Reactivity of Imine Anions with Esters: A General Method for the Synthesis of Enamino Ketones

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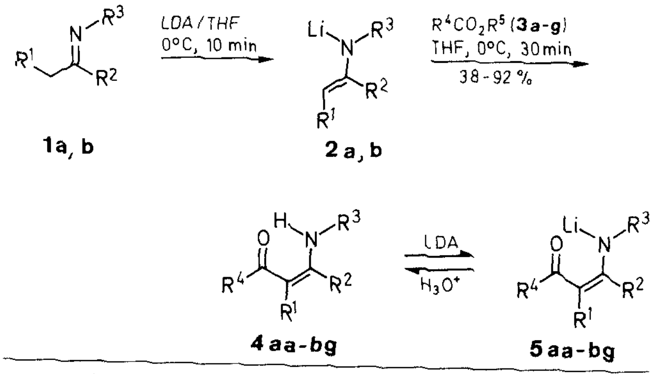
The reaction of α-metalated imines with esters under mild conditions leads to the Schiff base of unsymmetrical 1,3-diketones (enamino ketones) in good yields.

α-Metalated imines are versatile nucleophiles capable of carbon–carbon bond formation.[1] Therefore, they are a useful tool for the introduction of a masked carbonyl function in the β-position with respect to an electrophilic carbon, and the reaction of metalated Schiff bases with aldehydes and ketones has been widely studied.[2,3] The corresponding reaction with esters is reported in literature[4] in the case of lithiated α-alkylcycloenamines leading to enamino ketones.

In order to find a general entry to Schiff bases of unsymmetrical 1,3-diketones, we extended the study of this reaction to α-metalated acyclic imines of which only one example was hitherto reported.[2] When imine anions **2** (metalated Schiff bases[2]), prepared from imines **1**, according to standard methods,[2] are allowed to react with esters **3** at 0 °C in tetrahydrofuran for 30 minutes, enamino ketones were obtained in good to moderate yield.

In contrast to the reaction of alkyllithium derivatives with esters, which predominantly gives double alkylation leading to alcohols, the present reaction exclusively affords ketones. An overall twofold excess of base is required for the reaction to go to completion, thus indicating that a second equivalent of the lithium derivative preferentially metalates the imine nitrogen of compound **4** as soon as it is formed. Obviously, the anionic form of **4** prevents it from a further nucleophilic attack by the imine anions.[5]



1, 2	R^1	R^2	R^3	**3**	R^4	R^5
a	H	Me	*i*-Pr	**a**	Ph	Me
b	$-(CH_2)_3-$		*c*-C_6H_{11}	**b**	4-MeC_6H_4	Et
				c	4-ClC_6H_4	Me
				d	2-ClC_6H_4	Et
				e	$PhCH_2$	Et
				f	Me	Ph
				g	Pr	Et

4–5	R^1	R^2	R^3	R^4
aa	H	Me	*i*-Pr	Ph
ab	H	Me	*i*-Pr	4-MeC_6H_4
ac	H	Me	*i*-Pr	4-ClC_6H_4
ad	H	Me	*i*-Pr	2-ClC_6H_4
ae	H	Me	*i*-Pr	$PhCH_2$
af	H	Me	*i*-Pr	Me
ag	H	Me	*i*-Pr	Pr
ba	$-(CH_2)_3-$		*c*-C_6H_{11}	Ph
bb	$-(CH_2)_3-$		*c*-C_6H_{11}	4-MeC_6H_4
bc	$-(CH_2)_3-$		*c*-C_6H_{11}	4-ClC_6H_4
bg	$-(CH_2)_3-$		*c*-C_6H_{11}	Pr

Finally the reaction works well with both aliphatic and aromatic esters and provides a mild general method for the synthesis of unsymmetrical enamino ketones, which are reported to be obtained from direct condensation of amines and diketones, only when the two carbonyl groups exhibit largely different reactivity (i.e. aromatic vs. aliphatic carbonyls).[6,7] Unsymmetrical enamino ketones can be used as bidentate ligands in transition metal complexes.[7]

Table. Enamino Ketones **4** Prepared

Product	Yield[a] (%)	mp (°C)[b] (hexane)	Molecular Formula[b] or Lit. bp (°C)/mbar	IR[c] ν(cm^{-1})	^{1}H-NMR (CDCl$_3$/TMS) δ, J(Hz)	^{13}C-NMR (CDCl$_3$/TMS) δ	MS (70 eV) m/z (%)
4aa	68	56–58	83/0.013[7]	1600, 1550	1.16 (d, 6H, J = 6.4), 1.95 (s, 3H), 3.77 (d hept, 1H, J = 6.4, 8.8), 5.52 (s, 1H), 7.30–7.80 (m, 5H), 11.39 (d, 1H, J = 7.6)	19.18 (q), 23.82 (q), 44.98 (d), 91.71 (d), 126.80 (d), 128.11 (d), 130.31 (d), 140.49 (s), 163.59 (s), 187.33 (s)	203 (M^+, 43), 160 (21), 105 (72), 77 (100)
4ab	78	61	$C_{14}H_{19}NO$ (217.3)	1605, 1585	1.31 (d, 6H, J = 6.5), 2.10 (s, 3H), 2.36 (s, 3H), 3.72–3.91 (m, 1H), 5.57 (s, 1H), 7.15–7.78 (m, 4H), 11.35–11.57 (br s, 1H)	19.18 (q), 21.39 (q), 23.05 (q), 44.92 (d), 91.50 (d), 126.83 (d), 128.82 (d), 137.75 (s), 140.54 (s), 163.30 (s), 187.26 (s)	217 (M^+, 100), 174 (82), 119 (100), 98 (90), 84 (70)
4ac	87	75	$C_{13}H_{16}ClNO$ (237.7)	1590, 1580	1.27 (d, 6H, J = 6.4), 2.09 (s, 3H), 3.75–3.87 (m, 1H), 5.55 (s, 1H), 7.35 (d, 2H, J = 8.5), 7.79 (d, 2H, J = 8.5), 11.50 (br s, 1H)	19.17 (q), 23.77 (q), 45.07 (d), 91.47 (d), 128.21 (d), 128.31 (d), 136.32 (s), 138.87 (s), 163.96 (s), 185.76 (s)	237 (M^+, 97), 194 (70), 139 (100), 111 (78), 98 (89)
4ad	67	oil	$C_{13}H_{16}ClNO$ (237.7)	1600, 1515	1.30 (d, 6H, J = 6.4), 2.07 (s, 3H), 3.72–3.90 (m, 1H), 5.17 (s, 1H), 7.27–7.47 (m, 4H), 11.25 (br s, 1H)	19.00 (q), 23.72 (q), 45.15 (d), 95.85 (d), 126.46 (d), 129.14 (d), 129.60 (d), 130.00 (d), 130.70 (s), 141.57 (s), 163.73 (s), 188.24 (s)	237 (M^+, 66), 202 (100), 139 (97), 98 (70)
4ae	54 (74)[d]	oil	$C_{14}H_{19}NO$ (217.3)	1510, 1490	1.16 (d, 6H, J = 6.4), 1.85 (s, 3H), 3.49 (s, 2H), 3.62 (d hept, 1H, J = 6.4, 8.8), 4.87 (s, 1H), 7.25 (m, 5H), 10.86 (br d, 1H, J = 7.8)	18.75 (q), 23.75 (q), 44.79 (d), 48.91 (t), 94.15 (d), 126.20 (d), 128.38 (d), 129.37 (d), 137.56 (s), 162.75 (s), 194.24 (s)	217 (M^+, 31), 126 (100), 108 (71), 91 (64)
4af	47 (66)[d]	oil	85/4[7]	1600, 1505	1.18 (d, 6H, J = 6.4), 1.90 (s, 3H), 1.95 (s, 3H), 3.66 (d hept, 1H, J = 6.4, 8.9), 4.87 (s, 1H), 10.80 (br d, 1H)	18.54 (q), 23.76 (q), 28.67 (q), 44.58 (d), 94.83 (d), 161.77 (s), 194.41 (s)	141 (M^+, 72), 126 (59), 108 (26), 84 (100)
4ag	50 (71)[d]	oil	$C_{10}H_{19}NO$ (169.2)	1610, 1585	0.90 (t, 2H, J = 7.4), 1.21 (d, 6H, J = 6.4), 1.90 (s, 3H), 2.17 (t, 3H, J = 7.6), 1.59 (sext, 2H, J = 7.4), 3.64–3.76 (m, 1H), 4.85 (s, 1H), 10.87 (br s, 1H)	14.07 (q), 18.65 (q), 19.37 (t), 23.79 (q), 43.90 (t), 44.61 (d), 94.49 (d), 161.82 (s), 197.54 (s)	169 (M^+, 82), 126 (100), 108 (65), 84 (89)
4ba	86	80–83	$C_{18}H_{23}NO$ (269.3)	1605, 1580	1.19–1.47 (m, 5H), 1.54–1.63 (m, 1H), 1.73–1.98 (m, 6H), 2.67 (t, 2H, J = 7.3), 2.79 (t, 2H, J = 6.9), 3.31 (m, 1H), 7.36 (m, 3H), 7.62 (m, 2H), 10.55 (br d, 1H)	23.00 (t), 24.55 (t), 25.32 (t), 31.48 (t), 34.05 (t), 53.80 (d), 103.86 (s), 127.24 (d), 127.73 (d), 129.23 (d), 142.37 (s), 169.60 (s), 188.09 (s)	269 (M^+, 45), 186 (100), 105 (74), 77 (35)
4bb	92	96–98	$C_{19}H_{25}NO$ (283.4)	1605, 1575	1.27–1.47 (m, 5H), 1.65–1.52 (m, 1H), 1.67–2.00 (m, 6H), 2.35 (s, 3H), 2.57–2.80 (m, 4H), 3.42–3.22 (m, 1H), 7.17 (d, 2H, J = 7.9), 7.56 (d, 2H, J = 7.9), 10.52 (br s, 1H)	21.39 (q), 23.03 (t), 24.58 (t), 25.35 (t), 31.45 (t), 31.65 (t), 34.09 (t), 53.77 (d), 103.84 (s), 127.39 (d), 128.42 (d), 139.33 (s), 139.62 (s), 169.38 (s), 188.01 (s)	283 (M^+, 89), 264 (67), 200 (100), 119 (84), 91 (64)
4bc	53	89–90	$C_{18}H_{22}ClNO$ (303.8)	1605, 1570	1.27–1.47 (m, 5H), 1.55–1.65 (m, 1H), 1.75–2.00 (m, 6H), 2.60–2.75 (m, 4H), 3.25–3.40 (m, 1H), 7.32 (d, 2H, J = 8.5), 7.58 (d, 2H, J = 8.5), 10.57 (br s, 1H)	23.01 (t), 24.52 (t), 25.29 (t), 31.43 (t), 33.99 (t), 53.89 (d), 103.72 (s), 127.97 (d), 128.79 (d), 135.15 (s), 140.63 (s), 170.14 (s), 186.36 (s)	303 (M^+, 80), 220 (100), 139 (91), 111 (53)
4bg	87	oil	$C_{15}H_{25}NO$ (235.3)	1620, 1560	0.93 (t, 3H, J = 7.4), 1.22–1.37 (m, 6H), 1.62 (sext, 7H, J = 7.4), 1.70–1.88 (m, 6H), 2.28 (t, 2H, J = 7.4), 2.52–2.60 (m, 4H), 3.14–3.25 (m, 1H), 9.65 (br s, 1H)	14.11 (q), 17.84 (t), 21.47 (t), 24.48 (t), 25.26 (t), 29.38 (t), 31.22 (t), 34.13 (t), 42.09 (t), 53.28 (d), 103.67 (s), 165.36 (s), 195.22 (s)	235 (M^+, 90), 192 (100), 174 (78), 165 (70), 152 (78), 110 (90), 82 (71)

[a] Yield of isolated product **4** based on **3**.

[b] Satisfactory microanalyses obtained: C, H, N ±0.1.

[c] Oils are recorded as film and solids.

[d] GC yields are given in parenthesis. Compound partially hydrolyses to 1,3-diketones during workup.

Melting points are uncorrected and were determinated with a Büchi apparatus. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on VXR 300 spectrometers in $CDCl_3$ solutions with TMS as internal standard. Mass spectra were recorded on Hewlett-Packard 5988A and HP 88A spectrometers equipped with a 5870A Data System. IR spectra were recorded as films or nujol mulls on Perkin-Elmer 337 and 297 grating spectrophotometers. High Resolution Gas Chromatography (HRGC) was performed using a Carlo Erba Fractovap 4160 or a Varian 3300 instrument with FID detector (column: SPB^{TM} – 1, 30 m, 0.32 mm ID, 0.25 μm by Supelco). Imines **1a,b** were synthesized according to the literature.[8] Esters **3a–g** are commercial products or were prepared from the corresponding acids. Lithium diisopropylamide (LDA) was prepared from BuLi (1.6 M in hexane) and an equimolecular amount of diisopropylamine (3 M in dry THF) at r.t. under a N_2 atmosphere.

Reaction of Imine Anions 2 with Esters 3; General Procedure:

A freshly prepared LDA solution (10 mmol) is added to a stirred solution of the imine **1** (6 mmol) in THF (4 mL) at 0 °C under nitrogen. After 10 min a solution of ester 3 (4 mmol) in THF (3 mL) is added and the mixture is allowed to stand at 0 °C under stirring for about 30 min. Then water (15 mL) is carefully added, and the mixture is extracted with CH_2Cl_2 (2 × 20 mL), dried (Na_2SO_4), and concentrated at reduced pressure. Crude products **4** are chromatographed on a silica gel column (20 cm × 2 cm; 70–230 mesh) using a 95:5 mixture of hexane/EtOAc (95:5) as eluent (Table).

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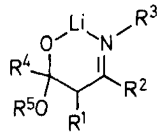
(5) Another possible explanation originates from the peculiar structure of the carbon tetrahedral intermediate, which is stabilized by an intramolecular coordination of lithium at the nitrogen atom as follows:



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