1,4-Addition of (Diphenylmethylene)amine to Acceptor Substituted Olefins. A Versatile Synthesis of Protected β-Amino Acids, Nitriles, and Ketones

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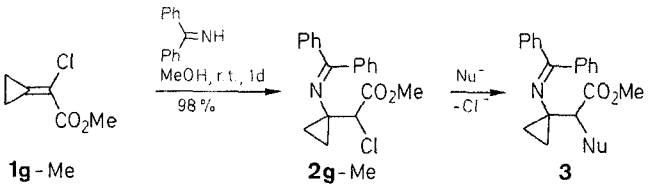
(Diphenylmethylene)amine [benzophenone imine, DPMA-H] cleanly reacts with a variety of α,β-unsaturated esters, nitriles, ketones, and aldehydes **1a–q** to give Michael type adducts **2a–q**, generally, in respectable to excellent yields. Sterically congested and donor-substituted Michael acceptors do not react. The β-amino-substituted products can be further transformed in their protected form, or selectively deprotected under mild conditions, e.g. by catalytic hydrogenation.

The (diphenylmethylene)amino (DPMA) group has extensively been used as a protected primary amino group in the context of α-amino acid[1-3] and peptide syntheses.[4] In many cases the BPI group served to increase the α-C-H acidity and accordingly, α-amino acid derivatives were obtained by electrophilic alkylation of α-(diphenylmethylene)amino ester enolates, e.g. α-(diphenylmethylene)aminoacetates as glycine derivates. The only report that has come to our attention in which DPMA-H has acted as nucleophile was its addition to dimethyl acetylenedicarboxylate.[5] As we have recently found, DPMA-H is reasonably reactive towards a variety of Michael acceptors under appropriate conditions.

In an effort to prepare suitable precursors to 2-(1-aminocyclopropyl)-2-chloroacetic acid by 1,4-addition of appropriate nitrogen nucleophiles onto methyl 2-chloro-2-cyclopropylideneacetate (**1g**-Me), which has been noted for its high Michael acceptor reactivity,[6] we found several methods for the introduction of a protected primary amino group[7] unsuitable, because they either gave poor yields, lacked selectivity, or the amino group could not be deprotected at all or not without cleavage of the three-membered ring. DPMA-H, however, cleanly and quantitatively adds to **1g**-Me in methanol at ambient temperature within 1 day. The product, methyl 2-[1-(diphenylmethylene)aminocyclopropyl]-2-chloroacetate (**2g**-Me) isolated in 98% yield (separated from traces of benzophenone by column chromatography) can be further converted to other α-substituted β-amino acid derivatives **3** by nucleophilic substitution, e.g. with azide ion[8] or alkylthiolates,[9] in high yields without side reactions.



1g-Me **2g**-Me **3**

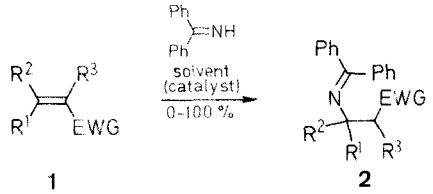
This rather useful transformation to a protected β-amino ester can be applied to less reactive Michael acceptors like methyl cyclopropylideneacetate (**1f**-Me),[10] methyl acrylate (**1a**-Me), and even diethyl maleate (**1k**-Et) (see Scheme **A** and Table 1).

In all these cases, products **2** were obtained in good to excellent yields without by-products. Methanol proved to be the best solvent, the reaction being much slower in aprotic and less polar solvents like dimethylformamide (DMF), diethyl ether and dichloromethane (see Table 1). Unlike **1g**-Me, all the other α,β-unsaturated esters do require a basic catalyst like triethylamine (TEA) or 1,4-diazabicyclo[2.2.2]octane (DABCO) to activate DPMA-H.

In contrast, sterically congested and donor-substituted Michael acceptors like methyl 3,3-dimethylacrylate (**1e**-Me), methyl cinnamate (**1d**-Me) and *N*-methyl-1,2,3,4-tetrahydropyridine-5-carboxylate **1i**-Me do not add DPMA-H, even under drastic conditions. Methyl crotonate (**1b**-Me) and methyl α-methacrylate (**1c**-Me) react very slowly in methanol at elevated temperatures. On the other hand, α-chloroacrylonitrile (**1m**), methyl vinyl ketone (**1n**) and acrolein (**1q**) react well and with very good yields. Cyclopentenone (**1o**) is less reactive than **1n**, and cyclohexenone is too slow.

A basic catalyst is mandatory with less reactive Michael acceptors in aprotic solvents. TEA proved to be the best with respect to yields and work-up convenience. Highly reactive systems such as **2g**-Me in alcoholic solvents can give alcohol adducts in the presence of TEA. Stronger bases such as DABCO, alkoxides, or sodium (diphenylmethylene)amide may cause side reactions and thus lead to product mixtures. Aside from alkoxide additions, transesterifications have been observed (see below). No evidence for Cu(I) or Cu(II) catalysis could be obtained. In the presence of copper(I) iodide, copper(II) acetate, and oxygen, DPMA-H did not add to methyl cinnamate, but oxidatively dimerized to benzophenoneazine (67% yield).[11]

In most cases β-DPMA carbonyl compounds and nitriles **2** are obtained in pure enough form to be used without further purification. Due to their hydrolytic sensitivity,[12,13] substantial losses may occur upon chromatography. In the absence of solvent, water, and oxygen, however, they are perfectly stable (except for **2n** and **2q**) and can be further transformed by nucleophilic substitution (e.g. **2g**-Me → **3**), transesterification (see below), or deprotection of the amino group with subsequent peptide formation. Products of the type **2** may also find direct



1 **2**

EWG = electron withdrawing group

1, 2	R^1	R^2	R^3	EWG
a-Me	H	H	H	CO_2Me
b-Me	H	CH_3	H	CO_2Me
c-Me	H	H	CH_3	CO_2Me
d-Me	H	Ph	H	CO_2Me
e-Me	CH_3	CH_3	H	CO_2Me
f-Me	CH_2CH_2		H	CO_2Me
g-Me	CH_2CH_2		Cl	CO_2Me
h-Et	CH_2CH_2		Br	CO_2Et
i-Me	H	$N(Me)(CH_2)_3$		CO_2Me
k-Et	CO_2Et	H	H	CO_2Et
l	H	H	H	CN
m	H	H	Cl	CN
n	H	H	H	$COCH_3$
o[a]				
p	CH_3	CH_3	H	$COCH_3$
q	H	H	H	CHO

[a] **1o** = 2-cyclopenten-1-one.

Scheme A

Table 1. Reaction Conditions and Yields for the Addition of (Diphenylmethylene)amine (DPMA-H) to Various Michael Acceptors **1**

Entry	DPMA-H (mmol)	Michael Acceptor (mmol)	Product	Solvent	Catalyst	Temp. (°C)	Time	Conversion (%, NMR)	Yield (%)
1	83	**1a**-Me (172)	**2a**-Me	MeOH	TEA	reflux	130 h	100	93[a]
2	28	**1a**-Me (55)	**2a**-Me	*t*-BuOH	TEA	70	123 h	100	72[a]
3	12	**1a**-Me (17)	**2a**-Me	DMF	TEA	100	64 h	45[b]	
4	23	**1a**-Me (28)	**2a**-Me	–	TEA	70	28 d	–	43
5	8.8	**1b**-Me (11)	**2b**-Me	MeOH	TEA	reflux	10 d	27[b]	21[b]
6	1.7	**1c**-Me (2.5)	**2c**-Me	MeOH	TEA	60	14 d	4[b]	4[b]
7	8.3	**1d**-Me (8.4)	–	MeOH	TEA	60	3 d	0	
8	21	**1e**-Me (20)	–	MeOH	DABCO	20	42 d	0	
9	0.9	**1f**-Me (1.0)	**2f**-Me	MeOH	TEA	20	14 d	100	90
10	6.6	**1f**-Me (6.6)	**2f**-Me	MeOH	TEA	reflux	2 d	100	100[c]
11	28	**1g**-Me (27.3)	**2g**-Me	MeOH	–	20	1 d	100	98[a]
12	5.5	**1g**-Me (5.0)	**2g**-Me	CH_2Cl_2	DABCO	20	< 42 d	–	96
13	8.8	**1g**-Me (8.7)	**2g**-Me	ether	–	20	2 d	–	70
14	5.2	**1h**-Et (4.8)	**2h**-Et	MeOH	–	20	1 d	–	20[a]
15	6.6	**1i**-Me (6.4)	–	MeOH	TEA	60	5 d	0	
16	6.1	**1k**-Et (6.4)	**2k**-Et	EtOH	TEA	80	8 d	–	55[b]
17	5.5	**1l** (9.4)	**2l**	MeOH	TEA	60	12 d	60[b]	57[b]
18	5.5	**1m** (11)	**2m**	MeOH	–	20	18 h	100	75
19	11	**1m** (22)	**2m**	–	–	20	16 h	50	27
20	7.3	**1m** (19)	**2m**	CH_2Cl_2/ benzene	cinchonine	40	5 d	–	45[b]
21	2.8	**1n** (2.7)	**2n**	EtOH	TEA	80	2 h	100	95
22	8.8	**1n** (10)[d]	**2n**	MeOH	TEA	20	2 d	92	
23	0.6	**1o** (0.5)	**2o**	EtOH	TEA	80	1 d	< 45	39
24	5.5	**1p** (5.5)	–	EtOH	TEA	80	2 d	0	
25	0.8	**1q** (3.6)	**2q**	MeOH	TEA	40	1.5 h	~80	74
26	5.0	**1q** (6.2)	**2q**	MeOH	TEA	40	5 h	–	76[a]

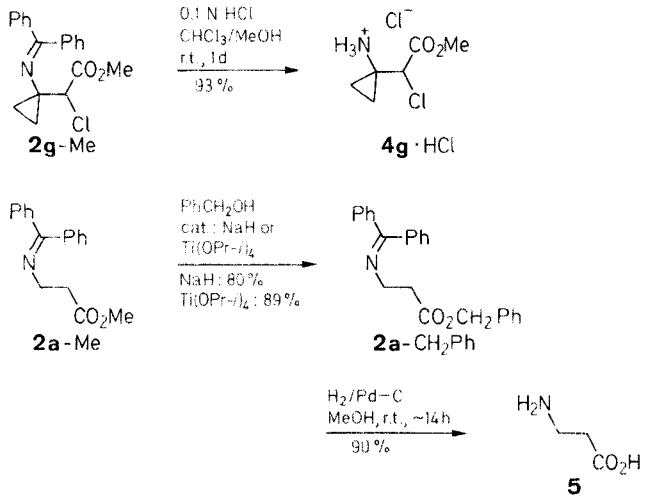
[a] Yield based on the purification of an aliquot of the crude product by column chromatography; the remaining part was used without further purification.

[b] The reaction was terminated before completion.

[c] Crude product used without purification.

[d] Starting material used without prior distillation.

use as *N*-protected building blocks in peptide synthesis,[4] and at least one of them, **2k**-Et, as a C-H acidic substrate in alkylation reactions, even under phase-transfer catalytic conditions.[1] The amino group in compounds **2** can be deprotected by hydrolysis under weakly acidic conditions (acetic acid, citric acid, dilute hydrochloric acid).[1-3,12,13] With strong acids (6 N hydrochloric acid) methyl ester and nitrile groups are hydrolyzed at the same time.[13] Mild acidic hydrolysis was exemplified with methyl 2-[1-(diphenylmethylene)aminocyclopropyl]-2-chloroacetate (**2g**-Me) to give the hydrochloride of the β-amino ester **4g** in 93% yield. The (diphenylmethylene)amino group can also be removed by hydrogenolysis. Catalytic hydrogenation of benzyl esters **2**-CH_2Ph obtained from **2**-Me by base-catalyzed (sodium hydride or titanium(IV) isopropoxide in benzyl alcohol) transesterification, directly yields free β-amino acids, e.g. β-alanine **5** from **2a**-Me via **2a**-CH_2Ph.



NMR spectra were recorded on Varian XL 300 and Bruker WH 270 spectrometers. IR spectra on a Perkin-Elmer 1310 spectrometer, and mass spectra on Varian micromass 7070 F (70 eV, 200 μA; CI with ammonia or isobutane) or CH 7 (70 eV) spectrometers. Melting points were determined on a Büchi apparatus according to Dr. Tottoli and are uncorrected. Microanalyses were done by the microanalytical laboratory of the "Institut für Organische Chemie, Universität Hamburg". For chromatographic purifications of β-(diphenylmethylene)amino carbonyl compounds and nitriles dried silica is preferred over alumina. Silica gel 60 (E-Merck, Darmstadt) was dried for 5 h at 50–100 °C/0.01 Torr, then treated with triethylamine (TEA) vapor or stirred with 1% TEA in the solvent to be used.

Addition of (Diphenylmethylene)amine (DPMA-H) to Acceptor-Substituted Alkenes 1a–q; General Procedure:

To DPMA-H[14] (1.81 g, 10 mmol) in MeOH (20 mL), reactant **1** (10.5 mmol for volatile substrates and 10.0 mmol for non-volatile substrates) is added at 20 °C. Less reactive volatile acceptors are employed in a larger excess (20 mmol). Addition of some TEA (0.5 mL) and refluxing accelerates the reaction, and may be mandatory in some cases (see Table 1). The progress of the reaction is monitored by ^{1}H-NMR; TLC detection is often unreliable, because DPMA-H hydrolyzes on the plates. For work-up, all the volatile components are removed under vacuum to leave, in most cases, spectroscopically pure products (reactive esters, nitriles, ketones). Some products can be crystallized from ether/heptane by the evaporation technique (see below).

Problematic products (e.g., from aldehydes) or incompletely converted mixtures can be separated on dried silica gel doted with ca. 1% TEA (see above). With petroleum ether (60–80 °C)/ether, 5:1, the products usually elute between benzophenone and DPMA-H.

Examples of Typical Procedures:

N-Diphenylmethylene-β-alanine Methyl Ester (**2a**-Me):

Methyl acrylate (**1a**-Me; 4.75 g, 55.2 mmol) is added to a solution of DPMA-H (5.0 g, 27.6 mmol) in *t*-BuOH (40 mL) and TEA (1 mL) and kept at 70 °C. After 5 d the conversion is complete; solvent, catalyst, and excess acrylate are distilled to leave 7.45 g product **2a**-Me (purity > 95%). Chromatography of an aliquot of 2.1 g crude product on silica (70 cm × 2.3 cm, petroleum ether (60–80 °C)/ether/TEA, 70:10:1) gives 1.5 g (72%) of oily **2a**-Me (R_f 0.27, pentane/ether, 2:1). Transesterification is not observed.

Table 2. ^{1}H-NMR Data of New β-(Diphenylmethylene)amino Carbonyl Compounds and Nitriles **2**[a]

Compound	δ, *J*(Hz)
2a-Me	2.71 (t, 2H, ^3J = 7, α-CH_2); 3.64 (t, 2H, ^3J = 7, β-CH_2); 3.66 (s, 3H); 7.14–7.19 (m, 2H_{arom}); 7.27–7.36 (m, 2H_{arom}); 7.37–7.50 (m, 3H_{arom}); 7.54–7.61 (m, 2H_{arom}); 7.77–7.82 (m, 1H_{arom})
2a-*t*-Bu	1.44 (s, 9H, $C(CH_3)_3$); 2.63 (t, 2H, α-CH_2); 3.60 (t, 2H, β-CH_2); 7.15–7.20 (m, 2H_{arom}); 7.27–7.41 (m, 3H_{arom}); 7.41–7.51 (m, 3H_{arom}); 7.56–7.62 (m, 2H_{arom})
2a-CH_2Ph	2.76 (t, 2H, ^3J = 6.8, α-CH_2); 3.65 (t, 2H, ^3J = 6.8, β-CH_2); 5.12 (s, 2H); 7.09–7.13 (m, 2H_{arom}); 7.26–7.46 (m, 11H_{arom}); 7.54–7.58 (m, 2H_{arom})
2b-Me	1.17 (d, 3H, ^3J = 6.3, $CHCH_3$); 2.71 (dd, 1H, ^2J = 15, ^3J = 8.2, CH_2); 2.49 (dd, 1H, ^2J = 15, ^3J = 4.8, CH_2); 3.59 (s, 3H, OCH_3); 3.90 (m$_c$, 1H, CH); 7.17–7.24 (m, 2H_{arom}); 7.25–7.35 (m, 3H_{arom}); 7.39–7.49 (m, 3H_{arom}); 7.55–7.59 (m, 2H_{arom})
2c-Me	1.19 (d, 3H, ^3J = 7.0, $CHCH_3$); 2.91 (m$_c$, 1H, CH); 3.46 (dd, 1H, ^2J = 13.7, ^3J = 6.8, CH_2); 3.62 (dd, 1H, ^2J = 13.7, ^3J = 6.6, CH_2); 3.68 (s, 3H, OCH_3); 7.14–7.18 (m, 2H_{arom}); 7.27–7.49 (m, 6H_{arom}); 7.56–7.61 (m, 2H_{arom})
2f-Me	0.88 (m$_c$, 4H, *c*-C_3H_4); 2.32 (s, 2H); 3.63 (s, 3H); 7.24–7.37 (m, 5H_{arom}); 7.40–7.45 (m, 3H_{arom}); 7.53–7.57 (m, 2H_{arom})
2f-Et[b]	0.90 (m$_c$, 4H, *c*-C_3H_4); 1.22 (t, 3H); 2.30 (s, 2H); 4.11 (q, 2H, OCH_2); ca. 7.23–7.61 (m, 10H_{arom})
2g-Me[b]	0.73–1.02 (m, 3H, *c*-C_3H_4); 1.22–1.38 (m, 1H, *c*-C_3H_4); 3.86 (s, 3H); 4.36 (s, 1H); 7.27–7.48 (m, 8H_{arom}); 7.55–7.59 (m, 2H_{arom})
2h-Et[b]	1.21 (t, 3H); 1.34–1.76 (m, 4H, *c*-C_3H_4); 3.48 (q, 2H); 3.84 (s, 1H); 7.25–7.70 (m, 10H_{arom})
2k-Et	1.22 (quint (2t), 6H, CH_3); 2.86 (dd, 1H, ^2J = 16, ^3J = 7.6, $CHCH_2$); 3.05 (dd, 1H, ^2J = 16, ^3J = 5.6, $CHCH_2$); 4.01–4.26 (m, 4H, OCH_2CH_3); 4.54 (dd, 1H, ^3J = 7.6, 5.6, $CHCH_2$); 7.24–7.49 (m, 8H_{arom}); 7.59–7.64 (m, 2H_{arom})
2l	2.69 (t, 2H, ^3J = 6.7, α-CH_2); 3.57 (t, 2H, ^3J = 6.7, β-CH_2); 7.14–7.18 (m, 2H_{arom}); 7.28–7.50 (m, 6H_{arom}); 7.61–7.66 (m, 2H_{arom})
2m	3.82 (d, 2H, ^3J = 6.5); 4.77 (t, 1H, ^3J = 6.5); 7.14–7.19 (m, 2H_{arom}); 7.30–7.52 (m, 6H_{arom}); 7.64–7.69 (m, 2H_{arom})
2n	2.16 (s, 3H); 2.79 (t, 2H, ^3J = 6.8, α-CH_2); 3.61 (t, 2H, ^3J = 6.8, β-CH_2); 7.13–7.18 (m, 2H_{arom}); 7.24–7.47 (m, 6H_{arom}); 7.55–7.60 (m, 2H_{arom})
2o	2.03–2.68 (m, 6H, 2-H, 4-H, 5-H); 3.61 (tt, 1H, ^3J = ca. 6.1, CHN); 7.13–7.17 (m, 2H_{arom}); 7.26–7.48 (m, 6H_{arom}); 7.55–7.62 (m, 2H_{arom})
2q	2.76 (td, 2H, ^3J = 1.8, 6.7, α-CH_2); 3.69 (t, 2H, ^3J = 6.7, β-CH_2); 7.14–7.19 (m, 2H_{arom}); 7.26–7.48 (m, 6H_{arom}); 7.56–7.60 (m, 2H_{arom}); 9.85 (t, 1H, ^3J = 1.8, CHO)

[a] Obtained on a Varian XL 300 spectrometer in $CDCl_3$/TMS.

[b] Obtained on a Bruker WH 270 spectrometer in $CDCl_3$ (δ = 7.26), except **2g**-Me ($CDCl_3$/TMS).

Methyl 2-[1-(Diphenylmethylene)aminocyclopropyl]-2-chloroacetate (**2g**-Me):

A) *In Methanol:* Methyl 2-chloro-2-cyclopropylideneacetate (**1g**-Me; 4.0 g, 27.3 mmol) in MeOH (40 mL) is added dropwise to a solution of DPMA-H (5.0 g, 27.6 mmol) in MeOH (100 mL). When the reaction is complete (ca. 1 d), the solvent is evaporated under vacuum to leave 8.96 g of spectroscopically pure (> 95%) product **2g**-Me. An aliquot of 2.0 g is purified by column chromatography on TEA-doted silica (50 cm × 1.8 cm, petroleum ether (60–80°C)/ether, 7:1) to give 1.95 g (98%) yellowish white crystals (R_f 0.43; pentane/ether, 2:1) with correct microanalytical data (see Table 4). Recrystallization from ether/hexane by slow evaporation of the ether furnishes large, clear plates; mp 64°C.

B) *In Dichloromethane:* A mixture of **1g**-Me (735 mg, 5.0 mmol), DPMA-H (1.0 g, 5.5 mmol) and DABCO (60 mg, 0.54 mmol) in CH_2Cl_2 (15 mL) is stirred for 6 weeks. After addition of pentane (10 mL), the ammonium salt from the reaction between DABCO and solvent is filtered off. The solvent is evaporated and the residue chromatographed on silica gel (54 cm × 1.2 cm) with pentane/ether/EtOAc, 50:5:2, to give **2g**-Me; yield: 1.57 g (96%); R_f 0.18.

N-Diphenylmethyleneaspartic Acid Diethyl Ester (**2k**-Et):

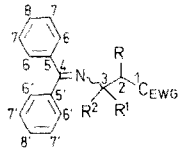
A mixture of DPMA-H (1.1 g, 6.07 mmol), diethyl maleate (**1k**-Et; 1.1 g, 6.39 mmol), TEA (0.3 mL), and EtOH (20 mL) is stirred at 80°C for 8 d. According to an ^{1}H-NMR spectrum the reaction is incomplete. The solvent is removed, and the product separated by column chromatography on silica (38 cm × 2.2 cm, hexane/EtOAc, 10:1) to give **2k**-Et; yield: 1.19 g (55%); R_f 0.09. DPMA-H, 0.45 g (41%), can be recycled. Recrystallization of **2k**-Et from heptane/ether gives clear plates; mp 69°C.

3-(Diphenylmethylene)amino-2-chloropropionitrile (**2m**):

DPMA-H (1.0 g, 5.5 mmol) and α-chloroacrylonitrile (**1m**; 0.96 g, 11.0 mmol) in MeOH (20 mL) are stirred under nitrogen for 18 h. The solvent and excess **1m** are evaporated to give 1.48 g crude product (purity > > 95%); further purification is achieved by twofold column chromatography on silica (50 cm × 1.8 cm, petroleum ether, (60–80°C)/ether, 7:1) to give **2m** as a solidifying oil; yield: 1.11 g

Table 3. ^{13}C-NMR Data of New β-(Diphenylmethylene)amino Carbonyl Compounds and Nitriles **2**[a,b]

Compound	C-1	C-2	C-3	C-4	C-5, C-5′	C-6,[c] C-6′[c]	C-7,[c] C-7′[c]	C-8, C-8′	Other Carbons
2a-Me	172.73	35.84	49.27	168.94	136.60, 139.58	127.61, 127.93	128.30, 128.46	128.39, 129.91	51.41
2a-CH_2Ph	172.17	36.14	49.32	168.94	136.60, 139.55	127.61, 127.93	128.36, 128.46	128.38, 129.91	66.00; 136.06 (*i*); 128.00 (*o*, *p*);[c] 128.36 (*m*)[c]
2b-Me	172.14	42.72	54.14	167.23	136.88, 139.97	127.63, 127.91	128.27, 128.38	128.22, 129.76	21.80 ($CH\underline{C}H_3$); 51.20 (OCH_3)
2c-Me	176.04	41.35	56.60	168.89	136.74, 139.75	127.83, 128.03	128.46, 128.54	128.46, 130.01	15.18 ($CH\underline{C}H_3$); 51.57 (OCH_3)
2f-Me	171.50	42.68	40.60	168.98	138.79, 141.00	128.33, 128.46	127.84, 128.17	128.46, 129.78	51.21 (OCH_3); 16.34 (CH_2 of *c*-Pr)
2g-Me	166.01[c]	64.59	46.60	168.61[c]	137.50, 140.41	127.89, 128.01	128.24, 128.52	128.62, 130.10	15.15, 16.66 (CH_2 of *c*-Pr); 52.64 (OCH_3)
2k-Et	171.61[c]	38.21	61.83	170.74[c]	136.06, 139.44	127.90, 127.90	128.31, 128.83	128.67, 130.33	14.03, 14.07 (CH_3); 60.38, 61.15 (CH_2); 170.74 (CO_2Et)
2l	118.79	19.83	48.99	170.57	136.11, 139.05	127.55, 128.54	128.10, 128.75	128.80, 130.45	
2m	116.56	42.96	57.38	172.08	135.62, 138.53	127.43, 128.12	128.72, 128.82	129.07, 131.81	
2n	207.87	44.87	48.85	168.78	136.61, 139.60	127.61, 127.99	128.28, 128.53	128.43, 129.93	30.39
2o	217.85	46.70	59.29	167.15	136.69, 139.33	127.47, 127.95	128.27, 128.37	128.52, 129.90	31.12 (γ-C); 36.79 (δ-C)
2q	202.06	45.04[c]	47.43[c]	169.19	136.51, 139.42	127.58, 128.36	128.04, 128.62	128.56, 130.10	

[a] 

[b] Obtained on a Varian XL 300 spectrometer (75.4 MHz).

[c] Assignment uncertain.

Table 4. New β-(Diphenylmethylene)amino Carbonyl Compounds and Nitriles **2**

Compound	Molecular Formula[a]	MS (70 eV) *m/z* (%)	IR (film) ν (cm^{-1})
2a-Me	$C_{17}H_{17}NO_2$ (267.3)	267 (M^+, 7.2), 266 (17.5), 193 (100)	1734 (C=O), 1655, 1275, 1170, 697
2a-*t*-Bu	$C_{20}H_{23}NO_2$ (309.4)	309 (M^+, 3.8), 252 (38.5), 236 (28.0), 193 (100)	2972 (C–H), 1727 (C=O), 1621 (C=N), 1100, 700
2a-CH_2Ph	$C_{23}H_{21}NO_2$ (343.4)	343 (M^+, 0.8), 107 (64.1), 91 (100)	2918, 1737 (C=O), 1165, 694
2b-Me	$C_{18}H_{19}NO_2$ (281.4)	281 (M^+, 4.5), 266 (10.1), 207 (100)	2960, 1740 (C=O), 1620 (C=N)
2c-Me	$C_{18}H_{19}NO_2$ (281.4)	281 (M^+, 2.9), 250 (4.5), 91 (100)	1735 (C=O), 1621 (C=N), 1441, 1193
2f-Me	$C_{19}H_{19}NO_2$ (293.4)	293 (M^+, 11.3), 265 (30.0), 166 (100)	1735 (C=O), 1618 (C=N), 1163, 697
2g-Me	$C_{19}H_{18}ClNO_2$ (327.8)	327 (M^+, 2.8), 292 (62.8), 232 (42.1), 105 (100)	[KBr]: 2970, 1715 (C=O), 1606, 1243, 1203
2k-Et	$C_{21}H_{23}NO_4$ (353.4)	[CI: NH_3] 345 (MH^+, 100), 280 (15.1), 265 (11.6)	[KBr]: 2967, 1733 (C=O), 1620 (C=N), 1030, 697
2l	$C_{16}H_{14}N_2$ (234.3)	234 (M^+, 12.7), 194 (31.4), 91 (100)	[KBr]: 2920, 2238 (C≡N), 1283, 698
2m	$C_{16}H_{13}ClN_2$ (268.8)	268 (M^+, 1.1), 233 (0.9), 232 (0.8), 91 (100)	[KBr]: 2880, 2240 (C≡N), 1615, 1316, 1288, 695
2n	$C_{17}H_{17}NO$ (251.3)	251 (M^+, 3.8), 208 (100), 180 (62.5)	1712 (C=O), 1619 (C=N), 779, 697
2o	$C_{18}H_{17}NO$ (263.3)	263 (M^+, 13.1), 206 (8.3), 180 (100)	
2q	$C_{16}H_{15}NO$ (237.3)	[CI: *i*-Bu] 238 (MH^+, 100), 208 (26.3)	2910, 2810 (CO–H), 1719 (C=O)

[a] Satisfactory microanalyses obtained: C ±0.16, H ±0.05, N ±0.27; except **2n**, **o**, **q** (dec) and **2a**-*t*-Bu and **2c**-Me (not obtained).

(75%); R_f 0.25 (pentane/ether, 2:1). Crystallization from ether/hexane gives colorless needles; mp 48°C.

4-(Diphenylmethylene)amino-2-butanone (**2n**):

A) A mixture of DPMA-H (0.5 g, 2.75 mmol), freshly distilled methyl vinyl ketone (**1n**; 0.19 g, 2.7 mmol), and TEA (0.5 mL) in EtOH (10 mL) is kept at 80°C for 2 h. The solvent is removed, and the residue is chromatographed on silica gel (40 cm × 2.2 cm, petroleum ether (60–80°C)/ether, 4:1) to give **2n**; yield: 0.65 g (95%); R_f 0.12 (pentane/ether, 2:1). The neat product decomposes slowly, but it can be kept in frozen benzene for an extended period of time.

B) DPMA-H (1.6 g, 8.78 mmol), undistilled **1n** (0.7 g, 10 mmol) (containing 5% water (!) and stabilizers), molecular sieves 3 Å (ca. 0.1 g), and TEA (0.1 mL) in MeOH (15 mL) are stirred at ambient temperature for 2 d. The conversion is > 92% (NMR).

3-(Diphenylmethylene)aminopropanal (**2q**): DPMA-H (0.15 g, 0.8 mmol), acrolein (**1q**; 0.2 g, 3.6 mmol), and TEA (0.1 mL) in MeOH (2 mL) are kept at 40°C for 1.5 h. After removal of all volatile components, the residue is immediately chromatographed on silica gel (35 cm × 0.8 cm, pentane/ether, 3:1) to give 140 mg (74%) **2q** (R_f 0.26; pentane/ether, 1:1). The product still contains some benzophenone and decomposes rapidly.

Transesterifications of Methyl 2-Diphenylmethyleneaminoalkanoates 2-Me:

N-Diphenylmethylene-β-alanine Benzyl Ester (**2a**-CH_2Ph):

A) Crude methyl ester **2a**-Me (0.95 g, 3.55 mmol) in benzyl alcohol (20 mL) is placed in a short-path distillation apparatus under nitrogen. Titanium(IV) isopropoxide (0.2 mL, ca. 0.7 mmol) is added via syringe, and the mixture is heated to 90°C. The pressure in the apparatus is reduced by evacuation up to a point at which the alcohol begins to boil; the apparatus is then kept closed at 90°C for 20 h. Thereafter the alcohol is distilled under vacuum, and the residue is separated by column chromatography on silica gel (45 cm × 1 cm, petroleum ether (60–80°C)/ether, 10:1) to give **2a**-CH_2Ph; yield: 1.08 g (89%); R_f 0.29 (pentane/ether, 2:1).

B) Crude **2a**-Me (0.8 g, 3 mmol) in benzyl alcohol (15 mL) and NaH (10 mg, 0.4 mmol) as catalyst at 60–80°C under otherwise similar conditions gives 0.82 g (80%) **2a**-CH_2Ph.

Ester **2a**-*t*-Bu is obtained in low yield (16%) from **2a**-Me with KOBu-*t* as catalyst in *t*-BuOH by stirring at ambient temperature for 24 h.

Deprotection of 2a-CH_2Ph to β-Alanine (5) by Catalytic Hydrogenation:

N-Diphenylmethylene-β-alanine benzyl ester (**2a**-CH_2Ph; 800 mg, 2.3 mmol) in MeOH (40 mL) is stirred overnight with 10% palladium on charcoal (60 mg) under hydrogen (balloon, ca. 1 atm). After the reaction is complete (TLC), the reaction mixture is filtered and the filtrate is concentrated on a rotary evaporator at 60°C until the solution becomes cloudy. Then water (0.3 mL) is added followed by acetone until precipitation starts again. From the cooled mixture, 100 mg (49%) crystals are collected; a 2nd and 3rd crop are collected in the same way giving a total yield of 185 mg (90%) or β-alanine (**5**). Alternatively, column filtration over silica gel is used for purification. The identities of diphenylmethane and β-alanine are evidenced by TLC and spectroscopy; for the MS of β-alanine, the benzamide is prepared.

Methyl 2-(1-Aminocyclopropyl)-2-chloroacetate Hydrochloride (4g):

A mixture of **2g**-Me (330 mg, 1.0 mmol), $CHCl_3$ (10 mL), MeOH (5 mL) and 0.1 N HCl (12 mL) is vigorously stirred at ambient temperature for 1 d. The solution is concentrated to approximately 10 mL; then water (15 mL) is added to the mixture, and the aqueous phase is thoroughly washed with $CHCl_3$ and ether (2 × 10 mL each). After evaporation of the solvent at 40°C under vacuum, the residue is dissolved in dry MeOH. This solvent is removed on a rotary evaporator at 40°C; the product is dried again under high vacuum, giving **4g** as a white solid, which is difficult to recrystallize; yield: 186 mg (93%); mp 138–140°C (dec).

$C_6H_{11}Cl_2NO_2$	calc.	C 36.02	H 5.54	N 7.00	Cl 35.44
(200.1)	found	36.14	5.50	7.09	35.59

IR (KBr): ν = 2850 (br N–H), 1735 (C=O), 1510, 1293 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS, 300 MHz): δ = 1.10–1.20 (m, 1 H); 1.24–1.47 (m, 3 H); 3.35 (s, 3 H); 4.59 (s, 1 H).

^{13}H-NMR ($CDCl_3$/TMS, 75.4 MHz): δ = 12.41, 13.12, 37.53, 54.22, 60.66, 168.76.

MS (70 eV): *m/z* (%) = 163 (M^+ – HCl, 0.6); 128 (M^+ – HCl – Cl, 57.0), 96 (M^+ – HCl – Cl – MeOH, 100); 41 (53.8); 38 (16.3); 36 (HCl, 47.3).

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