals while the reaction of β-chloro imines with potassium thiocyanate in methanol provides β-alkylamino acetals in addition to 4-methoxyperhydro-1,3-diazine-2-thiones.

Experimental Section

Infrared spectra were recorded with a Perkin-Elmer Model 1310 spectrophotometer. ^{1}H NMR spectra were measured with a Varian T-60 NMR spectrometer (60 MHz), while ^{13}C NMR spectra were obtained with a Varian FT-80 NMR spectrometer (20 MHz). Mass spectra were recorded with a Varian Mat 112 mass spectrometer (Direct inlet system). Melting points were determined with a Kofler hotstage apparatus. Gas chromatographic analyses were performed with Varian 1700 and Varian 920 gas chromatographs using preparative stainless steel columns (SE 30, 3 m).

Synthesis of β-Chloro Imines 1 (General procedure). β-Chloro imines **1** were synthesized according to our previous published method involving condensation of β-chloro ketones and β-chloro aldehydes with primary amines in ether or benzene.[1]

Synthesis of β-Alkylamino Acetals 4 (General procedure). A solution of β-chloro imine **1** (0.1 mol) in anhydrous methanol (150 mL) was refluxed during several hours as given in Table I and afterwards concentrated in vacuo to one-third of its volume. The reaction mixture was cooled, poured into 0.5 N aqueous sodium hydroxide (300 mL), and then extracted with dichloromethane (3 × 50 mL). After drying of the combined extracts with potassium carbonate (1 h) and evaporation of the solvent, the reaction mixture revealed only β-alkylamino acetals **4**, as verified by ^{1}H NMR and gas chromatographic analysis. The spectral data of compounds **4** are compiled in Tables II and III (supplementary material). As a typical example, the spectral data of *N*-(3,3-dimethoxy-2,2-dimethylbutyl)-*N*-isopropylamine (**4c**) are given here: IR (NaCl) 3340 cm^{-1} (ν_{NH}); ^{1}H NMR ($CDCl_3$) δ 0.93 (6 H, s, Me_2), 0.99 (6 H, d *J* = 6.4 Hz, Me_2), 1.27 (3 H, s, Me), 2.47 (2 H, s, CH_2) 2.65 (1 H, septet, *J* = 6.4 Hz, C*H*Me_2), 3.27 (6 H, s, $(OMe)_2$), NH invisible; ^{13}C NMR ($CDCl_3$) δ 16.5 (q, Me), 23.2 (q, Me_2), 22.4 (q, Me_2), 43.8 (s, CMe_2), 49.7 (d, NCH), 50.7 (q, OMe), 56.1 (t, CH_2), 105.2 (s, OCO). If the previous reaction mixture was not poured into 0.5 N aqueous sodium hydroxide but totally concentrated, β-alkylamino acetal hydrochlorides were isolated in pure form from the residue. Spectral data of *N*-isopropyl-3,3-dimethoxy-2,2-dimethylbutanamine hydrochloride (**4c**·HCl), (R = *i*-Pr; R^1 = Me): ^{1}H NMR ($CDCl_3$ δ 1.17 (6 H, s, Me_2), 1.47 (6 H, d, *J* = 6.4 Hz, CH(CH_3)$_2$), 1.45 (3 H, s, CH_3), 3.08 (2 H, s, CH_2), 3.48 (6

(15) Zigeuner, G.; Brunetti, H.; Ziegler, H.; Bayer, M. *Monatsh. Chem.* **1970**, *101*, 1767.
(16) Takeshima, T.; Imamoto, T.; Yokoyama, M.; Yamamoto, K.; Akano, M. *J. Org. Chem.* **1968**, *33*, 2877.
(17) Lloyd, D.; McNab, H.; Tucker, K. S. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1862.
(18) Singh, H.; Singh, P.; Kumar, S. *Indian J. Chem., Sect. B* **1983**, *22B*, 154.
(19) Singh, H.; Kumar, S.; Singh, P. *J. Chem. Res. (S)* **1984**, 137.
(20) Ignatova, L. A.; Shutalev, A. D.; Shingareeva, A. G.; Dymova, S. F.; Unkovskii, B. V. *Khim. Geterotsikl. Soedin.* **1985**, 260; *Chem. Abstr.* **1985**, *103*, 71271*v*.
(21) Shutalev, A. D.; Ignatova, L. A.; Unkovskii, B. V. *Khim. Geterotsikl. Soedin.* **1985**, 852.
(22) Ignatova, L. A.; Shitalev, A. D.; Unkovskii, B. V.; Sihilova, N. G.; Duplitsheva, A. P. *Khim. Farm. Zhurnal* **1985**, 1447.
(23) Unkovskii, B. V.; Ignatova, L. A.; Donskaya, H. M.; Zaitseva, M. G. *Probl. Organ. Sinteza, Akad. Nauk. SSSR, Otd. Obshch. i Tekhn. Khim.* **1965**, 202; *Chem. Abstr.* **1966**, *64*, 9719*a*.
(24) Ovechkina, G. I.; Ignatova, L. A.; Ratomskaya, M. A.; Unkovskii B. V. *Khim. Geterotsikl. Soedin.* **1971**, 1258.
(25) Unkovskii, B. V.; Ignatova, L. A.; Zaitseva, M. G. *Khim. Geterotsikl. Soedin.* **1969**, 889.
(26) Khachatryan, R. M.; Pirenyan, S. K.; Vartanyan, S. A. *Arm. Khim. Zh.* **1970**, *23*, 645.

H, s, $(OCH_3)_2$), 7.23 (2 H, s, br, NH_2), NC*H* covered by $C(OCH_3)_2$; ^{13}C NMR ($CDCl_3$) δ 107.2 (s, *O*CO), 52.2 (q, OCH_3), 51.2 (d, NHCH), 50.5 (t, CH_2), 42.4 (s, $C(CH_3)_2$), 22.3 (q, $C(CH_3)_2$), 18.9 (q, $C(CH_3)_2$), 13.0 (q, CH_3).

If the reaction mixture was totally concentrated in vacuo and afterwards hydrolyzed with aqueous HCl (10 molar equiv 5 N, room temperature, 1 day), the corresponding β-alkylamino ketones **13** were produced. A typical representive synthesis of a β-alkylamino ketone is described by the following experiment. A solution of β-chloro ketimine **1c** ($R^1 = CH_3$; R = *i*-Pr) (0.1 mol) in anhydrous methanol (150 mL) was refluxed during 2 h and afterwards totally concentrated in vacuo. The residue was then treated with aqueous HCl (10 molar equiv, 2 N). After vigorous stirring during 1 day at room temperature, the aqueous phase was made alkaline with 50% aqueous sodium hydroxide, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). The combined extracts were washed with brine (50 mL), and, after drying with magnesium sulfate (1 h), 3,3-dimethyl-4-(*N*-isopropylamino)-2-butanone (**13c**) ($R^1 = CH_3$; R = *i*-Pr) was obtained in pure form (≥95%; GLC–NMR) as a liquid (90% yield). Some spectral data on related β-alkylamino ketones have been reported already previously.[14]

Spectral data of 3,3-dimethyl-4-(*N*-(2-methylbenzyl)amino)-2-butanone (**13g**) ($R^1 = CH_3$; R = $CH(CH_3)C_6H_5$): IR (NaCl) $\nu_{C=O}$ 1712; ν_{NH} 3335 cm^{-1}; ^1H NMR δ ($CDCl_3$) 1.05 (6 H, s, $(CH_3)_2$), 1.28 (3 H, d, J = 6.6 Hz, CH_3CH), 1.48 (1 H, s, br, N*H*), 2.05 (3 H, s, CH_3C=O), 2.41 and 2.57 (2 H, 2 d, AB, J = 11.2 Hz, CH_2), 3.63 (1 H, q, J = 6.6 Hz, CH_3CH), 7.26 (5 H, s, C_6H_5); mass spectrum (70 eV), m/e 219 (M^+, 0.5), 204 (4), 135 (3), 134 (27), 118 (4), 106 (12), 105 (100), 104 (5), 103 (6), 91 (6), 79 (11), 77 (13), 72 (4), 56 (6), 55 (4), 51 (4), 44 (5), 43 (25), 42 (4), 41 (6), 40 (14), 39 (4); ^{13}C NMR δ ($CDCl_3$) 213.5 (s, *C*=O), 145.8 (s, C_q), 128.3, 126.6, and 126.9 (3 d, C_o, C_m, and C_p), 58.9 (d, CH_2NC), 56.4 (t, CH_2), 48.5 (s, $C(CH_3)_2$), 25.1 (q, CH_3C=O), 24.6 (q, $NCH(CH_3)$), 23.0 and 23.1 (2 q, $C(CH_3)_2$).

The reaction of β-chloro ketimines **1d,e** with methanol gave rise to the expected β-alkylamino acetals **4d,e** in addition to enol ether **5**. The two reaction products were separated by preparative gas chromatography or after hydrolysis. In the last case the reaction mixture, prepared according to the procedure described above, was hydrolyzed with aqueous HCl (10 molar equiv, 2 N, room temperature, 2 days) and afterwards extracted with ether (3 × 100 mL). After drying of the combined extracts ($MgSO_4$) and evaporation of the solvent, isobutyrophenone was present as the sole product (^1H NMR; GLC). The aqueous phase of the above extraction was then made alkaline with 50% aqueous sodium hydroxide, the organic layer was separated, and the aqueous phase was extracted with dichloromethane (3 × 50 mL). After drying of the combined extracts ($MgSO_4$; 1 h), β-alkylamino ketones **13d** (R = *i*-Pr) or **13e** (R = $CH_2C_6H_5$) were isolated in pure form (>95%; ^1H NMR–GLC). Spectral data of 1-methoxy-2-methyl-1-phenyl-1-propene (**5**): ^1H NMR ($CDCl_3$) δ 1.66 (3 H, s, CH_3), 1.83 (3 H, s, CH_3), 3.30 (3 H, s, OCH_3), 7.33 (5 H, s, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 149.0 (s, C_q), 135.6 (s, *C*=), 129.5, 127.9, and 127.4 (3 d, C_o, C_m, and C_p), 115.4 (s, *C*=C), 57.2 (q, OCH_3), 19.7 and 17.5 (2 q, 2 CH_3); mass spectrum (70 eV), m/e 162 (M^+, 64), 161 (36), 147 (15), 131 (15), 129 (19), 119 (11), 117 (15), 115 (23), 107 (14), 106 (19), 105 (100), 104 (15), 91 (36), 79 (15), 77 (87), 59 (79), 51 (38), 50 (12), 43 (36), 42 (9), 41 (38), 40 (43), 39 (17). Spectral data of 2,2-dimethyl-3-(*N*-benzylamino)-1-phenyl-1-propanone (**13e**) (R = $CH_2C_6H_5$): IR (NaCl) $\nu_{C=O}$ 1677; ν_{NH} 3341 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (6 H, s, $(CH_3)_2$), 1.79 (1 H, s, br, N*H*), 2.80 (2 H, s, CH_2N), 3.70 (2 H, s, $CH_2C_6H_5$), 7.21 (5 H, s, C_6H_5), 7.00–7.80 (5 H, m, C_6H_5); mass spectrum (70 eV), m/e no M^+, 148 (4), 121 (6), 120 (49), 119 (5), 118 (4), 106 (6), 105 (20), 92 (9), 91 (100), 89 (3), 78 (3), 77 (19), 65 (11), 56 (4), 55 (3), 51 (9), 44 (3), 43 (5), 42 (9), 41 (13), 40 (15), 39 (7); ^{13}C NMR ($CDCl_3$) δ 209.2 (s, *C*=O), 140.4 and 139.3 (2 s, 2 C_p), 128.7–126.7 (6 d, 2 (C_o, C_m, and C_p)), 58.5 (t, $CH_2C_6H_5$), 54.4 (t, CH_2N), 48.8 (s, $C(CH_3)_2$), 24.5 (q, $(CH_3)_2$).

Synthesis of Enol Ether 5. To a solution of 0.01 mol of isobutyrophenone in dry toluene (10% solution) was added 0.01 mol of sodium amide. The reaction mixture was refluxed (2 h) and afterwards 0.015 mol of dimethyl sulfate was added. After reflux (2–10 h) the reaction mixture was worked up in an identical way as described above during the synthesis of β-alkylamino acetals **4**. Analyses of the residue by means of preparative gas chromatography and the usual spectroscopic methods revealed 24–28% enol ether **5** and 72–76% 2,2-dimethyl-1-phenyl-1-propanone.

Synthesis of Perhydro-1,3-diazine-2-thiones 6. A solution of β-chloro ketimine **1** (0.1 mol) and potassium thiocyanate (0.02 mol) in anhydrous methanol (150 mL) was refluxed during several hours as mentioned in Table I. The reaction mixture was cooled and then poured into 0.5 N aqueous sodium hydroxide (500 mL). After extraction with dichloromethane (3 × 50 mL), the combined extracts were dried ($MgSO_4$), the drying agent was removed, and the solvent was evaporated. The solid perhydro-1,3-diazine-2-thiones **6** (10–55% yield) were easily separated from the other compounds by crystallization (−20 °C). The other compounds, i.e. β-alkylamino acetals **4** if $R^1 \neq C_6H_5$, β-alkylamino acetals **4** and enol ether **5** if $R^1 = C_6H_5$, were easily separated as described above. The spectral data of perhydro-1,3-diazine-2-thiones **6** are compiled in Tables IV and V (supplementary material).

X-ray Crystallographic Analysis of 1-Isopropyl-4-methoxy-4-phenyl-5,5-dimethylperhydro-1,3-diazine-2-thione (6d). The principal crystallographic parameters of compound **6d** (R^1 = Ph, R = *i*-Pr) are as follows: monoclinic; M_r = 292.45; $P2_1/n$; a = 15.774 (5), b = 12.090 (3), and c = 8.356 (2) Å; β = 93.81 (2)°; v = 1587 (1) Å^3; Z = 4; D_x = 1.22 g cm^{-3}; Mo Kα; λ = 0.710 69 Å; μ = 2.01 cm^{-1}; $F(000)$ = 632; T = 291 K; R = 0.037 for 1870 observed reflections. The other data of this X-ray crystallographic analysis are given in Tables VI–IX of the supplementary material section.

Synthesis of Perhydro-1,3-diazine-2-thione 15. A solution of 0.01 mol of perhydro-1,3-diazine-2-thione **6d** in ether (10% solution w/v) was treated with 0.02 mol of lithium aluminium hydride at room temperature. After stirring (5 h), the reaction mixture was poured cautiously into 200 mL of water and extracted with ether (3 × 50 mL). The combined extracts were dried ($MgSO_4$), the drying agent was removed, and the solvent was evaporated. Perhydro-1,3-diazine-2-thione **15** is a solid material (mp 179 °C) and was isolated in quantitative yield. The spectral data of compound **15** are presented in Tables IV and V (supplementary material).

Synthesis of Methiodide 16. To a solution of 0.01 mol of perhydro-1,3-diazine-2-thione **15** in 20 mL of acetone was added 0.02 mol of methyl iodide, and the reaction mixture was stirred at room temperature during 1 day. After evaporation of the solvent and the excess of methyl iodide, methiodide **16** was isolated in nearly quantitative yield (yield ~100%). The spectral data of methiodide **16** are compiled in Tables IV and V (supplementary material).

Registry No. **1a**, 99315-25-0; **1b**, 99315-26-1; **1c**, 99315-28-3; **1d**, 99315-27-2; **1e**, 99315-24-9; **1f**, 99315-22-7; **1g**, 119639-94-0; **4a**, 119639-95-1; **4b**, 119639-96-2; **4c**, 119639-97-3; **4c**·HCl, 119640-07-2; **4d**, 119639-98-4; **4e**, 119639-99-5; **4f**, 119640-00-5; **5**, 50407-04-0; **6b**, 119640-02-7; **6c**, 119640-01-6; **6d**, 119640-03-8; **6e**, 119640-04-9; **6f**, 119640-05-0; **6g**, 119640-06-1; **13c**, 119640-08-3; **13d**, 119640-09-4; **13e**, 110871-26-6; **13g**, 119656-25-6; **15**, 119640-10-7; **16**, 119640-11-8; isobutyrophenone, 611-70-1; 2,2-dimethyl-1-phenyl-1-propanone, 938-16-9.

Supplementary Material Available: Tables II and III describing the spectral data (^1H NMR, ^{13}C NMR, IR) of β-(alkylamino)acetals **4**, Tables IV and V compiling the spectral data (^1H NMR, ^{13}C NMR, IR, MS) of perhydro-1,3-diazine-2-thiones **6**, **15**, and methiodide **16**, Table VI describing the atomic coordinates and equivalent temperature factors of compound **6d**, Table VII presenting the bond distances of this compound, Table VIII showing bond angles of compound **6d**, Table IX compiling torsion angles, and Table X presenting the nitrogen analysis of compounds **4** and **6** (11 pages). Ordering information is given on any current masthead page.