Synthesis of α,α-Dialkoxy Imines and α-Keto Acetals

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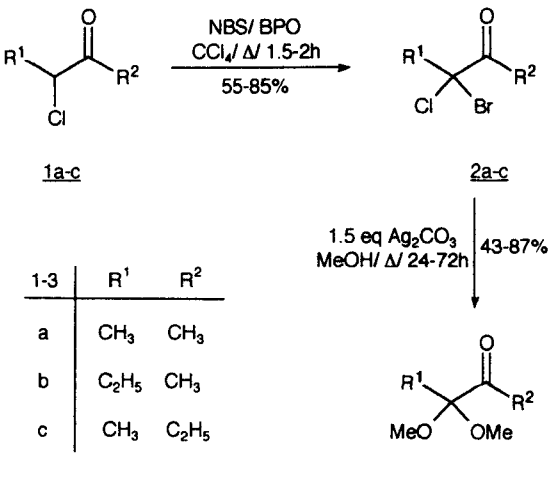
A convenient synthesis of monoacetals of α-diones, i.e. α-keto acetals, was developed by silver ion induced alcoholysis of regiospecifically formed α-bromo-α-chloro ketones. Similarly, the corresponding α,α-dialkoxy ketimines were synthesized from silver ion induced alcoholysis of α-bromo-α-chloro ketimines. Both methods provide an easy access to protected forms of α-diones, useful as building blocks in organic chemistry.

The chemistry of α-diones has always attracted a great deal of interest because of the synthetic potential of these compounds[1,2] and because of the numerous applications associated with their chemistry (e.g. enzyme inactivation,[3] flavour chemistry,[4] etc...). In order to utilize α-diones in synthetic procedures, a variety of methods for the synthesis of monoacetals of α-diones has been developed already. Direct acetalization of unsymmetrical α-diones is very rare (it works only conveniently for aryl alkyl ketones[5]) and often difficult.[6] The problems associated with direct acetalization of α-diones are circumvented by the synthesis of the target α,α-dialkoxy ketones via alternative routes, including Grignard addition across α,α-dialkoxy esters[5] and nitriles,[2] rearrangement of α-bromo-α-fluoro ketones with alkoxides,[7] oxidation of α-hydroxy acetals,[8] epoxidation of enol ethers and subsequent oxidation of the acyloin acetals,[5] selenium catalyzed oxidation of methyl ketones,[9] etc... Despite the wealth of methodologies available for the synthesis of these monoacetals of α-diones, the synthesis of regiospecifically monoacetalized α-diones remains problematic. Novel straightforward methods for the synthesis of monoacetals of α-diones are highly desirable because of the synthetic potential of these masked compounds. For instance, they have been used for the synthesis of a variety of oxygen heterocycles,[10,11] tropolonoids,[12] α-imino ketones,[13] enones,[14] α-allenic ketones[15] and benzocyclobutenol,[16] to mention only but a few.

In the foregoing list of methods, useful strategies for attaining this goal are available but often the problem is due to the difficultly accessible starting material. Here we report a convenient synthesis of mono(dimethyl)acetals of α-diones via a straightforward and easy to accomplish method.

α-Chloro ketones **1**, which can be generated in a regiospecific way (vide infra), were converted into α-bromo-α-chloro ketones **2** by reaction with *N*-bromosuccinimide (NBS) in carbon tetrachloride in the presence of benzoyl peroxide (Scheme 1).[17] Silver ion induced reactions of α-bromo ketones have been the subject of numerous studies, the diversity of the occurring reactions being large. Depending on the reaction conditions and the substrates used, these reactions are known to give rise to Favorskii-type rearrangements (semi-benzilic type), 1,2-dehydrobrominations, α-alkoxy epoxides and α-alkoxy ketones.[18] In the majority of cases (unless carbenium ion stabilizing factors determine the outcome of the reaction, e.g. for α-aryl-α-bromo ketones) it is not possible to direct the reaction to an α-alkoxylation process. In the case of α-bromo-α-chloro ketones **2**, a silver ion induced alcoholysis would be highly feasible because of the ready formation of an α-acyl cation, which is stabilized by the α-chloro atom. When performed with silver carbonate in methanol, the former ionized species undergoes trapping by methanol to form an intermediate α-chloro ether, which further solvolyses to α,α-dimethoxy ketones **3**. The method proceeds well with aliphatic ketones, the strength of this procedure being the straightforward formation of the desired monoacetal of α-diones starting from an α-chloro ketone with the same carbon skeleton. This synthetic methodology allows the construction of α,α-dimethoxy ketones **3** in a regiospecific way. The regiospecific chlorination of ketones at the α-position is a difficult problem, but can be performed by a procedure which we disclosed recently.[19] This procedure, together with the transformations discussed above, offers an attractive route to regiospecifically constructed monoacetals of α-diones (Table 1), as exemplified for the synthesis of 3,3-dimethoxy-2-pentanone **(3b)**. Base induced ethylation of methyl acetoacetate to methyl 2-ethyl-3-oxobutanoate and subsequent chlorination with sulfuryl chloride at the active methine position provides the corresponding α-chloro-β-keto ester, which is demethoxycarbonylated in boiling 50 % sulfuric acid to afford 3-chloro-2-pentanone **(1b)**.[19] α-Bromination with NBS followed by silver induced methanolysis gives rise to 3,3-dimethoxy-2-pentanone **(3b)** in good yield. However, the reaction of 2-bromo-2-chloro-3-pentanone **(2c)** with methanol in the presence of silver carbonate afforded a complex reaction mixture. Among the reaction products, the desired 2,2-dimethoxy-3-pentanone **(3c)** (27 %), the isomeric 3,3-dimethoxy-2-pentanone **(3b)** (14 %) and methyl 2-methyl-2-butenoate (15 %) were identified, the latter being a product of the Favorskii rearrangement.



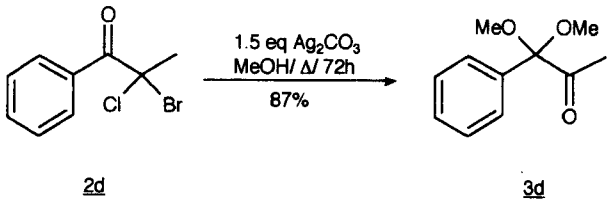
Scheme 1

Table 1. Compounds **2** and **3** Prepared

Product	Yield (%)	bp (°C)/Torr	Lit. bp (°C)/Torr
2a[a]	56	35–37/14	
2b[a]	85	53–57/17	48/15
2c[a]	55	51–55/18	
2d[a]	~ 100	–	
3a[b]	50	55–57/21	145–146/760
3b[b]	70	–	
3c[b]	27[c]	–	162.5/760
3d[d]	87		

[a] From the reaction of **1a–c** with NBS/CCl_4 during 1.5–2 h under reflux. Compound **2d** was obtained by chlorination of α-bromopropiophenone according to the literature.[7b]
[b] From the reaction of **2a–c** with Ag_2CO_3/MeOH during 24 h under reflux.
[c] Calculated on the basis of the ^1H NMR spectrum of the product isolated by preparative GC.
[d] From rearrangement of **2d** with Ag_2CO_3/MeOH during 72 h under reflux.

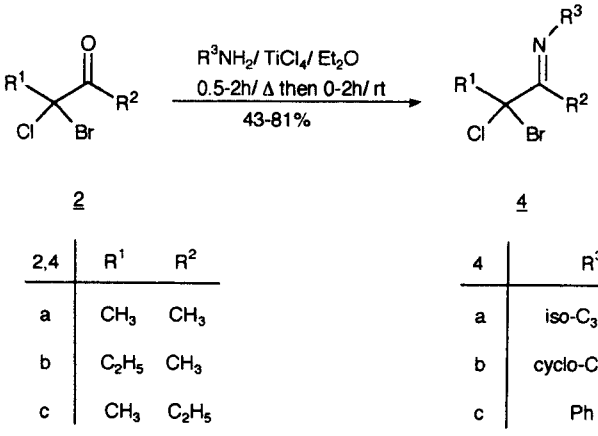
It is noteworthy that aromatic α-bromo-α-chloro ketones, such as 2-bromo-2-chloropropiophenone **(2d)**, under the given reaction conditions, rearrange to the isomeric α,α-dimethoxy ketones (Scheme 2). It seems that the presence of silver ions does not prevent the starting aromatic α-bromo-α-chloro ketones rearranging via α-alkoxyepoxides, as previously shown for rearrangements induced by alkoxides.[7]



2d 3d

Scheme 2

Another form of protected α-diones, suitable for evaluation in organic synthesis, is the α,α-dialkoxy imines.[2,20] These useful masked α-diones can be regiospecifically synthesized in a related way as discussed above. α-Bromo-α-chloro ketones **2** were converted into the corresponding new α-bromo-α-chloro ketimines **4** by reaction with primary amines in the presence of stoichiometric quantities of titanium(IV) chloride (Scheme 3, Table 2).



2 4

2,4	R^1	R^2
a	CH_3	CH_3
b	C_2H_5	CH_3
c	CH_3	C_2H_5

4	R^3
a	iso-C_3H_7
b	cyclo-C_6H_{11}
c	Ph

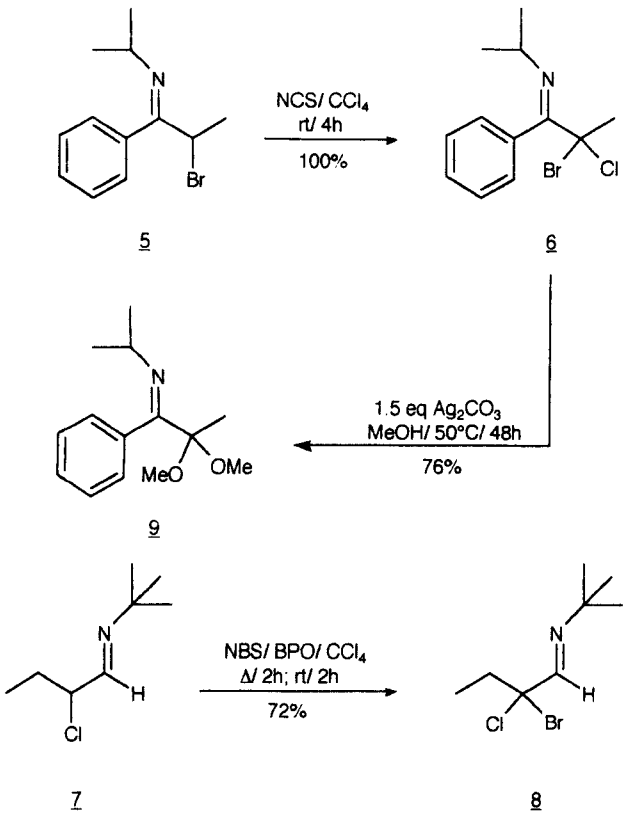
Scheme 3

An alternative method has been used for the synthesis of the aromatic α-bromo-α-chloro ketimine **6** (Scheme 4). α-Bromopropiophenone was converted to the corresponding *N*-isopropyl imine **5** in the usual manner (titanium(IV) chloride/isopropylamine/diethyl ether or benzene),[21] followed by chlorination with *N*-chlorosuccinimide in carbon tetrachloride.[7a] According to the combined way of mixed dihalogenation, the α-bromo-α-chloro aldimine **8** was prepared by bromination of α-chloro aldimine **7** with NBS (Scheme 4).

Table 2. Compounds **4,6,8–10** Prepared

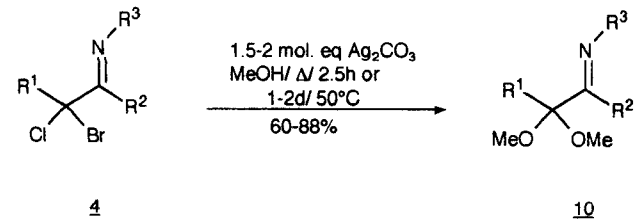
Product[a]	Reaction Conditions Time (h)/Temp.	Yield (%)	bp. (°C)/Torr	Product[b]	Reaction Conditions Time (h)/Temp. (°C)	Yield (%)
4aa	2/r.t.	67	58–63/14	**10aa**[c]	2.5/Δ	81
4ab	2/Δ	59	–[d]	**10ab**	2.5/Δ	88
4ac	0.5/Δ + 2/r.t.	43	57–59/0.1	–	–	–
4ba	0.5/Δ + 2/r.t.	81	85–89/17	**10ba**	24/50	60
4ca	2/Δ + 1/r.t.	43	81–85/16	**10ca**	48/30[e]	88
6[f]	4/r.t.	100	–	**9**	48/50	76
8[g]	2/Δ + 2/r.t.	67	83–86/12	–	–	–

[a] From the reaction of ketones **2** with $R^2NH_2/TiCl_4/Et_2O$.
[b] From the reaction of α,α-dihalo compounds **4, 6, 8** with 1.5 mol equiv of Ag_2CO_3 in MeOH.
[c] bp 60–63°C/11 Torr.
[d] Crude product was used in the next step.
[e] The reaction was carried out using 2 mol equiv of Ag_2CO_3.
[f] Prepared from **5**.
[g] Prepared from **7**.



Scheme 4

The reaction of *N*-(3-bromo-3-chloro-2-butylidene)isopropylamine **(4aa)** with silver carbonate in methanol at room temperature for 3 days revealed a 46% conversion into *N*-(3,3-dimethoxy-2-butylidene)isopropylamine **(10aa)**, together with the recovery of the rest of the starting material (Scheme 5). However, a complete conversion was observed after a reflux period of 2.5 hours, to give α,α-dimethoxy ketimine **10aa** in an isolated yield of 81%. Similarly, a variety of other α,α-dimethoxy ketimines **10** has been prepared in this way, including the *N*-cyclohexyl analogue **10ab** of the previous compound, the regioisomeric diprotected α-diones **4ba** and **4ca**, and the aromatic α,α-dimethoxy ketimine **9**. This methodology allows the regiospecific construction of α,α-dimethoxy ketimines, as proven by the synthesis of each of the isomer pair **4ba** and **4ca**. It is worth noting that α-bromo-α-chloro ketimine **6** was converted without rearrangement into α,α-dimethoxy ketimine **9** under the given reaction conditions. Contrary to this result is the conversion with rearrangement of the corresponding α-bromo-α-chloro ketone **2d** with silver carbonate in methanol into α,α-dimethoxy ketone **3d**. Thus, in this case, masking of the carbonyl group directs the reaction to proceed in a totally different way.



Scheme 5

Finally, α-bromo-α-chloro aldimine **8** with silver carbonate in methanol did not give rise to a clean reaction mixture, probably because of the instability of the α,α-dialkoxy imine. The spectroscopic data of compounds **4**, **6**, **8–10** are compiled in Table 3.

α-Chloro ketones **1b**,[19] **1c**[22] and α-bromo-α-chloro ketone **2d**[7b] were prepared according to literature procedures. 3-Chloro-2-butanone **(1a)** is commercially available. α-Bromo ketimine **5** and α-chloroaldimine **7** were prepared by condensation of the corresponding α-halocarbonyl compound with the appropriate primary amine in the presence of $TiCl_4$.[21] Satisfactory microanalyses were obtained for all the new compounds: C ± 0.15, H ± 0.13, N ± 0.15.

α-Bromo-α-chloro Ketones 2a–c; General Procedure:
According to an analogous procedure described in the literature,[17] a stirred solution (10% w/v) of α-chloro ketone **1** (0.1 mol) in CCl_4 was treated with NBS (0.1 mol) and benzoyl peroxide (2.42 g, 0.01 mol) and refluxed for 1.5–2 h. After cooling, the succinimide was filtered and washed with CCl_4. The solvent was distilled using a short Vigreux column (15 cm) and the residue distilled under vacuum.

3-Bromo-3-chloro-2-butanone **(2a)**; yield: 48%; bp 35–37°C/14 Torr.

^{1}H NMR (CCl_4): δ = 2.30 (3H, s, CH_3), 2.56 (3H, s, $CH_3C{=}O$).
IR (NaCl): ν = 1730 cm^{-1} (C=O).

3-Bromo-3-chloro-2-pentanone **(2b)**; yield: 85%; bp 53–57°C/17 Torr (Lit.[17] bp 48°C/15 Torr).

^{1}H NMR (CCl_4): δ = 1.17 (3H, t, *J* = 7 Hz, CH_3), 2.36 (2H, q, *J* = 7 Hz, CH_2), 2.52 (3H, s, $CH_3C{=}O$).
IR (NaCl): ν = 1725 cm^{-1} (C=O).
MS: *m/z* (%) = 198, 200, 202 (M^+, 3), 155, 157, 159 (0.5), 119, 121 (1), 77 (2), 75 (3), 61 (1), 53 (1), 51 (1), 49 (1), 43 (100), 42 (2), 41 (4), 40 (4), 39 (6).

2-Bromo-2-chloro-3-pentanone **(2c)**; yield: 55%; bp 51–55°C/18 Torr.

^{1}H NMR (CCl_4): δ = 2.32 (3H, s, CH_3CClBr), 1.19 (3H, t, *J* = 7 Hz, CH_3), 2.8–3.3 (2H, m, CH_2CO).
IR (NaCl): ν = 1729 cm^{-1} (C=O).
MS: *m/z* (%) = 198, 200, 202 (M^+, 1), 166, 168 (2), 141, 143, 145 (2), 119, 121 (4), 91 (2), 77 (4), 57 (100), 55 (11).

α,α-Dimethoxy Ketones 3; General Procedure:
A stirred solution (10% w/v) of α-bromo-α-chloro ketone **2** (0.03 mol) in anhydr. MeOH was treated with Ag_2CO_3 (0.045 mol) and the mixture was refluxed for 24 h, well protected from light (aluminum foil) and moisture. After cooling, the reaction mixture was filtered through a pad of K_2CO_3 and the solid was washed with CH_2Cl_2. The solvents were evaporated in vacuo to give the crude α,α-dimethoxy ketones **3** in high purity (> 94%) as evidenced by ^{1}H NMR and GC analysis. Analytical samples were obtained by preparative GC (5% SE 30, 3 m glass column). All spectroscopic data of α,α-dialkoxy ketones **3** were in good agreement with the literature data. Distillation in vacuo or column chromatography (silica gel, Et_2O/pentane, 1:1) afforded the pure α,α-dimethoxy ketones **3**.

3,3-Dimethoxy-2-butanone **(3a)**; bp 38–40°C/11 Torr (Lit.[23] bp 145–146°C/760 Torr). This compound was identical in all aspects with a commercial sample.

3,3-Dimethoxy-2-pentanone **(3b)**:

^{1}H NMR ($CDCl_3$): δ = 0.78 (3H, t, *J* = 7 Hz, CH_3), 1.6–2.1 (2H, m, CH_2), 2.23 (3H, s, CH_3CO), 3.23 (6H, s, OMe).
IR (NaCl): ν = 1730 (C=O), 2835 cm^{-1} (OMe).
MS: *m/z* (%) = no M^+, 115 (37), 103 (96), 57 (96), 43 (100).

2,2-Dimethoxy-3-pentanone **(3c)**:

^{1}H NMR ($CDCl_3$): δ = 1.36 (3H, s, CH_3), 1.06 (3H, t, *J* = 7 Hz, CH_3), 2.63 (2H, q, *J* = 7 Hz, CH_2), 3.26 (6H, s, OMe).

Table 3. Spectroscopic Data of Compounds **4,6,8–10** Prepared

Product	IR (film/KBr) $\nu_{C=N}$	^{1}H NMR (solvent/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	MS (70 eV) m/z (%)
4aa	1655	(CCl_4): 1.12 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 2.23 (3H, s, CH_3CBr), 2.48 (3H, s, CH_3C=N), 3.65 (1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	13.36 (q, $\underline{C}H_3C$=N), 22.69, 22.97 [2 q, $(CH_3)_2$], 35.80 (q, $\underline{C}H_3CBrCl$), 50.93 (d, NCH), 80.47 (s, CBrCl), 162.48 (s, C=N)	no M^+, 146, 148 (4), 135 (9), 103 (7), 84 (54), 67 (4), 58 (4), 62 (4), 43 (22), 42 (100), 41 (9), 40 (9)
4ab	1660	(CCl_4): 1.0–2.0 (10H, m, $5CH_2$), 2.23 (3H, s, CH_3CClBr), 2.46 (3H, s, CH_3C=N), 3.1–3.6 (1H, m, NCH)	13.38 (q, CH_3), 24.21, 25.82, 32.60, 32.90 (4t, $4CH_2$), 35.78 (q, $\underline{C}H_3CClBr$), 58.96 (d, NCH), 80.63 (s, CBrCl), 162.64 (s, C=N)	265, 267, 269, (M^+, 0.2), 280, 282 (0.5), 185, 187 (6), 170, 172 (2), 151 (2), 150 (5), 124 (42), 108 (2), 106 (3), 104 (8), 83 (100), 82 (3), 81 (5), 68 (6), 67 (6), 55 (48), 54 (8), 53 (13), 42 (29), 41 (25), 39 (6)
4ac	1655	($CDCl_3$): 2.20 (3H, s, CH_3CClBr), 2.60 (3H, s, CH_3C=N), 6.5–7.5 (5H, m, C_6H_5)	15.71 (q, $\underline{C}H_3C$=N), 35.68 (q, CH_3), 78.44 (s, CBrCl), 118.39 (d, C_{ortho}), 128.91 (d, C_{meta}), 123.96 (d, C_{para}), 149.25 (s, C_{quat}), 167.37 (s, C=N)	259, 261, 263 (M^+, 3), 180, 182 (5), 145 (3), 144 (10), 143 (1), 130 (3); 118 (100); 77 (25), 58 (24), 51 (13), 43 (36)
4ba	1660	($CDCl_3$): 1.09 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.19 (3H, t, J = 7, CH_3), 2.23 (s, CH_3C=N), 2.62 (2H, q, J = 7, CH_2), 3.66 [1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	11.38 (q, CH_3), 14.03 (q, CH_3), 22.63, 23.00 [2 q, $CH(\underline{C}H_3)_2$], 38.90 (t, CH_2), 51.07 (d, NCH), 88.20 (s, CClBr), 162.06 (s, C=N)	239, 241, 243 (M^+, 0.2), 224, 226, 228 (0.5), 210, 212, 214 (1), 160, 162 (5), 132 (1), 130 (1), 118, 20 (6), 110 (1), 99 (6), 84 (40), 82 (2), 68 (1), 67 (1), 65 (1), 55 (2), 53 (2), 42 (100), 41 (17), 40 (10)
4ca	1650	($CDCl_3$): 1.10 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.23 (3H, t, J = 7, CH_3), 1.23 (3H, s, CH_3C=N), 2.63 (2H, q, J = 7, CH_2), 3.68 [1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	13.08 (q, CH_3), 21.91 (q, CH_3), 23.06, 23.44 [2 q, $CH(\underline{C}H_3)_2$], 36.30 (t, CH_2), 50.70 (d, NCH), 80.50 (s, CClBr), 166.24 (s, C=N)	239, 241, 243 (M^+, 0.1), 224, 226, 228, 204, 206 (0.3), 160, 162 (3), 118, 120 (4), 98 (39), 57 (5), 56 (100), 55 (3), 43 (18), 42 (8), 41 (11), 39 (3)
6[a]	1638	(CCl_4): 1.06 (6H, d, J = 6, $CH(C\underline{H}_3)_2$], 2.66 (3H, s, CH_3CClBr), 3.22 (1H, septet, J = 7, $C\underline{H}(CH_3)_2$], 7.38 (5H, br s, C_6H_5)	23.01, 23.20 [2 q, $CH(\underline{C}H_3)_2$], 36.85 (q, CH_3), 52.86 (d, NCH), 77.73 (s, CClBr), 127.56, 129.16 (2 d, $C_{ortho+meta}$), 128.35 (d, C_{para}), 134.02 (s, C_{quat}), 165.21 (s, C=N)	287, 289, 291 (M^+, 0.2), 208, 210 (2), 166 (1), 146 (42), 139 (1), 131 (2), 130 (4), 115 (10), 104 (100), 103 (6), 89 (2), 77 (9), 63 (2), 51 (3), 44 (2), 43 (8), 41 (6)
8	1665	($CDCl_3$): 1.21 (9H, s, t-C_4H_9), 1.2 (3H, t, J = 7, CH_3), 2.55 (2H, q, J = 7, CH_2), 7.79 (1H, s, CH=N)	10.81 (q, CH_3), 30.28 (q, t-C_4H_9), 37.82 (t, CH_2), 56.65 (s, N$\underline{C}$-But), 82.87 (s, CClBr), 155.32 (d, CH=N)	no M^+, 224, 226, 228 (M^+ – Me, 2), 145 (4), 130 (6), 110 (3), 104 (23), 99 (27), 84 (27), 57 (100)
9	1650	($CDCl_3$): 1.10 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.48 (3H, s, CH_3), 3.25 [sept, 1H, J = 6, $CH(CH_3)_2$], 3.28 [6H, s, $(OCH_3)_2$], 6.9–7.6 (5H, m, C_6H_5)	22.19 (q, CH_3), 23.04 [q, $CH(\underline{C}H_3)_2$], 49.20, [q, $(OCH_3)_2$], 52.67 (d, NCH), 102.21 [s, $\underline{C}(OCH_3)_2$], 127.06, 127.85 (2 d, $C_{ortho+meta}$), 127.68 (d, C_{para}), 136.84 (s, C_{quat}), 167.79 (s, C=N)	no M^+, 204 (M^+ – OMe, 6), 203 (6), 145 (10), 105 (9), 104 (64), 103 (8), 90 (6), 89 (100), 77 (12), 51 (4)
10aa[b]	1670	($CDCl_3$): 1.16 [6H, d, J = 6, $CH(C\underline{H}_3)_2$], 1.41 (3H, s, CH_3), 1.88 (3H, s, CH_3C=N), 3.26 [6H, s, $(OCH_3)_2$], 3.75 [1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	13.00 (q, CH_3C=N), 20.99 (q, CH_3), 23.20 [q, $CH(\underline{C}H_3)_2$], 49.16 [q, $(OCH_3)_2$], 50.92 (d, NCH), 102.42 (s, OCO), 165.55 (s, C=N)	no M^+, 142 (M^+ – OMe, 8), 89 (84), 84 (27), 58 (13), 43 (54), 42 (100), 41 (21)
10ab	1668	($CDCl_3$): 1–2 (10H, m, $5CH_2$), 1.37 (3H, s, CH_3CC=N), 1.85 (3H, s, CH_3C=N), 3.21 [6H, s, $(OCH_3)_2$], 3.3 (1H, m, NCH)	13.16 (q, CH_3C=N), 21.03 (q, CH_3), 25.01 (t, $2CH_2$), 25.74 (t, CH_2), 33.14 (t, $2CH_2$), 49.19 [q, $(CH_3O)_2$], 29.81 (d, CH), 102.38 (s, OCO), 165.63 (s, C=N)	no M^+ 182 (M^+, –OMe, 7), 124 (MeC≡$N^+C_6H_{11}$, 26), 100 (7), 89 (Me(OMe)C≡O^+Me, 100], 83 (54), 55 (26), 43 (23), 42 (19), 41 (16)
10ba	1666	($CDCl_3$): 0.75 (3H, t, J = 7, $C\underline{H}_3CH_2$), 1.15 [6H, d, J = 6, $CHC\underline{H}_3)_2$], 1.81 (2H, q, J = 7 Hz, CH_2), 1.86 (3H, s, CH_3C=N), 3.21 [6H, s, $(OCH_3)_2$], 3.80 (1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	7.69 (q, CH_3), 13.95 (q, CH_3C=N), 23.33 [q, $CH(\underline{C}H_3)_2$], 26.76 (t, CH_2), 48.70 [q, $(OCH_3)_2$], 51.14 (d, NCH), 104.47 [s, $\underline{C}(OCH_3)_2$], 164.75 (s, C=N)	187 (M^+, 1), 140 (4), 114 (5), 104 (6), 103 (100), 98 (4), 84 (45), 82 (4), 59 (4), 58 (13), 57 (29), 56 (4), 55 (4), 43 (16), 42 (99), 41 (13)
10ca	1660	($CDCl_3$): 0.98 (3H, t, J = 7.5, $C\underline{H}_3CH_2$), 1.08 (6H, d, J = 6.4, $CH(C\underline{H}_3)_2$], 1.32 (3H, s, CH_3C=N), 2.22 (2H, q, J = 7.5, CH_2), 3.12 [6H, s, $(OCH_3)_2$], 3.73 [1H, sept, J = 6, $C\underline{H}(CH_3)_2$]	12.09 (q, $\underline{C}H_3CH_2$), 20.38 (t, CH_2), 22.23 (q, CH_3), 23.43 [q, $CH(\underline{C}H_3)_2$], 48.75 [q, $(OCH_3)_2$], 50.10 (d, NCH), 102.57 (s, OCO), 169.86 (s, C=N)	no M^+, 156 (7), 155 (7), 140 (16), 138 (9), 112 (13), 110 (9), 98 (22), 89 (36), 84 (33), 57 (16), 56 (100), 44 (18), 43 (31), 42 (18), 41 (18), 40 (27)

[a] Crystallizes in the refrigerator at – 20 °C.

[b] This compound was identical in all aspects to an authentic sample prepared from 3,3-dimethoxy-2-butanone and $(CH_3)_2CHNH_2$ in the presence of $TiCl_4$ (0 °C → r.t., 30 min).

IR (NaCl): ν = 1730 cm^{-1} (C=O); 2835 cm^{-1} (OMe).

MS: *m/z* (%) = no M^+, 115 (30, M^+ − OMe), 89 (100), 57 (12), 55 (9), 47 (9), 43 (84).

The reaction of 2-bromo-2-chloropropiophenone **(2d)** with Ag_2CO_3 (1.5 mol equiv) in MeOH, according to the general procedure, gave rise to the rearranged 1,1-dimethoxy-1-phenyl-2-propanone **(3d)**.

1,1-Dimethoxy-1-phenyl-2-propanone **(3d)**: This compound was identical in all aspects with the known compound.[7]

α-Bromo-α-choro Ketimines 4; General Procedure

A stirred and cooled (0 °C) solution of α-bromo-α-chloro ketone **2** (0.05 mol) in anhydr. Et_2O (5% w/v) was treated with the appropriate primary amine (0.2 mol) in one portion, immediately followed by the slow (dropwise) addition of $TiCl_4$ (0.03 mol), dissolved in pentane (10 mL). The heterogeneous mixture was further stirred at 0 °C for 1 h and, additionally, at r.t. or reflux for 1 h (depending on the substrate). The mixture was then poured into 1 N NaOH (150 mL), the Et_2O layer was separated and the aqueous layer was extracted with Et_2O (2 × 100 mL). The combined extracts were dried with anhydr. K_2CO_3 (4 h or overnight). Evaporation of the solvent afforded an oily residue which was distilled in vacuo to give pure α-bromo-α-chloro ketimines **4aa**, **4ab**, **4ac**, **4ba** and **4ca**.

***N*-(2-Bromo-2-chloro-1-phenyl-1-propylidene)isopropylamine (6):**

A solution of α-bromo ketimine **5** (7.62 g, 0.03 mol) in CCl_4 (75 mL) was treated with *N*-chlorosuccinimide (4.4 g, 0.033 mol). The mixture was stirred at r.t. for 4 h. Workup as in the previous experiment afforded α-bromo-α-chloro ketimine **6** in quantitative yield. This compound was used as such in the next experiment. In addition to the spectral data (Table 3), the structure of compound **6** was proven further by hydrolysis (2N $HCl/H_2O/CH_2Cl_2$/r.t., 10 h) into the known[7b] α-bromo-α-chloropropiophenone **(2d)**; yield: 91%.

***N*-(2-Bromo-2-chloro-1-butylidene)-*tert*-butylamine (8):**

A solution of α-chloro imine **7** (6.46 g, 0.04 mol) in CCl_4 (65 mL) was treated with NBS (7.12 g, 0.04 mol) and benzoyl peroxide (BPO) (0.48 g, 0.002 mol). The stirred mixture was refluxed for 2 h and then stirred at r.t. for 2 h. Succinimide was filtered and washed with a small amount of CCl_4, the solvent was evaporated in vacuo and the residue was distilled to give **8**; yield: 6.41 g (67%); bp 82–87 °C/14 Torr.

α,α-Dimethoxy Ketimines 10; General Procedure:

A stirred solution of α-bromo-α-chloro imines **4** and **6** (0.005 mol) in anhydr. MeOH (10% w/v) was treated with Ag_2CO_3 (0.0075 mol) and heated at the temperature and for the time indicated in Table 2. (In the case of **10ca**, 2 mol equiv of Ag_2CO_3 were used). The reaction vessel was protected from light (aluminum foil) and moisture. The mixture was filtered through a pad of K_2CO_3, which was washed thoroughly with CH_2Cl_2. The filtrate was shaken with aq 1 N NaOH (20–30 mL). The organic layer was separated, dried (K_2CO_3) and evaporated in vacuo. The mixture was treated with pentane (20 mL), filtered and again evaporated. The residue contained α,α-dimethoxy imines **10** of sufficient purity (92–97%) for further elaboration (yield 60–88%). Attempts to purify these functionalized imines by column chromatography did not result in better purities due to partial hydrolysis into the corresponding α,α-dimethoxy ketones.

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(1) Macomber, D.P.; Macomber, R.S. *J. Org. Chem.* **1975**, *40*, 1990, and references cited therein.
(2) Babler, J.; Marcuccilli, C.J. *Tetrahedron Lett.* **1987**, *28*, 4657, and references cited therein.
(3) (a) Riordan, J.F.; McElvany, K.C.; Borders Jr., C.L. *Science* **1977**, *195*, 884.
(b) Riordan, J.F. *Mol. Cell Biochem.* **1979**, *26*, 71.
(4) Flament, I. *Food Reviews Int.* **1989**, *5*, 317.
(5) Huet, F.; Pellet, M.; Lechevallier, A.; Conia, J.-M. *J. Chem. Res.* (S) **1982**, 246.
(6) Gregoire, B.; Carre, M.-C.; Caubère, P. *J. Org. Chem.* **1986**, *51*, 1419.
(7) (a) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Tetrahedron Lett.* **1980**, *21*, 2257.
(b) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *J. Org. Chem.* **1980**, *45*, 2803.
(8) Tamura, Y.; Ko, T.; Kondo, H.; Annoura, H. *Tetrahedron Lett.* **1986**, *27*, 2117.
(9) Tiecco, M.; Testaferri, L.; Tingoli, M.; Bartoli, D. *J. Org. Chem.* **1990**, *55*, 4523.
(10) Yu, Y.; Chen, G.-q.; Zhu, J.; Zhang, X.-s.; Chen, S.-x.; Tang, H.-t.; Zhang, P. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2239.
(11) Wenkert, E. *Heterocycles* **1980**, *14*, 1703.
(12) Murray, D.H.; Albizati, K.F. *Tetrahedron Lett.* **1990**, *31*, 4109.
(13) De Kimpe, N.; Verhé, R.; De Buyck, L.; Schamp, N. *Bull. Soc. Chim. Belg.* **1982**, *91*, 99.
(14) Pellet, M.; Huet, F.; Conia, J.-M. *J. Chem. Res.* (S) **1982**, 248.
(15) Bernard, D.; Doutheau, A.; Gore, J. *Tetrahedron* **1987**, *43*, 2721.
(16) Carré, M.C.; Grégoire, B.; Caubère, P. *J. Org. Chem.* **1984**, *49*, 2050.
(17) Ricard, D.; Cantacuzène, J. *Bull. Soc. Chim. Fr.* **1969**, 628.
(18) De Kimpe, N.; Verhé, R. *The Chemistry of α-Halo Ketones, α-Halo Aldehydes and α-Halo Imines*, Patai, S.; Rappoport, Z. Eds.; Wiley: Chichester, 1988.
(19) De Kimpe,N.; Brunet, P. *Synthesis* **1990**, 595.
(20) For some leading references on α,α-dialkoxy imines, see:
Babler, J. *Synth. Commun.* **1989**, *19*, 355.
Afarinkia, K.; Rees, C.W.; Cadogan, J.I.G. *Tetrahedron* **1990**, *46*, 7175.
Reynolds, L.J.; Morgan, B.P.; Hite, G.A.; Mihelich, E.D.; Dennis, E.A. *J. Am. Chem. Soc.* **1988**, *110*, 5172.
Honek, J.; Mancini, M.L.; Belleau, B. *Tetrahedron Lett.* **1983**, *24*, 257.
(21) De Kimpe, N.; Verhé, R.; De Buyck, L.; Moëns, L.; Schamp, N. *Synthesis* **1982**, 43.
(22) Föhlisch, B.; Gottstain, W. *Liebigs Ann. Chem.* **1979**, 1768.
(23) Aldrich, product number 34 355-2.
(24) Calder, D.S.; Fleer, K.B. US Patent, 2401335 (1946); *Chem. Abstr.* **1946**, *40*, 5069[8].
(25) Calder, D.S.; Fleer, K.B. US Patent, 2401336 (1946); *Chem. Abstr.* **1946**, *40*, 5069[9].