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Phase-transfer-catalysed Additions of Methyl *N*-(Diphenylmethylidene)glycinate to Azomethines†

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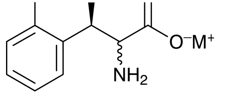
Methyl 3-aryl-3-arylamino-2-[(diphenylmethylidene)amino]propanoates are prepared by phase-transfer-catalysed reactions of methyl *N*-(diphenylmethylidene)glycinate with arylmethylideneanilines.

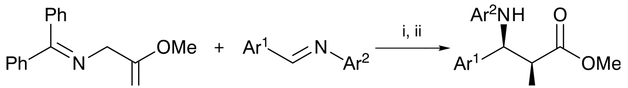
Glycine ester Schiff bases have been widely used in recent years as anionic glycine synthons in reactions with a variety of electrophiles to prepare higher, or possessing another functional group α-amino acids.[7–14] However, reactions with azomethines, giving access to α,β-diamino acids, have not received any attention.[1] We now report on the preparation and stereochemistry of methyl 3-aryl-3-arylaminopropanoates **3** by phase-transfer-catalysed reactions of methyl *N*-(diphenylmethylidene)glycinate (**1**) with the azomethines **2**.

The reaction of **1** and **2a** was investigated using different solvents, catalysts and bases, at both room temperature and 0 °C in order to optimize the yields and the stereoselectivities (Scheme). In general, low to moderate yields and low stereoselectivities were observed in all cases. Somewhat better results were obtained when performing the reaction in MeCN using 50% NaOH and benzyltriethylammonium chloride (TEBA) at both room temperature and 0 °C for 10 min: 54–60% yield of the diastereoisomers of **3a** from which, after recrystallization, *syn*-**3a** was isolated in a yield of 40–45%. Prolonging the reaction time to 60 min did not change the yield of *syn*-**3a** when carried out at 0 °C (40%); however, after 60 min at room temperature no **3a** was detected. In addition, small amounts of the sodium salt **4a** was isolated, indicating that cleavage of the azomethine bond, beside retro-addition and hydrolysis reactions, was also taking place. HPLC analysis of the reaction of **1** and **2a** within 1 h confirmed these results (Table 4).



4a R = H, M = Na
b R = Me, M = Na
c R = H, M = K

Similar behaviour was observed when **1** was reacted with substituted arylmethylideneanilines **2** except for *N*-(2-methylphenyl)methylideneaniline (**2f**). At room temperature and 0 °C using the standard procedure (50% NaOH–TEBA–MeCN) the diamino esters **3** were obtained in low to moderate yields (Table 5). In the case of the reaction of **1** with **2f**, the cleavage of the azomethine bond and hydrolysis of the ester function was observed even at shorter reaction times. After 10 min the sodium salt **4b** was isolated in a yield of 22%, while the corresponding protected diamino ester **3f** was obtained at 0 °C.



1 **2** **3**

2,3	Ar^1	Ar^2
a	Ph	Ph
b	2-ClC$_6$H$_4$	Ph
c	Ph	2-ClC$_6$H$_4$
d	4-ClC$_6$H$_4$	Ph
e	Ph	4-ClC$_6$H$_4$
f	2-MeC$_6$H$_4$	Ph
g	Ph	2-MeC$_6$H$_4$
h	4-MeC$_6$H$_4$	Ph
i	Ph	4-MeC$_6$H$_4$
j	4-MeOC$_6$H$_4$	Ph
k	Ph	4-MeOC$_6$H$_4$

Scheme 1 *Reagents and conditions*: i, 50% NaOH, TEBA, MeCN, room temperature or 0 °C; ii, 4% NaOH, DMSO

Low yields of compounds **3** were also obtained when performing the reaction in the DMSO–NaOH system (Table 5). A lower yield of *syn*-**3a** (28%) was also observed upon performing the reaction without any catalyst.

Attempts to convert **3a** into the free acid failed owing to degradation processes. However, its sodium salt (**4a**) and potassium salt (**4c**) were easily prepared in good yields (72 and 85%, respectively) by refluxing an ethanol solution of **3a** with aqueous sodium hydroxide or solid potassium hydroxide, respectively.

Table 4 Ratio of *anti* **3a**/*syn* **3a** obtained at r.t. under standard conditions[a]

	Anti/*syn*[b]	
Reaction time	r.t.	0 °C
10 s	35:65	37:63
30 s	32:68	33:67
60 s	32:68	32:68
2 min	32:68	31:69
5 min	31:69	30:70
10 min	25:75	27:73
30 min	—[c]	25:75
60 min	—[d]	—[e]

[a]50% NaOH–TEBA–MeCN, 10 min. [b]Measured by HPLC. [c]Only traces of **3a** were detected. [d]No **3a** was detected. [e]Not measured.

Table 5 Yields of compounds **3a**–**k** prepared

	Yield (%)[a]		
	r.t.	0 °C	NaOH, DMSO
3a	45	40	36
3b	56	64	21
3c	66	64	55
3d	28	—[b]	33
3e	52	51	41
3f	—[c]	28	9
3g	12	12	5
3h	27	22	—[d]
3i	18	37	13
3j	15	22	—[d]
3k	9	—[b]	6

[a]Yield of pure *syn* diastereoisomer. [b]The reaction was not carried out at 0 °C because of crystallization of the azomethine. [c]The sodium salt **4b** was isolated in yield of 22%. [d]No product was isolated.

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†Part 15. For Part 14 see ref. 1.

The amino esters **3** and the salts **4a**–**c** are new compounds. Their structures were confirmed by elemental analyses, IR and ^{1}H NMR spectra. *Syn* configuration[19] was assigned to the amino esters **3** on the basis of the low values of their vicinal coupling constants (2–2.3 Hz) and literature data for α-amino-β-hydroxy acid derivatives with known configuration,[15,20] for which $J_{\mathrm{syn}} < J_{\mathrm{anti}}$. The crystal structure of **3a** (Fig. 1) confirmed these assignments.

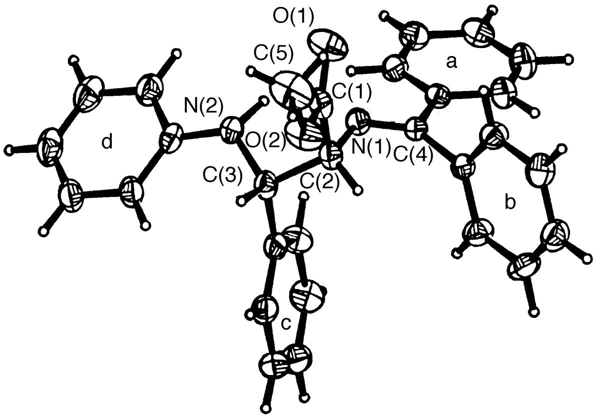

Fig. 1 X-Ray structure of **3a**

Experimental

Crystal Data for syn-**3a**.—$C_{29}H_{26}N_2O_2$, $M_r = 434.54$, $F(000) = 920$, monoclinic, $a = 9.560(3)$, $b = 27.713(4)$, $c = 9.762(2)$ Å, $\beta = 112.37(1)°$, $V = 2391.7(6)$ Å^3, space group $P2_1/c$ (no. 14), $Z = 4$, $D_x = 1.206$ g cm^{-1}, μ(Mo-Kα) = 0.07 cm^{-1}. The experimental data were collected on a CAD-4 diffractometer using graphite monochromated Mo-Kα radiation ($\lambda = 0.710$ 73 Å) at 292 K. The structure was solved by direct methods[23] and refined by full-matrix least-squares.[24] The final R value was 0.059 ($R_w = 0.065$). The estimated standard deviation for the geometrical parameters involving non-hydrogen atoms: bond lengths 0.003–0.005 Å; bond angles 0.2–0.4°.

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Techniques used: ^{1}H NMR, IR, HPLC, X-ray diffraction

References: 24

Table 1: Yields of **3a** obtained under different conditions

Table 2: Yields of **3a** obtained with different catalysts

Table 3: Effect of the base used on the ration of **1** with **2a**

Table 6: Amino esters **3** prepared

Table 7: IR and ^{1}H NMR data of amino esters **3**

Tables 8–11: X-Ray data

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