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AMINATION OF α,β-UNSATURATED γ-DICARBONYL COMPOUNDS WITH METHOXYAMINES

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ABSTRACT: Methoxyamines were found to be efficient aminating agents for α,β-unsaturated γ-dicarbonyl compounds to give the corresponding α,β-diacyl enamines by a one-pot, two-step procedure.

Enamines are of great importance for carbon-carbon bond formations in organic synthesis.[1] However, there are few reports on intermolecular replacement of a vinylic hydrogen by an amino group, despite it being one of the most simple synthetic routes to enamines. As examples of transition metal catalyzed amination of olefins, palladium-catalyzed arylamination[2] and amidation[3], and rhodium-catalyzed secondary amination[4] are known, but oxidants are required in these reactions. Some aminating agents such as

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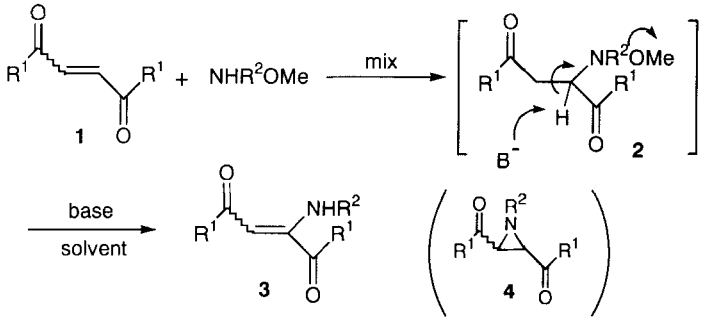
sulfilimines[5] or *N*-ethoxycarbonyliminopyridinium ylide[6] can aminate α,β-unsaturated γ-dicarbonyl compounds to afford *N*-unsubstituted α,β-diacyl enamines. However, the reactions with these aminating agents often produced aziridines or *N*-ethoxycarbonyl derivatives as side reaction products. To the best of our knowledge very few simple and practical aminations of olefins to give enamines have been reported so far. Recently we found that methoxyamine was a highly efficient aminating agent for nitroarenes,[7] nitroolefins[8] and chalcons.[9] In this report we describe an amination of α,β-unsaturated γ-dicarbonyl compounds with methoxyamines to give α,β-diacyl enamines.

We found that amination of *trans*-1,2-dibenzoylethylene **1a** with methoxyamine gave 1-amino-1,2-dibenzoylethylene **3a** in 83% yield (Table 1, entry 1). The amination was comprised of two subsequent reactions, namely a Michael addition followed by a base-induced β-elimination, in a one-pot process. The presence of a base in the first step resulted in formation of a complex mixture of products. However, after formation of the Michael-adduct **2** in the reaction of the α,β-unsaturated γ-dicarbonyl compound **1** with methoxyamine without a base was completed, subsequent treatment of **2** with a base gave the desired α,β-diacyl enamine **3**. In a similar manner, dimethyl maleate **1c**, dibutyl maleate **1e** and *N*-phenylmaleimide **1f** were successfully aminated to give dimethyl 2-aminofumarate **3c**, dibutyl 2-aminofumarate **3e** and 2-amino-*N*-phenylmaleimide **3f** in 54, 71 and 54% yields, respectively (entries 3, 5 and 6). Methylamination with *N*,*O*-dimethylhydroxylamine also took place to give **3b** and **3d** in 86 and 68% yields (entries 2 and 4). The anticipated aziridine derivative **4** was not produced in any cases. Analogous aminations using sulfilimines[5] or *N*-ethoxycarbonyliminopyridinium ylide[6] as aminating agents proceeded in the absence of a base and the mechanisms were explained by a 1,2-hydride shift or a prototropic migration of the Michael adduct. In contrast, in our

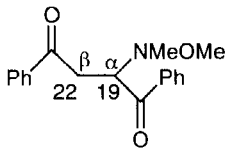
Table 1. Amination of α,β-unsaturated γ-dicarbonyl compounds **1** with methoxyamines[a]



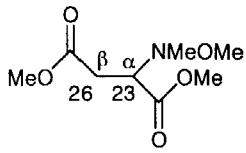
entry		R^1	R^2	base	time for Michael addition	solvent	yield of **3** (%)[b]
1	**a**	Ph	H	NaOMe	4 h	MeOH	83[c]
2	**b**	Ph	Me	NaOMe	6 h	MeOH	86[c]
3	**c**	OMe	H	NaOMe	10 d	MeOH	54[d]
4	**d**	OMe	Me	NaOMe	10 d	MeOH	68[d]
5	**e**	O^nBu	H	DBU	7 d	dioxane	71
6	**f**	—N—Ph	H	NaOMe	1 h	EtOH	54[c]

[a] Unless otherwise noted, after Michael-adduct **2** was once obtained by neat reaction of **1** with NHR^2OMe (1.5 equiv.) at room temperature for 1 h - 10 d, the base (1 equiv.) in the solvent was added to the reaction mixture. See typical experimental procedure. [b] Isolated yield. [c] In the first step, 1.0 equivalent of NHR^2OMe was used in methanol solvent. [d] The Michael-adduct **2** obtained in the first step was added to the base in the solvent.

amination the reaction proceeds presumably *via* a simple base-induced β-elimination in the Michael-adduct **2** (Table 1). The p*K*a values of **2** predicted by CAMEO[10] suggest that the base can abstract an α-proton rather than a β-proton (Scheme 1). Therefore, only one equivalent of a base was sufficient for this base-induced β-elimination and **4** was not formed in this case. This feature is different from that in the amination of chalcones with methoxyamine.[9]



2b



2d

Scheme 1

In summary, we have demonstrated a facile one-pot synthesis of α,β–diacyl enamines utilizing a novel amination of α,β–unsaturated γ–dicarbonyl compounds with methoxyamines. Methoxyamine has been established as an efficient and broadly applicable aminating agent not only for nitroarenes but also for some electron deficient olefins.

Typical experimental procedure: A mixture of α,β–unsaturated γ–dicarbonyl compound **1** (1 mmol) and methoxyamine (1.5 mmol) was stirred at room temperature for 1 h-10 d. After **1** was completely consumed the solvent (3 ml) was added to the reaction mixture followed by addition of a base (1 mmol) in the solvent (2 ml) at room temperature. After stirring for 10 min. at the same temperature the reaction was quenched with saturated aq. NH_4Cl, and the product was extracted with AcOEt and purified by silica gel column chromatography.

1-Amino-1,2-dibenzoylethylene (3a)[5a]

mp 136 - 138 °C (Lit.[5a] 136 - 137 °C); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 6.07 (br s, 1H), 6.21 (s, 1H), 7.36 - 7.89 (m, 10H), 9.53 (br s, 1H).; ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 97.36, 127.26, 128.39, 128.45, 129.72, 131.82, 133.32, 135.31, 139.19, 152.63, 191.57, 193.48.

1-Methylamino-1,2-dibenzoylethylene (3b)[11]

mp 100 - 103 °C (Lit.[11] 102 - 104 °C); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 2.92 (d, J = 5.61 Hz, 3H), 5.77 (s, 1H), 7.35 - 8.07 (m, 10H), 10.76 (br s, 1H).; ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 31.38, 90.46, 127.06, 128.25, 129.00, 130.01, 131.23, 134.43, 134.77, 139.43, 161.64, 189.94, 191.61

Dimethyl 2-aminofumarate (3c)[6]

^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.71 (s, 3H), 3.87 (s, 3H), 5.50 (s, 1H).; ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 50.82, 53.03, 88.55, 146.04, 164.06, 170.19

Dimethyl 2-(methylamino)fumarate (3d)[12]

^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 3.02 (d, J = 5.28 Hz, 3H), 3.67 (s, 3H), 3.84 (s, 3H), 5.09 (s, 1H), 8.00 (br s, 1H).; ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 31.54, 50.53, 52.45, 86.36, 152.02, 163.95, 170.48.

Dibutyl 2-aminofumarate (3e)[13]

^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 0.94 (t, J = 7.26 Hz, 3H), 0.96 (t, J = 7.26 Hz, 3H), 1.34 - 1.48 (m, 4H), 1.59 - 1.75 (m, 4H), 4.12 (t, J = 6.60 Hz, 2H), 4.25 (t, J = 6.60 Hz, 2H), 5.50 (s, 1H).

2-Amino-*N*-phenylmaleimide (3f)[5a]

mp 105 - 106 °C (Lit.[5a] 108 °C); ^{1}H-NMR ($CDCl_3$, 270 MHz) δ: 5.11 (s, 1H), 5.35 (br s, 2H), 7.33 - 7.47 (m, 5H).; ^{13}C-NMR ($CDCl_3$, 67.8 MHz) δ: 88.61, 125.86, 127.40, 128.93, 131.72, 147.89, 166.70, 171.32

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