Phase-transfer catalysed reactions of mono- and disubstituted N-(benzylidene)-benzylamines with cinnamic acid derivatives†

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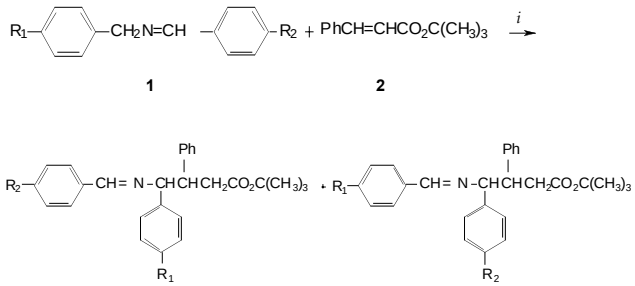
Tert-butyl esters **3** and 3-cyanopyrrolidines **6** are prepared by phase-transfer-catalysed reactions of symmetrical 4,4′-disubstituted N-(benzylidene)benzylamines with *tert*-butyl cinnamate and α-phenylcinnamonitrile, respectively; similar reactions of mono-substitited N-(benzylidene)benzylamines afforded mixtures of compounds **3**, respectively **6**, and their regioisomers **3(A)** and **6(A)**.

We have recently reported the synthesis of some esters of 4-amino-3,4-diphenylbutanoic acid by phase-transfer catalysed reactions of N-(benzylidene)benzylamine and esters of cinnamic acid.[1] Now we report on the reactions of mono- and disubstituted N-(benzylidene)benzylamines **1a-i** with *tert*-butyl cinnamate (Scheme 1) and α-cinnamonitrile (Scheme 3). The site of alkylation of ambident anions, generated from unsymmetrical N-(benzylidene)benzylamines is known to be dependent upon the nature of the substituent and proceeds preferentially at the carbon atom α to the more deficient system.[2,3] Similar behaviour of mono-substituted N-(benzylidene)benzylamines was observed when they were reacted with aromatic aldehydes.[4] However, it was reported recently that reactions of mono-substituted N-(benzylidene)benzylamines with ethyl cinnamate led to 4-amino-3,4-diphenylbutanoic acid in all cases whatever the substituent.[5]



1,3,3(A)	R_1	R_2
a	Cl	Cl
b	CH_3	CH_3
c	CH_3O	CH_3O
d	Cl	H
e	H	Cl
f	CH_3	H
g	H	CH_3
h	CH_3O	H
i	H	CH_3O
j	CH_3	Cl

Scheme 1 *Reagents and conditions*: i, 50% NaOH, TEBA, MeCN, room temperature

Following the developed procedure (50% NaOH, TEBA, MeCN, room temperature),[1] the reactions of the disubstituted N-(benzylidene)benzylamines **1a-c** with *tert*-butyl cinnamate (**2**) afforded the esters **3a-c** with high *erythro* diastereoselectivity (TLC, ^{1}H NMR) in yields of 19-84%. Under the same conditions the reactions of **2** with the mono-substituted N-(benzylidene)benzylamines **1d-i** proceeded with satisfactory to good chemical yields (19-74%). However, low to modest regioselectivity and diastereoselectivity was observed in nearly all cases. The ^{1}H NMR spectra of the crude products revealed four signals for the proton of the azomethine group, an indication that mixtures of the diastereoisomers of the regioisomers **3** and **3(A)** were formed. As can be seen from Table 1, *erythro* isomers, in general, were the predominating ones in the mixtures obtained by the reaction of N-(benzylidene)benzylamines possessing a methyl or methoxy group as substituents. On the contrary, *threo* diastereoselectivity was observed when chloro-substituted N-(benzylidene)benzylamines were reacted with *tert*-butyl cinnamate. However, a few exceptions were observed (**3g**, **3h**, **3j**), suggesting that the selectivity was mainly dependent on the solubility of the diastereoisomers in the solvent used (DMSO). In all cases attempts to separate the isomers either by recrystallization or column chromatography failed. Therefore, the mono-substituted N-(benzylidene)benzylamines **1d-i** are not useful as reagents for the preparation of γ-amino acid derivatives.

Table 1 Yields of isolated products **3** and **3+3(A)**

Product	Yield[a]	Ratio ***e*-3**:***t*-3**:***e*-3(A)**:***t*-3(A)**	
	(%)	b	c
3a	84[d]	97:3	pure **3a**
3b	57	90:10	pure **3b**
3c	19	90:10	pure **3c**
3d+3d(A)	53	0:71:29:0	17:58:14:11
3e+3e(A)	34	29:0:3:68	19:2:4:75
3f+3f(A)	54[d]	82:10:8[f]	–[e]
3g+3g(A)	56	79:7:14[f]	52:13:35[f]
3h+3h(A)	19	21:45:32:2	9:40:36:15
3i+3i(A)	74[d]	–[e]	64:2:32:2
3j+3j(A)	64	17:5:5:73	16:4:4:76

[a]Yield of recrystallized product unless stated otherwise. [b]Ratio determined in crude products. [c]Ratio in recrystallized products. [d]Yield obtained after treatment of crude products with ethanol. [e]Not determined. [f]Ratio *erythro*-(**3**+**3(A)**):*threo*-**3**:*threo*-**3(A)** is given because both *erythro* isomers have a coincident chemical shift.

Treatment of the esters **3a-c** with 10% HCl at room temperature yielded the hydrochlorides of the corresponding *tert*-butyl 4-amino-4-aryl-3-phenylbutanoates **4a-c**, while refluxing with 6N HCl afforded the hydrochlorides of the acids **5a-c** (Scheme 2).

The reactions of **1a-i** with α-phenylcinnamonitrile, like N-(benzylidene)benzylamine,[6] resulted in the 3-cyanopyrrolidines **6**, or mixtures of **6** and their regioisomers **6(A)** (Scheme 3). The reactions were performed at room temperature in both 50% NaOH/TEBA/DMSO and 4% NaOH/DMSO systems[6]. The best yield was obtained for the compound **6a**, formed by reaction of N-(4-chlorophenylmethylene)-4-chlorobenzylamine (**1a**) and α-phenylcinnamonitrile (77%,

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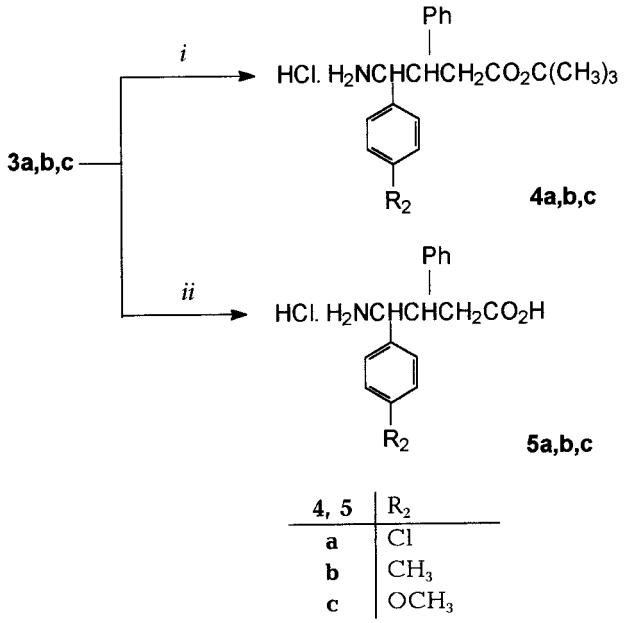
† Part 18. For Part 17 see ref. 1.

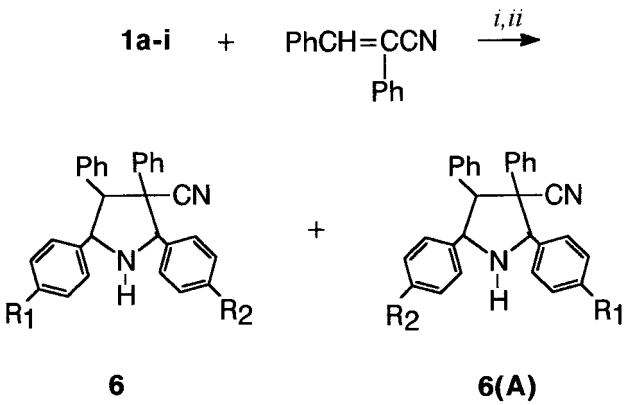
Table 3 Yields of isolated products **6** and **6+6(A)**

Product	Yield[a]		Ratio[b]	
	Method A[c]	Method **B**[d]	**6:6(A)**	**6-I:6-III**
6a	77	80	–	100:0 (A,B)[e]
6b	60	33[f]	–	100:0 (A)[e] 85:15 (B)[e]
6c	38[f]	–[g]	–	66:34 (A)[e]
6d+6d(A)	67	67	50:50 (A[e],B[h])	
6e+6e(A)	69	73	50:50 (A)[e]	
6f+6f(A)	57	74	50:50 (A[e],B[h])	
6g+6g(A)	63	72	50:50 (B[e,h])	
6h+6h(A)	–[g]	6	68:32 (B)[h]	66:34 (B)[e]
6i+6i(A)	36[f]	5	100:0 (A)[e]	

[a]Yield of recrystallized product. [b]Determined by integration of H-2 signal. [c]50% NaOH, TEBA, DMSO, r.t. [d]4% NaOH, DMSO, r.t. [e]Ratio determined after recrystallization. [f]Mixture of diastereoisomers. [g]No reaction product was isolated. [h]Ratio of crude product.



Scheme 2 *Reagents and conditions: i,* 10% HCl, r.t.; *ii,* 6N HCl, reflux



Scheme 3 *Reagent and conditions: i,* 50% NaOH, TEBA, DMSO, room temperature; *ii,* 4% NaOH, DMSO, room temperature

respectively 80%, Table 3). In this case excellent stereoselectivity was also observed, the crude product consisting of a single diastereoisomer, while the same reactions of both **1b** and **1c** proceeded with lower yields and diastereoselectivity. The reactions of **1d-j** with α-phenylcinnamonitrile, similar to their reactions with *tert*-butyl cinnamate, afforded in good yields

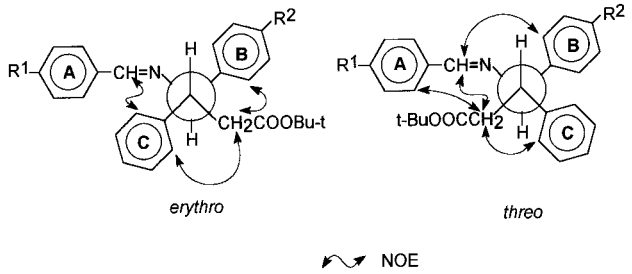


Fig. 1 NOE effects for the *erythro* and *threo* diastereoisomers of compounds **3**.

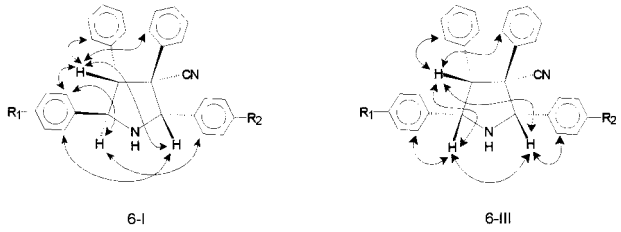


Fig. 3 NOE effects for the isomers of compounds **6a,b,c**.

mixtures of 3-cyanopyrrolidines **6** and their regioisomers **6(A),** the ratio **6:6(A)** in most cases being about 1:1.

The stereochemical assignments of the diastereoisomers of compounds **3** and **6**, and of their regioisomers **3(A)** and **6(A)** were made by using a combination of inverse heterocorrelation spectra HSQC and NOESY spectra. *Erythro* and *threo* configuration was assigned on the basis of different nuclear Overhauser enhancements to the signal of the methylene group (Fig. 1). Compounds **6a, 6b,** and **6c** (major diastereoisomer), were assigned a configuration with *trans* phenyl group at C-2 and C-5, respectively at C-4 and C-5 (Fig. 3, structure **6-I**) The same stereochemistry was assumed for the major diastereoisomers in the mixtures **6** and **6(A)**, while structure **6-III** was assigned to the minor isomers **6b** and **6c** (Fig. 3).

In conclusion, phase-transfer-catalysed reactions of symmetrical N-(benzylidene)benzylamines with *tert*-butyl cinnamate and α-phenylcinnamonitrile provide a useful method for the preparation of 4-amino-3,4-diarylbutanoic acids and 3-cyano-2,3,4,5-tetraarylpyrrolidines; the reactions of monosubstituted N-(benzylidene)benzylamines occur through the formation of the corresponding ambident anions and afford mixtures of regioisomers.

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Techniques used: ^{1}H and ^{13}C NMR, IR

References: 11

Schemes: 3

Figures: 3

Table 1: Yields of isolated products **3** and **3+3(A**)

Table 2: Selected ^{1}H NMR data for compounds **3a,b,c** and the isomers **3a-I** and **3a-II**

Table 3: Yields of isolated products **6** and **6**+**6(A)**

Table 4: Selected ^{1}H NMR parameters of 3-cyano-2,3,4,5-tetraarylpyrrolidines **6**

Table 5: ASIS-values for **6c-III**

Table 6: Compounds **3, 4, 5** and **6** prepared

Table 7: IR and ^{1}H NMR data of compounds **3**, **4, 5** and **6**

Table 8: ^{13}C NMR data for compounds **3a,b,c** and **6a,b,c**

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