Esters of 2-Dialkylamino-2-propenoic Aids

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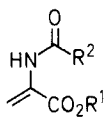
The title compounds (**2a–d**), representing α,β-didehydroalanine derivatives and reactive equivalents of pyruvic acid, have been obtained by the reaction of methyl or *tert*-butyl pyruvate with dimethylamine, piperidine or morpholine in the presence of arsenous trichloride. The synthesis of dimethyl 2,4-dioxopentanedioate is given as an example of the versatile reactivity of these compounds.

Unlike 2-acylamino-2-propenoic acid esters **1**, widely studied α,β-didehydroalanine derivatives, esters of 2-dialkylamino-2-propenoic acids **2** remained practically unexplored until now.[1] This is rather surprising as several areas of attractive chemistry can be anticipated for these compounds combining in their molecules both enamine and ester groupings. The accumulated knowledge of enamine chemistry can be applied to them, and as reactive derivatives of pyruvic acid, they could be used *inter alia* for introduction of this structural fragment into many organic and particularly bioorganic molecules. The title esters are also of interest from the viewpoint of the so-called captodative olefins.[2,3]



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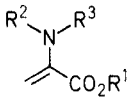

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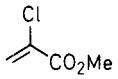
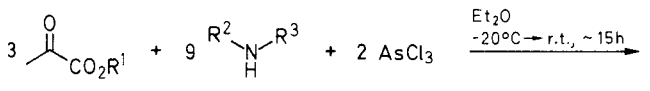
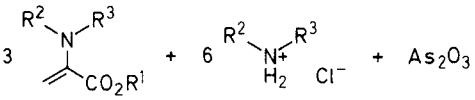


3

2	R^1	R^2	R^3
a	Me	Me	Me
b	*t*-Bu	Me	Me
c	Me	$-(CH_2)_5-$	
d	Me	$-(CH_2)_2O(CH_2)_2-$	

In this connection, a reaction of methyl 2-chloro-2-propenoate (**3**) with piperidine has been described,[3] resulting in the formation, though in a very poor yield (5–10%), of a compound described also in this paper, methyl 2-piperidino-2-propenoate (**2c**). The principle of the method reported in this paper[4] is the transformation of alkyl pyruvates into the corresponding enamines, 2-dialkylamino-2-propenoates **2**.





2

The well-known sensitivity of alkyl pyruvates towards both acidic and alkaline reagents prevented us from using most of the current procedures of enamine synthesis. Even when applying the method described by White and Weingarten[5] some important preconditions have to be fulfilled. Most important, alkyl pyruvates can at no stage of the procedure be in contact with a free amine. This is achieved by using the stoichiometry of the reaction components shown in the equation above and by preparing first the reagent by adding inorganic chloride to the solution of the amine in some inert solvent. Comparing titanium tetrachloride recommended by the mentioned authors[5] with arsenic(III) chloride, we ascertained that the latter, evidently as a milder reagent, gives better results – not only higher yields but also, what is even more important, purer products. As seen from the Table, the yields of products **2** are very satisfactory. Some limitations to the developed procedure seem still to exist; e.g., with pyrrolidine, only a very low yield of impure product was obtained.

Table. Alkyl 2-Dialkylamino-2-propenoates **2**

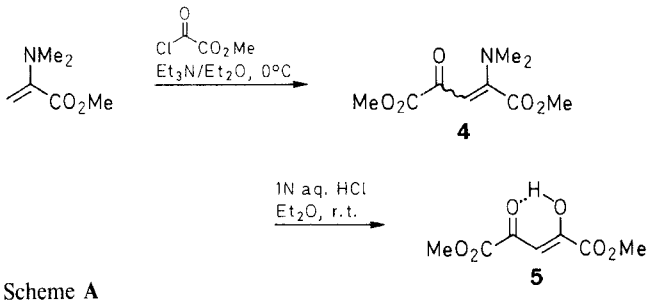
Product	Yield (%)	bp (°C) mbar	Molecular Formula[a]	^{1}H-NMR ($CDCl_3$/TMS) δ
2a	82	48–51 12	$C_6H_{11}NO_2$ (129.2)	2.65 (s, 6H, CH_3NCH_3), 3.8 (s, 3H, OCH_3), 4.43, 5.04 (s, s, 1H, 1H, $=CH_2$)
2b	68	72–74 14	$C_9H_{17}NO_2$ (171.2)	1.54 (s, 9H, *t*-C_4H_9), 2.64 (s, 3H, OCH_3), 4.28, 4.87 (2 × s, 1H, 1H, $=CH_2$)
2c	73	57–59 0.9	$C_9H_{15}NO_2$ (169.2)	1.5–1.8 (m, 6H, 3 × CH_2), 2.74–3.0 (m, 4H, CH_2NCH_2), 3.79 (s, 3H, OCH_3), 4.54, 5.11 (s, s, 1H, 1H, $=CH_2$)
2d	75[b,c]	47–50[d]	$C_8H_{13}NO_3$ (171.2)	2.82–2.96 (m, 4H, CH_2NCH_2), 3.75–3.91 (m, 4H, CH_2OCH_2), 3.79 (s, 3H, OCH_3), 4.63, 5.26 (s, s, 1H, 1H, $=CH_2$)

[a] Satisfactory microanalyses obtained: C, H, N ± 0.28.
[b] A two-fold volume of Et_{20} was used during the preparation procedure.
[c] Yield of the purified product. Crude product, obtained in 86% yield (mp 45–47 °C), was purified by freezing out from MeOH (15 g of **2d** from 50 mL).
[d] Melting point of the purified product.

Products **2a–c** are well distillable liquids, the morpholine derivative **2d** is a solid which can be purified by crystallizaon at low temperatures. All these compounds are rather unstable, but if kept in a refrigerator they can be stored for several months.

As an example of the reactivity of the products described, we investigated the acylation of ester **2a** with methyl oxalyl chloride (Scheme **A**). The primary product **4** can easily be hydrolyzed to the symmetrical dimethyl 2,4-dioxo-1,5-pentanedioate **5** depicted here in the form

identified by NMR spectroscopy. On similar lines a general synthesis of 2,4-dioxoacids, with incorporated β-diketo system, can be anticipated.



Scheme **A**

Melting points were determined of Kofler block and are uncorcted. ^{1}H-NMR spectra were recorded on spectrometers Tesla BS-467 and/or Tesla BS-597A (at 60 and/or 100 MHz) IR Spectra were recorded on a Zeiss (Jema) UR-20 spectrophotometer.

The starting *tert*-butyl pyruvate was prepared by shaking a suspension of silver pyruvate in dry ether with *tert*-butyl bromide, removing the silver salts by suction, washing the solution with aq. $KHCO_3$ and drying ($MgSO_4$); yield: 50%; bp 63–65°C/30 mbar (for other methods, see Refs. 6, 7) Et_2O.

Methyl 2-Dimethylamino-2-propenoate (2a); Typical Procedure:
To a three-necked 2000 mL flask equipped with mechanical stirrer, dropping funnel, and protected against moisture is added a solution of Me_2NH (67.7 g, 1.5 mol) in dry Et_2O (1200 mL). The solution is cooled to −25°C and a solution of $AsCl_3$ (28 mL, 0.33 mol) in dry Et_2O (200 mL) is added during 30 min at −20°C. After the reaction mixture has been stirred for 15 min, a solution of methyl pyruvate (51 g, 0.5 mol) in dry Et_2O (100 mL) is added, again at −20°C. The cooling is removed, and the reaction mixture stirred for several hours and left overnight. The solid precipitate is removed by suction and washed well with dry Et_2O (3 × 200 mL); the combined ethereal solutions are filtered through a thin layer of silica gel, Et_2O is removed over a small column under slightly reduced pressure, and the product is isolated by distillation; yield: 53 g (82%); bp 48–51.5°C/12 mbar.

Dimethyl 2-Dimethylamino-4-oxo-2-pentenedioate (4):
To a three-necked 500 mL flask equipped with a mechanical stirrer and dropping funnel is added a solution of the ester **2a** (5.17 g, 0.04 mol) in dry Et_2O (100 mL). Under cooling with an ice/water bath, Et_3N (6.7 mL, 0.048 mol) is added followed by a solution of methyl oxalyl chloride (5.4 g, 0.044 mol) in dry Et_2O (100 mL) during 30 min. From the thick suspension, Et_2O is removed *in vacuo*, and the residue is shaken between $CHCl_3$ (150 mL) and 5% aq. $NaHCO_3$ (90 mL). After separation, the aqueous layer is extracted with $CHCl_3$ (2 × 25 mL), and the combined organic extracts are washed with water (2 × 50 mL) and dried ($MgSO_4$). After filtration, the solvent is removed and the product is isolated by chromatography (silica gel, 400 g; EtOAc/ether, 1:1; yield: 6 g (70%); mp 61.5–63.5°C.

$C_9H_{13}NO_5$	calc.	C 50.23	H 6.09	N 6.51
(215.2)	found	50.07	6.03	6.54

^{1}H-NMR ($CDCl_3$, TMS): δ = 3.05 (s, 6 H, CH_3NCH_3), 3.8 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 5.83 (s, 1 H, =CH).

IR (CCl_4): ν = 1749 s, 1731 s, 1662 m (C=O), 1558 cm^{01} (C=C).

Dimethyl 2,4-Dioxopentanedioate (5):
To a solution of enamine **4** (4.3 g, 0.02 mol) in ether (150 mL) 1 N HCl (40 mL) is added, and the reaction mixture is stirred intensily at room temperature. The reaction is monitored by TLC (EtOAc/Et_2O, 1:1). After about 1 h, the aqueous layer is saturated with NaCl; the organic layer separated and washed with brine (2 × 25 mL). The aqueous layers are extracted with Et_2O (2 × 30 mL); the ethereal extracts are combined and dried ($MgSO_4$). Product **5** is purified by distillation; yield: 3 g (80%); bp 100°C (bath temperature)/0.3 mbar; mp 36–38°C.

$C_7H_8O_6$	calc.	C 44.69	H 4.29	
(188.1)	found	44.67	4.27	

^{1}H-NMR ($CDCl_3$, TMS): δ = 3.95 (s, 6 H, 2 × OCH_3), 7.13 (s, 1 H, =CH), 11.93 (br s, OH).

IR (CCl_4): ν = 1760 s, 1747 s (CO_2CH_5), 1650 s, 1599 s (chelate C=O, C=C), ~ 3050 cm^{-1}, w, v, br (OH).

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