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A SIMPLE ONE-POT SYNTHESIS OF FUNCTIONALIZED KETIMINES FROM KETONES AND AMINE HYDROCHLORIDE SALTS

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Abstract. Functionalized ketimines of the general formula RR'C(=NCH$_2$Y) [R and R' = Ph, alkyl; Y= CN (**1**), CH$_2$Cl (**2**), COOMe (**3**)] have been prepared by the condensation of ketones with the corresponding primary amine hydrochloride salts [NH$_2$CH$_2$CN·HCl (**4**), NH$_2$CH$_2$CH$_2$Cl·HCl (**5**) and NH$_2$CH$_2$COOMe·HCl (**6**), respectively]. The reported reaction proceeds mildly in a single step without the need of a previous isolation of the free amine from its salt. N,N-Dimethylformamide (DMF) is used as the solvent and TiCl$_4$ as the drying agent.

The synthesis of ketimines is often accomplished by the direct condensation of ketones with primary amines: this reversible reaction can be forced towards products by azeotropic distillation of the formed water[1] or using drying-catalyst agents such as TiCl$_4$[1a,2], BuSnCl$_2$ [3], Al$_2$O$_3$ [4] and molecular sieves [5]. Also, ketimines can be prepared by the reaction of ketones with different iminating agents such as PhN(AlCl$_2$)$_2$ [6], N,N-bis(trimethylsylil) amines[7] and ArN(MgBr)$_2$.[8]

In order to test other substrates during our recent study on [3,3] sigmatropic rearrangements promoted by dimethyl carbonate, [9] we were interested in the preparation of the ketimine derivatives of aminoacetonitrile and glycine alkyl esters (**1** and **3**).

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However, starting from the available commercial aminoacetonitrile hydrochloride or glycine methyl ester salts, in the synthesis of derivatives **1** and **3** by the direct ketone-amine condensation,[10-12] the free base [NH_2CH_2Y; Y = CN (**1**); COOMe (**3**)] has to be isolated and readily reacted; in addition, long reaction times at high temperatures and water azeotropic distillation are always required. Other simple methods reported for the reaction of glycine ethyl ester hydrochloride with 1,3-diketones [13] and aldehydes [14] give poor results when applied to ketones [15]. Also, the reported transimination reactions are a valuable alternative [16], but the limit is the need of simple imines isolable only as diarylketone derivatives (Ar_2C=NH). [17]

We report here that, in the presence of DMF solvent and $TiCl_4$, the dialkyl, alkylaryl and diaryl ketones can directly condense with functionalized primary amine hydrochlorides (**4-6**) to give the corresponding ketimines under mild reaction conditions (Eq. 1).

$$RR'CO \xrightarrow[DMF,\ TiCl_4]{NH_2CH_2Y\cdot HCl} RR'C(=NCH_2Y) \qquad (1)$$

Y = CN (**1**); CH_2Cl (**2**); COOMe (**3**)

At first, the synthesis of derivatives **1** is considered. In the reaction of ketones with **4**, the use of $TiCl_4$ [1a,2a] in the presence of Et_3N, is very unsatisfactory when diethyl ether, hydrocarbons (benzene, hexane), THF or methanol are the solvents (for example, only 2-13% conversion is reached in the reaction of acetophenone with **4**). Indeed, we found that the solvent does play a crucial role: in fact, only in the presence of DMF, the reaction outcome dramatically changes: under mild conditions (1h at 35 °C and 14 h at rt), ketones may quantitatively react to give the corresponding products **1**. Results are reported in the Table (entries 1-5) where two different conditions (**A** and **B**), referring to

Table. Preparation of Ketimines RR'C(=NCH$_2$Y) using DMF and TiCl$_4$[a].

Entry	Substrate	Reagent Salt	Convn. (%, by GC) Conditions A[b]	Convn. (%, by GC) Conditions B[c]	Product	(%, by GC) Conditions A[b]	(%, by GC) Conditions B[c]	Isolated Yield (%) Conditions A[b]	Isolated Yield (%) Conditions B[c]
1	Acetophenone	**4**	95	95	**1a**: PhC(=NCH$_2$CN)CH$_3$	94	94	68	91
2	Propiophenone	**4**	80	95	**1b**: PhC(=NCH$_2$CN)Et	78	94	62	86
3	Benzophenone	**4**	70	99	**1c**: PhC(=NCH$_2$CN)Ph	68	97	61	83
4	Cyclohexanone	**4**		99	**1d**: Cy=NCH$_2$CN		93		81
5	4-Heptanone	**4**		92	**1e**: PrC(=NCH$_2$CN)Pr		88		85
6	Acetophenone	**5**		96	**2a**: PhC(=NCH$_2$CH$_2$Cl)CH$_3$		95		80
7	Propiophenone	**5**		97	**2b**: PhC(=NCH$_2$CH$_2$Cl)Et		96		89
8	Cyclohexanone	**5**		91	**2c**: Cy=NCH$_2$CH$_2$Cl		85		d
9	Acetophenone	**6**		96	**3a**: PhC(=NCH$_2$CO$_2$CH$_3$)CH$_3$		75		44

[a] For details on the reaction conditions, see experimental. [b] **A** conditions: data is referred to reactions carried out by using substrate : primary amine salt : TiCl$_4$: Et$_3$N in 1 : 3 : 0.5 : 4 molar ratio, respectively. [c] **B** conditions : data is referred to reactions carried out by using substrate : primary amine salt : TiCl$_4$: Et$_3$N in 1 : 1.3 : 0.9 : 8 molar ratio, respectively. [d] The pure product cannot be distilled because it rapidly polymerizes during heating.

the two reactant molar ratios used, are indicated. Under **A** conditions (a stoichiometric amount of $TiCl_4$ and a 3 molar excess of **4** are used), the reaction is sensitive to steric hindrance [2a,3]: conversion markedly decreases when hindered ketones are involved; moreover, the obtained moderate yields (61-68%; entries 1-3, **A** conditions) are also due to the relatively high excess of the salt **4**: in fact, tars form during the *in vacuo* distillation of the reaction mixtures [16], so that product purification becomes difficult. Instead, under **B** conditions (an overstoichiometric amount of $TiCl_4$ and a large excess of Et_3N are used), both higher conversions and good yields result (entries 1-3, **B** conditions); even the highly hindered benzophenone is quantitatively converted into the corresponding **1c** derivative (entry 3, **B**). Noticeably, the use of a slight excess of the reagent salt **4** (1.3 molar excess) may render this procedure attractive for the preparation of ketimines from costly glycino nitrile salt **4** derivatives.

Under **B** conditions , this method is also valuable for the synthesis of ketimine derivatives **2** [18] from β-chloroethylamine hydrochloride **5**. The reaction proceeds well for acetophenone, propiophenone and cyclohexanone giving the corresponding azomethines **2a-c** (entries 6-8, columns **B**).

Also in the reaction of acetophenone with **6**, the ketone completely reacts; however, due to the formation of a high boiling by-product (25% by GC), the isolated yield in the corresponding derivative **3a** is 44% (entry 9, column **B**).

The reported method represents a convenient, one-pot procedure for the ketimine synthesis by the direct condensation of ketones with functionalized primary amine salts, valuable for unstable free amines. Indeed, the promoting effect of $TiCl_4$ on the reaction rate may be exhibited only when a proper solvent is used: DMF does particularly serve this purpose. The observed behaviour is probably due to two reasons: i) DMF may assure the right polar aprotic environment to favour the coordination of the ketone carbonyl

oxygen with the titanium atom [1a]; ii) the reactant salts (**4-6**) are soluble in DMF [19], but a white precipitate (Et_3NHCl) rapidly forms when Et_3N is added so that, the acid-base equilibrium involving (**4-6**) and their conjugate bases (NH_2CH_2Y; **4a-6a**) may be favourably shifted to the right: an increased concentration of the corresponding free amine nucleophiles (**4a-6a**) result in the reaction mixture. In fact, the reagent **4-6** are also well-soluble in methanol but, contrary to DMF, an homogeneous solution is still observed after the addition of the Et_3N . Other solvents are unefficient because they scarcely solubilize the salts **4-6**.

In addition, appropriate reaction conditions allows the reaction to proceed also for highly hindered ketones.

Experimental

General. All compounds were ACS grade and were employed without further purification. Melting points were determined on a Buchi 535 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker (200 MHz) spectrometer using $CDCl_3$ with TMS as the internal standard. GC analyses were performed on a Varian GC 3300. GC/MS analyses were performed on a HP 5971 mass detector coupled to a HP 5890 gas chromatograph.

General Procedure for The Preparation of Ketimines 1-3 (Table, B Conditions). A mixture of the ketone, the amine hydrochloride salt (**4-6**), Et_3N (in 1 : 1.3 : 8 molar ratio, respectively) and DMF (7 mL/g ketone) was loaded in a round-bottomed, two-necked flask fitted with a refluxing condenser and a dropping funnel both capped with $CaCl_2$ tubes. A white precipitate (Et_3NHCl) was rapidly formed; then, the suspension was thoroughly stirred magnetically for 30 min at rt [19]. A n-pentane (1 M) solution of $TiCl_4$ (0.9 molar with respect to the substrate) was carefully added dropwise to the slurry (10 mL addition required ~10 min, being the reaction exothermic). After the

addition was completed, the mixture was refluxed (35-40 °C) for 1 h and then allowed to stand 14 h at rt. The suspension was poured into diethyl ether (~30 mL/g substrate) and stirred at rt for 40 min: a further precipitation occurring. Then, the solid was filtered and washed with diethyl ether. The light solvents (n-pentane and ether) and Et_3N were removed by rotary evaporation while DMF was distilled under vacuum (bp= 48-50 °C/20 mm Hg). The crude brown residue was recrystallized from n-pentane-diethyl ether (95 : 5 v/v; products **1a-c** and **3a**) or distilled (products **1d-e** and **2a-b**).

Under **A** conditions, the reactions were carried out using the same procedure, but a different substrate: amine hydrochloride salt (**4**), Et_3N molar ratio was employed (1 : 3 : 4 molar ratio, respectively).

The following data refers to ketimines **1-3** obtained according to **B** conditions.

N-(1-Phenylethylidene)-cyanomethylamine 1a. Starting from 2.0 g of acetophenone, 2.4 g of **1a** was isolated (99% pure by GC; 91% yield); mp =38-40 °C. ^1H NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 4.40 (s, 2H, CH_2), 7.32-7.95 (m, 5H, Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 158 (M^+, 21), 157 (56), 144 (11), 143 (100), 116 (28), 103 (43), 81 (10), 77 (15), 51 (11).

N-(1-Phenylpropylidene)-cyanomethylamine 1b. Starting from 3.0 g of propiophenone, 3.3 g of **1b** was isolated (98% pure by GC; 86% yield); mp =45-46 °C. ^1H NMR ($CDCl_3$) δ: 1.15 (t, 3H, CH_3), 2.75 (q, 2H, CH_2), 4.45 (s, 2H, CH_2), 7.30-7.95 (m, 5H, Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 172 (M^+, 12), 171 (43), 144 (12), 143 (100), 116 (20), 103 (37), 77 (11), 51 (7).

N-(1,1-Diphenylmethylidene)-cyanomethylamine 1c. Starting from 3.0 g of acetophenone, 3.0 g of **1c** was isolated (97% pure by GC; 83% yield); mp =80-82 °C (Lit.[16] mp=81-82 °C). ^1H NMR ($CDCl_3$) δ: 4.25 (s, 2H, CH_2), 7.12-7.75 (m, 10H, 2Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 220 (M^+, 58), 219 (100), 193 (25), 180 (62), 166 (10), 165 (36), 116 (25), 103 (53), 77 (31), 76 (14), 51 (22).

N-Cyclohexylidene-cyanomethylamine 1d.[20] Starting from 4.0 g of cyclo hexanone, 4.5 g of **1d** was isolated (95% pure by GC; 81% yield); bp = 87-89 °C/0.1 mm Hg. ^{1}H NMR ($CDCl_3$) δ: 1.35-1.85 (m, 6H, $3CH_2$), 2.15-2.35 (m, 4H, $2CH_2$), 4.15 (s, 2H, CH_2). Mass spectrum (70 eV) *m/z* (relative intensity): 136 (M^+, 25), 135 (11), 121 (19), 108 (20), 107 (24), 94 (10), 93 (100), 80 (35), 67 (10), 66 (9), 53 (13).

N-(4-epthylidene)-cyanomethylamine 1e. Starting from 5.0 g of 4-heptanone, 5.6 g of **1e** was isolated (98% pure by GC; 85% yield); bp = 72-74 °C/0.1 mm Hg. ^{1}H NMR ($CDCl_3$) δ: 1.35 and 1.4 (2t, 6H, $2CH_3$), 1.35-1.6 (2q, 4H, $2CH_2$), 2.05-2.25 (2q, 4H, $2CH_2$), 4.15 (s, 2H, CH_2). Mass spectrum (70 eV) *m/z* (relative intensity): 152 (M^+, 1), 151 (1), 137 (28), 124 (33), 110 (16), 109 (100), 96 (94), 82 (31), 67 (26), 54 (7).

N-(1-Phenylethylidene)-2-chloroethylamine 2a. Starting from 2.0 g of acetophenone, 2.4 g of **2a** was isolated (96% pure by GC; 80% yield); bp = 103-105 °C/ 0.7 mm Hg. ^{1}H NMR ($CDCl_3$) δ: 2.25 (s, 3H, CH_3), 3.70-3.80 (m, 4H, $2CH_2$), 3.85-3.95 (m, 4H, $2CH_2$), 7.35-7.85 (m, 5H, Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 183 (3), 181 (M^+, 9), 168 (6), 166 (19), 146 (12), 132 (70), 104 (55), 103 (14), 91 (100), 77 (35), 65 (15), 63 (34), 51 (23). The colorless freshly-distilled product turned to yellow in few days even when stored at 0-4 °C.

N-(1-Phenylpropylidene)-2-chloroethylamine 2b. Starting from 4.0 g of propiophenone, 5.2 g of **2b** was isolated (99% pure by GC; 89% yield); bp = 88-90 °C / 0.3 mm Hg. ^{1}H NMR ($CDCl_3$) δ: 1.15 (t, 3H, CH_3), 2.75 (q, 2H, CH_2), 3.70-3.80 (m, 4H, $2CH_2$), 3.85-3.95 (m, 4H, $2CH_2$), 7.35-7.85 (m, 5H, Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 197 (3), 196 (10), 195 (M^+, 9), 194 (29), 168 (20), 166 (63), 146 (9), 117 (10), 105 (11), 104 (100), 103 (14), 91 (39), 77 (30), 65 (16), 63 (45), 51 (16). The pale yellow freshly-distilled product brownished in few days even when stored at 0-4°C.

N-Cyclohexylidene-2-chloroethylamine 2c. [18] According to the above reported procedure, cyclohexanone (5.0 g) gave the corresponding **2c**: at 91% conversion, **2c** was 85% (by GC; the structure was confirmed by GC/MS); the product was not isolable by distillation because polymerization occurred during heating. Mass spectrum (70 eV) *m/z* (relative intensity): 161 (3), 159 (M^+, 10), 118 (10), 116 (29), 110 (100), 105 (4), 103 (11), 81 (11), 65 (7), 63 (17), 54 (14)

Methyl N-(1-Phenylethylidene)-glycinate 3a. Starting from 2.0 g of acetophenone, 1.4 g of **3a** was isolated (98% pure by GC; 44% yield); mp = 54-56 °C. ^1H NMR ($CDCl_3$) δ: 2.25 (s, 3H, CH_3), 3.80 (s, 3H, CH_3), 4.35 (s, 2H, CH_2), 7.30-7.85 (m, 5H, Ph). Mass spectrum (70 eV) *m/z* (relative intensity): 191 (M^+, 7), 132 (53), 118 (9), 103 (11), 91 (100), 77 (17), 51 (8).

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precipitate appeared. Before adding the n-pentane solution of $TiCl_4$, the suspension was cooled to rt.

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