Alkyl 2-(Diphenylmethyleneamino)acrylates in the Synthesis of α-Amino Acids

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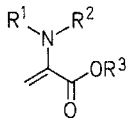
Stable alkyl 2-(diphenylmethyleneamino)acrylates, readily prepared from glycine, are useful synthons for the synthesis of racemic 3-substituted alkyl alaninates via Michael type and Lewis acid catalyzed additions.

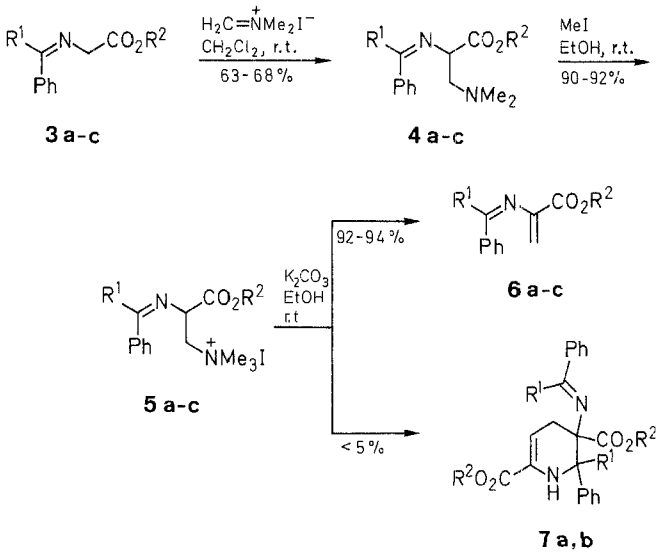
Stable derivatives of 2-aminoacrylic acid (e.g. **1a–c**) are known to undergo a variety of reactions[1–11] to give α-amino acids. The final deprotection of the amino group proceeds well in the case of the *tert*-butoxycarbonyl derivative **1c**,[9] but in the case of the *N*-acyl derivatives **1a, b** requires prolonged heating in concentrated acids[1–3,10] or alkali,[5] which is not compatible with selective *N*-deprotection, or with sensitive compounds. Nevertheless, it is worth noting that the final deprotection of the amino group in the case of *N*-acyl derivative **1a** is possible under very mild conditions (pH 7, 37°C) by the use of the hydrolytic enzyme acylase.[12]



1a-c, 2

	R^1	R^2	R^3		R^1	R^2	R^3
1a	H	COMe	H	**1c**	H	CO_2Bu-*t*	Me
1b	H	COMe	Et	**2**		=CHPh	Me

Recently, methyl 2-(benzylideneamino)acrylate (**2**) was found to be useful for the preparation of α-amino acids;[13–14] however, whereas it is possible to deprotect the amino group selectively under mild conditions, the reagent itself is rather unstable and undergoes an extensive dimerization into 3-(benzylideneamino)-3,6-bis(methoxycarbonyl)-2-phenyl-1,2,3,4-tetrahydropyridine (**7b**, Scheme A) in solution at room temperature.[14]



Scheme A

3–6	R^1	R^2	7	R^1	R^2
a	Ph	Et	**a**	Ph	Et
b	Ph	Me	**b**	H	Me
c	Ph	*t*-Bu			

Table 1. Alkyl 2-(Diphenylmethyleneamino)acrylates **6a–c** and Intermediates **4a–c** and **5a–c**

Product	Yield (%)	bp (°C)/mbar or mp (°C) (solvent)	Molecular Formula	IR (neat or nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ
4a	65	150–155/0.7	$C_{20}H_{24}N_2O_2$ (324.4)	1735, 1625	1.25 (t, 3H); 2.1 (s, 6H); 2.6–3.0 (m, 2H); 4.2 (m, 3H); 7.5 (m, 10H)
4b	63	145/0.5	$C_{19}H_{22}N_2O_2$ (310.4)	1735, 1620	2.1 (s, 6H); 2.4–3.0 (m, 2H); 3.7 (s, 3H); 4.2 (t, 1H); 7.5 (m, 10H)
4c	68	130–3/0.2	$C_{22}H_{28}N_2O_2$ (352.5)	1730, 1625	1.4 (s, 9H); 2.05 (s, 6H); 2.6–3.0 (m, 2H); 4.05 (m, 1H); 7.5 (m, 10H)
5a	92	178 ($EtOH/Et_2O$)	$C_{21}H_{27}IN_2O_2$ (466.4)	1735, 1620	1.2 (t, 3H); 3.07 (s, 9H); 3.95–4.15 (m, 4H); 4.5 (m, 1H); 7.5 (m, 10H)[a]
5b	90	168 ($MeOH/Et_2O$)	$C_{20}H_{25}IN_2O_2$ (452.3)	1735, 1610	3.1 (s, 9H); 3.70 (s, 3H); 3.9–4.2 (m, 2H); 4.5 (m, 1H); 7.5 (m, 10H)[a]
5c	90	173 ($EtOH/Et_2O$)	$C_{23}H_{31}IN_2O_2$ (494.4)	1725, 1625	1.4 (s, 9H); 3.08 (s, 9H); 3.9–4.1 (m, 2H); 4.4 (m, 1H); 7.5 (m, 10H)[a]
6a	92	oil[b]	$C_{18}H_{17}NO_2$ (279.3)	1725, 1630	1.2 (t, 3H); 4.05 (q, 4H); 4.85 (s, 1H); 5.5 (s, 1H); 7.5 (m, 10H)
6b	93	oil[b]	$C_{17}H_{15}NO_2$ (265.3)	1725, 1625	3.7 (s, 3H); 4.8 (s, 1H); 5.6 (s, 1H); 7.5 (m, 10H)
6c	94	oil[b]	$C_{20}H_{21}NO_2$ (307.4)	1710, 1625	1.4 (s, 9H); 4.9 (s, 1H); 5.55 (s, 1H); 7.5 (m, 10H)

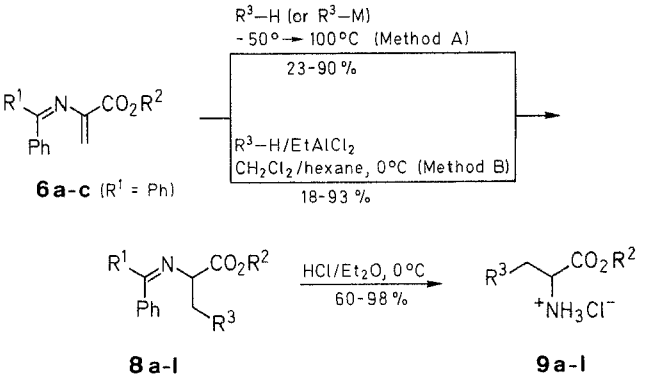
[a] Measured in DMSO-d_6.

[b] Compound decomposes above 120°C.

We found that the alkyl 2-(diphenylmethyleneamino)acrylates **6a–c**, easily prepared with minor modifications of standard procedures[15–18] from glycine via **3a–c**, **4a–c** and alkyl *N*-diphenylmethylene-3-trimethylammonioalaninate iodides **5a–c** (Scheme **A**, Table 1), are stable derivatives of 2-aminoacrylic acid. Their stability was verified by storage of **6a** for several months at 0–4 °C and in solution at room temperature for a month. However, during the preparation of **6a**, the dimer **7b** was isolated in about 3% yield.

Compounds **6a–c** allow an easy synthesis of racemic α-amino acids. Thus, **6a–c** undergo Michael type (Method A) and Lewis acid catalyzed (Method B) additions to give in synthetically useful yields alkyl 3-substituted *N*-diphenylmethylenealaninates **8a–l** (Tables 2 and 3), and the corresponding alkyl aminocarboxylates **9** by a two-phase hydrolytic cleavage[15] of the diphenylmethyleneamino moiety (hydrogen chloride/ether, 0 °C) (Scheme **B**, Table 4).

The Michael additions are widely studied reactions in the case of *N*-protected 2-aminoacrylates.[2,3,9,11] In our experimental conditions (examples, **8a–f**) a relevant limitation was the failure in the addition of phenoxy anions. Lewis acid catalyzed additions with derivatives of 2-aminoacrylic acid are new, but less general.



Product	R^2	R^3	Product	R^2	R^3
8a	Et	$CH(CO_2Et)_2$	**8g, 9g**	Et	2-pyrrolyl
9a	H	CH_2CO_2H	**8h, 9h**	Et	$4\text{-}CH_3NHC_6H_4$
8b, 9b	Et	Ph	**8i, 9i**	Et	$4\text{-}(CH_3)_2NC_6H_4$
8c, 9c	Et	SEt	**8j, 9j**	Et	5-HO-3-indolyl
8d, 9d	Et	SPh	**8k, 9k**	Me	3-indolyl
8e, 9e	Et	SCH_2Ph	**8l**	*t*-Bu	3-indolyl
8f, 9f	Et	3-indolyl	**9l**	H	3-indolyl

Scheme **B**

Table 2. Alkyl 3-Substituted *N*-Diphenylmethylene-DL-alaninates **8a–f** Prepared by Nucleophilic Addition (Method A)

Product	Nucleophile (R^3–H)	Base	Yield (%)	bp (°C)/mbar or mp (°C) (solvent)	Molecular Formula or Lit. mp (°C)	IR (film) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ
8a	$NaCH(CO_2Et)_2$	–	90	175–180/0.2	$C_{25}H_{29}NO_6$ (439.5)	1740, 1625	1.15 (3t, 9H); 2.4–2.7 (m, 2H); 3.5 (t, 1H); 3.9–4.3 (m, 7H); 7.5 (m, 10H)
8b	$Li_2Ph_2Cu(CN)$	–	70	68 (Et_2O-Hexane)	68.5–69[15]	–	–
8c	EtSH	Piperidine	89	135–140/0.2	$C_{20}H_{23}NO_2S$ (341.5)	1735, 1620	1.15 (2t, 6H); 2.4 (q, 2H); 2.9–3.15 (m, 2H); 4.0–4.4 (m, 3H); 7.5 (m, 10H)
8d	PhSH	Piperidine	87	155–160/0.3	$C_{24}H_{23}NO_2S$ (389.5)	1735, 1620	1.25 (t, 3H); 3.2–3.6 (m, 2H); 4.0–4.4 (m, 3H); 7.0–7.6 (m, 15H)
8e	$PhCH_2SH$	Piperidine	83	oil[a]	$C_{25}H_{25}NO_2S$ (403.5)	1735, 1620	1.25 (t, 3H); 2.9–3.1 (m, 2H); 3.6 (s, 2H); 4.0–4.4 (m, 3H); 7.0–7.8 (m, 15H)
8f	Indole	$LiN(SiMe_3)_2$	23	215/0.2	$C_{26}H_{24}N_2O_2$ (396.5)	3400, 1720, 1620	1.2 (t, 3H); 3.2–3.6 (m, 2H); 3.9–4.4 (m, 3H); 6.5–7.7 (m, 15H); 8.0 (br. s, 1H)

[a] The product decomposes on heating.

Table 3. Alkyl 3-Substituted *N*-Diphenylmethylene-DL-alaninates **8f–l** Prepared by Lewis Acid Catalysis (Method B)

Product	Yield (%)	bp (°C)/mbar or mp (°C) (solvent)	Molecular Formula	IR (neat or nujol) ν (cm^{-1})	^{1}H-NMR ($CDCl_3$) δ
8f	93[a]	–	–	–	–
8g	64	80–81	$C_{22}H_{22}N_2O_2$ (346.4)	3370, 1725, 1625	1.2 (t, 3H); 3.2 (d, 2H); 4.0–4.4 (m, 3H); 5.9 (m, 1H); 6.1 (m, 1H); 6.65 (m, 1H); 7.5 (m, 10H); 8.5 (br s, 1H)
8h	62	165–169/0.13	$C_{25}H_{26}N_2O_2$ (386.5)	3400, 1730, 1620	1.2 (t, 3H); 2.7 (s, 3H); 3.0–3.25 (m, 2H); 3.4 (s, 1H); 3.95–4.25 (m, 3H); 6.4–7.8 (m, 14H)
8i	74	168–173/0.3	$C_{26}H_{28}N_2O_2$ (400.5)	1725, 1620	1.2 (t, 3H); 2.9 (s, 6H); 3.0–3.2 (m, 2H); 3.95–4.2 (m, 3H); 6.4–7.7 (m, 14H)
8j	–[b]	–	–	–	–
8k	70	89–90 (Et_2O-hexane)	$C_{25}H_{22}N_2O_2$ (382.5)	–[c]	–[c]
8l	18[d]	–[c]	$C_{28}H_{28}N_2O_2$ (424.5)	3390, 1725, 1620	1.5 (s, 9H); 3.2–3.35 (m, 2H); 4.1–4.4 (m, 1H); 6.6–7.7 (m, 15H); 8.0 (br. s, 1H)

[a] See Table 2 for physical and spectral data.
[b] Compound not isolated; the crude material was directly hydrolized to ethyl 5-hydroxy-DL-tryptophanate hydrochloride (**9j**).
[c] Spectroscopical data are identical to those reported for the L-form, mp 114–115 °C.[15]
[d] The product was obtained according to the general procedure, but at −30 °C.
[e] Compound decomposes on heating.

Table 4. Alkyl 3-Substituted DL-Alaninate Hydrochlorides **9a–l**

Product	Yield (%)	mp (°C) (EtOH/Et_2O)	Molecular Formula or Lit. mp (°C)	IR (nujol) ν (cm^{-1})	^{1}H-NMR (DMSO-d_6) δ
9a[21]	–	–	–	–	–
9b[15]	–	–	–	–	–
9c	98	124	$C_7H_{16}ClNO_2S$ (213.7)	1740	1.05 (2t, 6H); 2.5 (q, 2H); 2.9–3.1 (m, 3H); 4.0–4.3 (m, 2H); 8.8 (br s, 3H)
9d	97	113	$C_{11}H_{16}ClNO_2S$ (261.8)	1760	1.1 (1t, 3H); 2.4 (q, 2H); 3.9–4.3 (m, 3H); 7.3 (m, 5H); 8.95 (br s, 3H)
9e	97	135	135[22]	–	–
9f	94	219–221	219–221[23]	–	–
9g	60	147	$C_9H_{15}ClN_2O_2$ (218.7)	3290, 1740	1.25 (t, 3H); 3.0–3.3 (m, 2H); 3.8–4.3 (m, 3H); 5.9 (m, 2H); 6.65 (m, 1H); 8.0 (br s, 3H); 10.85 (br s, 1H)
9h	90	177–179	$C_{12}H_{20}Cl_2N_2O_2$[a] (295.2)	1735	1.1 (t, 3H); 2.85 (s, 3H); 3.1–3.3 (m, 2H); 4.1–4.4 (m, 3H); 7.4 (s, 4H); 8.8 (br s, 5H)
9i	90	170–172	$C_{13}H_{22}Cl_2N_2O_2$[a] (309.2)	1735	1.1 (t, 3H); 3.1 (s, 6H); 3.1–3.3 (m, 2H); 3.9–4.2 (m, 3H); 7.6 (q, 4H); 8.85 (br s, 4H)
9j	45[b]	235 (dec.)	234–235[24]	–	–
9k	96	125–126	127[27]	–	–
9l[c]	–	–	–	–	–

[a] As dihydrochloride.
[b] From crude **8j**, the overall yield was calculated based on starting **7a**.
[c] See General Procedure for **8f–l**.

In this case **6a–c** reacted with some substrates, namely indole, 5-hydroxyindole, pyrrole, *N*-methyl and *N*-dimethylaniline, preferably in the presence of ethylaluminum dichloride, but also with aluminum trichloride or titanium tetrachloride,[19] to give **8f–l** however, compound **6a** failed to react under the same conditions with benzene, phenol, anisole, and aniline. A similar resistance to Lewis acid catalyzed *C*-substitution of pyrrole and in general of aromatic compounds by acrylonitrile, acrylic acid and acrylic esters was reported.[20]

We wish to propose that esters **6a–c** of 2-(diphenylmethyleneamino)acrylic acid are useful reagents for the synthesis of racemic α-amino acids. They offer the advantage over the method previously described[13,14] of being stable when stored, useful in solution up to 100 °C (see general procedure for the synthesis of **8c–e**), and of allowing mild and selective deprotection of the amino group in the final compounds.

Melting points were determined on a Büchi SMP-510 capillary apparatus and are uncorrected. Boiling points are given as bath temperature of bulb-to-bulb distillations. IR spectra were obtained on a Perkin-Elmer 257 spectrometer. Mass spectra were taken on a Hitachi RMU 6L (70 eV) instrument and ^{1}H-NMR spectra were recorded on a Varian EM 360L spectrometer and are reported in δ using TMS as internal standard. Satisfactory elemental analysis (C, H, N, ± 0.4% from the theoretical value) were done at the Analytical Department of Lepetit SpA, Milano.

Alkyl *N*-Diphenylmethylene-2-dimethylaminoalaninates 4a–c; General Procedure:
A solution of dimethyl(methylene)ammonium iodide[26] (16.19 g, 87.5 mmol) and the appropriate alkyl *N*-diphenylmethyleneglycinate **3**[15] (50 mmol) in CH_2Cl_2 (500 mL) is stirred for 12 h at room temperature with exclusion of moisture. A sat. aq. solution of $NaHCO_3$ (120 mL) is added to the ice cooled reaction mixture with stirring. The layers are separated, the organic phase is washed with water (2 × 150 mL), dried (Na_2SO_4), and evaporated *in vacuo*. Crude **4a–c** are obtained as oils that can be used without further purification. Flash column chromatography (silica gel, $CHCl_3$) is used to obtain pure samples of **4a–c** (see Table 1).

Alkyl *N*-Diphenylmethylene-3-trimethylammonioalaninate Iodides 5a–c; General Procedure:
A solution of methyl iodide (14.2 g; 100 mmol) in dry EtOH (250 mL) is added dropwise to a solution of **4** (50 mmol) in the same solvent (125 mL) and the mixture is stirred for 10 h at room temperature. After cooling at 0 °C, ether (500 mL) is added and the resulting white solid is filtered and crystallized (see Table 1).

Alkyl 2-(Diphenylmethyleneamino)acrylates 6a–c; General Procedure:
Solid K_2CO_3 (13.85 g, 100 mmol) is added to a solution of **5** (50 mmol) in dry EtOH (MeOH for **5b**) (250 mL) and the mixture is stirred for 16 h at room temperature with exclusion of moisture. After cooling at 0 °C and filtering of the tetramethylammonium iodide, the solvent is evaporated *in vacuo*, the residue is dissolved in ether (250 mL) and the organic phase is washed twice with water (50 mL) and dried (Na_2SO_4). Evaporation of the solvent and column chromatography (silica gel; hexane/$CHCl_3$, 3:7) gives **6a–c** as oils (see Table 1).

3-(Diphenylmethyleneamino)-3,6-bis(ethoxycarbonyl)-2,2-diphenyl-1,2,3,4-tetrahydropyridine (7a):
The Diels–Alder adduct **7a** is isolated as a white crystalline solid during the purification step of the above preparation of **6a**; yield: 0.835 g (3%); mp 147–149 °C (CH_2Cl_2/hexane).

$C_{36}H_{34}N_2O_4$ (558.7)	calc.	C 77.40	H 6.13	N 5.01
	found	77.17	6.16	5.05

MS: m/z = 559 (M + 1).

IR (Nujol): ν = 3360, 1720, 1690, 1670, 1630 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 0.73 (t, 3H, CH_3CH_2O); 1.05 (t, 3H, CH_3CH_2O); 2.03, 2.38 (2d, 2H, CH_2, J_{AB} = 12.2 Hz); 3.61 (s, 1H, NH); 3.68–4.0 (m, 4H, $2CH_3CH_2O$); 4.57 (s, 1H, CH_{vinyl}); 6.92–7.61 (m, 20 H_{arom}).

Examples of Method A, Table 2:

Diethyl *N*-Diphenylmethylene-4-(ethoxycarbonyl)-DL-glutamate (8a):
A solution of **6a** (2.8 g, 10 mmol) in dry EtOH (10 mL) is added dropwise to a stirred mixture of ethanolic NaOEt (0.23 g, 10 mg/atom of Na and 40 mL of dry (EtOH) and diethyl malonate (1.6 g, 10 mmol) and the mixture is refluxed for 14 h. The EtOH is removed at reduced pressure, the resulting oil is taken up in EtOAc (75 mL), washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography on silica gel (cyclohexane/EtOAc, 9:1) gives **8a**; yield: 3.95 g (90%).

Ethyl *N*-Diphenylmethylene-DL-phenylalaninate (8b):
An ethereal solution (20 mL) of **6a** (2.8 g, 10 mmol) is added dropwise to an ethereal solution (40 mL) of diphenyllithium cyanocuprate[25] (11 mmol) at −50 °C under N_2. At the same temperature, the mixture is stirred for 5 h, then a sat. solution of NH_4Cl (3 mL) is added at 0 °C. The layers are separated, the ether layer is washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated. Column chromatography on silica gel (hexane/$CHCl_3$ 3:7) gives **8b**; yield: 2.5 g (70%).

S-Substituted N-Diphenylmethylene-DL-cysteine Ethyl Esters 8c–e; General Procedure:

Compound **6a** (2.79 g, 10 mmol), the appropriate thiol (20 mmol) and piperidine (1 mmol) are refluxed in dioxane (40 mL) for 12 h (in sealed vessel for **6c**). The solvent is removed *in vacuo*, the oily residue is taken up in CH_2Cl_2 (100 mL), washed with water (2 × 10 mL), dried (Na_2SO_4) and evaporated. Flash column chromatography on silica gel (hexane/$CHCl_3$ 3:7) gives **8c–e** as oils.

Ethyl N-Diphenylmethylene-DL-tryptophanate (8f):

A solution of **6a** (2.8 g, 10 mmol) in THF (30 mL) is added dropwise at 0 °C to a solution of lithium bis(trimethylsilyl)amide (10 mmol) and indole (1.17 g, 10 mmol) in dry THF (30 mL). The mixture is stirred for 48 h on ice-bath, water (150 mL) is then added, the aqueous phase extracted with EtOAc (4 × 50 mL), the extract dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography on silica gel ($CHCl_3$) gives **8b**; yield: 0.910 g (23%).

Examples of Method B, Table 3:

Alkyl 3-Substituted N-Diphenylmethylenealaninates 8f–l; General Procedure:

The appropriate aromatic substrate (20 mmol), **6a–c** (10 mmol) in CH_2Cl_2 (100 mL) (0 °C, N_2 atmosphere) is treated with 1 M solution of $EtAlCl_2$ in hexane (20 mL) and the solution is stirred for 1 h at 0 °C (−30 °C in the case of **6c**). The reaction is quenched by careful addition of 0.6 N aq. solution of $NaHCO_3$ (100 mL), the mixture is filtered, the organic layer is separated, washed with water (2 × 20 mL), dried (Na_2SO_4) and evaporated *in vacuo*. Column chromatography on silica gel (hexane/$CHCl_3$, 2:8) gives compounds **8f–l**.

According to the above general procedure, but quenching the reaction with 2N HCl (5 mL), DL-tryptophane **(9l)** is obtained from **6c** (3.07 g, 10 mmol); overall yield: 1.76 g (86%).

N-Deblocking of 8a–l to the Corresponding α-Amino Acid Ester Hydrochlorides 9a–k; General Procedure:[15]

A solution of 2-(diphenylmethylene)amino acid esters **8a–k** (5 mmol) in ether (10 mL) is stirred overnight at 0 °C with 1N HCl (6 mL). The layers are separated, the aqueous phase is washed with ether (2 × 10 mL) and evaporated *in vacuo* to obtain, after crystallization, α-amino acid ester hydrochlorides **9a–k** (see Table 4).

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