Synthesis of α-Acylamino-β-oxo Acid Esters[1]

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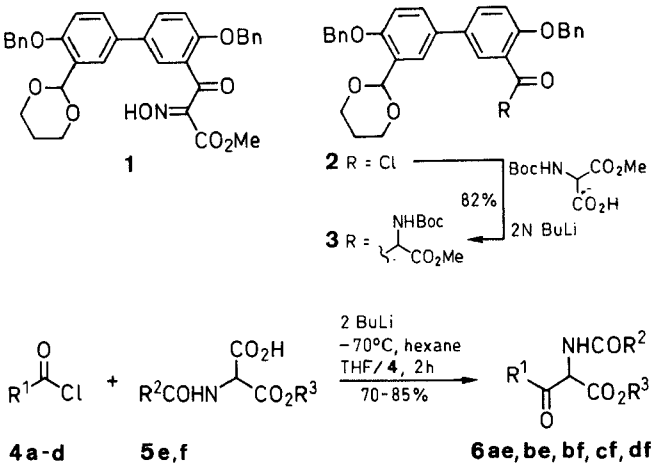
α-Acylamino-β-oxo acid esters are prepared by reaction of carboxylic acid chlorides with the dilithium derivative of alkyl hydrogen (acylamino)malonate.

The title α-acylamino-β-oxo acid esters **6** can be hydrogenated via dynamic kinetic resolution using ruthenium BINAP catalysts to yield *erythro*-α-amino-β-hydroxy esters with excellent enantio- and diastereoselectivities.[2] The configurations of the two new stereogenic centres are determined by the configuration of the ligand in the homogeneous catalyst.

Suitably protected α-acylamino-β-oxo acid esters are usually prepared by a reaction sequence comprising Claisen condensation, oximation of the β-oxo acid esters by nitrous acid, and reduction with concomitant acylation. Few published methods concern the acylation of CH-acidic glycine esters, i.e. of dilithiated methyl hippurate[3] or of isocyano acetate.[4] In the course of the total synthesis of biphenomycin A,[5] however, we were not able to achieve reduction of the oxime **1**. Therefore, we have developed a smooth, one-step synthesis of the α-amino-β-oxo acid ester **3** by reaction of the carboxylic acid chloride **2** with the dilithium derivative of alkyl hydrogen (*tert*-butoxycarbonylamino)malonate.[5] We now describe further examples of this methodology.

Alkyl hydrogen (acylamino)malonate **5** is easily accessible from the corresponding commercially available dialkyl aminomalonate hydrochloride, and is metalated to the dianion by treatment with 2 equivalents of butyllithium. The use of more than two equivalents of the lithium derivative is visualized with benzylidenebenzylamine as the indicator.



4,6	R^1	4,6	R^1	5,6	R^2	R^3
a	n-C_5H_{11}	c	Bn	e	BnO	Me
b	Ph	d	$(CH_2)_2Ph$	f	*t*-BuO	Et

Acylation of the dilithium derivative was best achieved with carboxylic acid chlorides; other active carboxylic acid derivatives were found to be less suitable. Yields of up to 70% were realized with 1.2 equivalents of the dilithium compound and in excess of 80% with 2 equivalents of the dilithium derivative. The acylation of magnesium and lithium salts of malonyl monoesters and α-alkyl-substituted malonyl monoesters have been reported repeatedly.[6]

The ^{1}H NMR spectra were recorded on a Bruker AC-F (250 MHz). Melting points (Reichert microscope) are uncorrected. TLC was

Table. α-Amino-β-oxo Esters Prepared via Aminomalonic Acid Monoester

Product	Yield[5] (%)	mp (°C)	t_R (min)	^{1}H NMR (250 MHz, TMS) δ, J (Hz)
6ae	70	oil	4.10[a]	0.84 (t, 3H, J = 6.8), 1.1–1.35 (m, 4H), 1.35–1.55 (m, 2H), 2.59 (t, 2H, J = 7.2), 3.33 (s, 3H), 5.05 (d, 1H, 8.2), 5.07 (s, 2H), 7.36 (s, 5H), 8.15 (d, 1H, J = 8.2)[c]
6be	80	oil	5.77[a]	3.68 (s, 3H), 5.07 (s, 2H), 6.00 (d, 1H, J = 8.3), 7.33 (s, 5H), 7.50–7.75 (m, 3H), 7.96 (d, 2H, J = 7.2), 8.42 (d, 1H, J = 8.3)[c]
6bf	85	70–73	2.90[a]	1.13 (t, 3H, J = 7.1), 1.38 (s, 9H), 4.13 (dq, 2H, J = 1.5, 7.1), 5.85 (d, 1H, J = 8.5), 7.50–7.75 (m, 3H), 7.82 (d, 1H, J = 8.3), 7.95 (d, 2H, J = 7.4)[c]
6cf	82	oil	3.18[a]	1.19 (t, 3H, J = 7.1), 1.41 (s, 9H), 3.95 (d, 2H, 2.7), 4.14 (dq, 2H, J = 2.4, 7.1), 5.02 (d, 1H, J = 8.2), 7.15–7.40 (m, 5H), 7.7 (d, 1H, J = 8.2)[c]
6df	87	oil	2.82[a]	1.17 (t, 3H, J = 7.1), 1.39 (s, 9H), 2.78 (t, 2H, J = 6.8), 2.93 (t, 2H, J = 6.8), 4.11 (dq, 2H, J = 2.1, 7.1), 4.95 (d, 1H, J = 8.1), 7.10–7.35 (m, 5H), 7.59 (d, 1H, J = 8.1)[c]
3[2]	82	foam	5.50[b]	1.43 (s, 9H), 1.95 (m, 1H), 2.27 (m, 1H), 3.59 (s, 3H), 4.00 (dt, 2H, J = 2.3, 12.0), 4.26 (dd, 2H, J = 5.0, 10.9), 5.14 (s, 2H), 5.26 (s, 2H), 5.83 (d, 1H, J = 7.8), 5.95 (s, 1H), 6.08 (d, 1H, J = 8.0), 6.96 (d, 1, J = 8.6), 6.98 (d, 1H, J = 8.6), 7.25–7.50 (m, 11H), 7.65 (dd, 1H, J = 2.4, 8.6), 7.83 (d, 1H, J = 2.4), 7.93 (d, 1H, J = 2.4)[d]

[a] Merck Si60 [LiChrosorb (7 μ), 250-4, 2,0 mL/min]; eluent: hexane/EtOAc (8 : 2).
[b] Merck Si60 [LiChrosorb (7 μ), 250-4, 2,0 mL/min]; eluent: hexane/EtOAc (7 : 3).
[c] Solvent DMSO-d_6.
[d] Solvent $CDCl_3$.

done on silica gel (Merck Silica 60 F_{254} sheets) and MPLC using Merck LiChroprep Si 60 (15–25 μ). HPLC was done with a LKB Instrument and a silica gel column (Merck LiChroCART 250-4 mm), LiChroSorb Si 60 7 μ. Satisfactory microanalyses were obtained for **6ae, be, bf, cf, df, 3, 5 e,f**: C ± 0.24, H ± 0.13, N ± 0.19.

Methyl Hydrogen (Benzyloxycarbonylamino)malonate (5e); Typical Procedure:

To a stirred solution of dimethyl aminomalonate hydrochloride (10 g, 54.5 mmol) in 2 M aq $KHCO_3$ (70 mL) and dioxane (70 mL) benzyl chloroformate (9.1 mL, 64.5 mmol) was added at 0 °C over a period of 10 min. The mixture was stirred for 24 h at r.t., dioxane was evaporated in vacuo and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was recrystallized from EtOAc/hexane to give dimethyl (benzyloxycarbonylamino)malonate (12.2 g). The solution of crude dimethyl (benzyloxycarbonylamino)malonate (12.2 g, 45.7 mmol) in dioxane (50 mL) was treated with 1 M aq NaOH (45.7 mL) over a period of 3 h. The mixture was stirred for 15 h at r.t. and dioxane was evaporated in vacuo. The aqueous residue was washed with Et_2O (50 mL), then diluted with EtOAc (50 mL), acidified with 1 M H_2SO_4 (25 mL) at 0 °C (stirring), separated and extracted with EtOAc (2 × 50 mL). The combined organic layers were dried ($MgSO_4$), concentrated and dried in vacuo (0.001 mbar); yield: 10.9 g (75 % from dimethyl aminomalonate hydrochloride); mp 83–85 °C.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 3.69 (s, 3 H); 4.85 (d, 1 H, J = 8.1 Hz); 5.06 (s, 2 H); 7.36 (s, 5 H); 8.17 (d, 1 H, J = 8.1 Hz); 13.45 (br s, 1 H).

Ethyl Hydrogen (tert-Butoxycarbonylamino)malonate (**5f**): Compound **5f** was prepared analogously from diethyl aminomalonate hydrochloride using di-*tert*-butyl dicarbonate; yield[5]: 10.8 g (80 %); mp 98–99 °C.

^{1}H NMR (250 MHz, DMSO-d_6/TMS): δ = 1.19 (t, 3 H, J = 7.1 Hz); 1.38 (s, 9 H); 4.14 (dq, 2 H, J = 1.2, 7.1 Hz); [4.64 (br) and 4.71 (d, J = 8.1 Hz) 1 H, ratio: 1:7]; [6.86 (br) and 7.50 (d, J = 8.1 Hz) 1 H ratio: 1:7]; 14.4 (br s, 1 H).

α-Acylamino-β-oxo Acid Esters 6; General Procedure:

To a solution of N-protected alkyl hydrogen aminomalonate (2 mmol) in THF (10 mL) at − 80 °C, BuLi (2.5 mL, 4 mmol; 1.6 M solution in hexane) and the acid chloride (1 mmol) were added successively over a period of 10 min. The mixture was stirred for a further 2 h during which the temperature reached − 50 °C. The reaction was quenched with sat. aq NH_4Cl (10 mL), stirred at r.t. for another 10 min and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by MPLC (eluent hexane/EtOAc) to give the pure α-amino-β-oxo ester.

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