Chemoselective N-Alkylation of Di-N,O-protected Tyrosine through Specific Oxy-Anion Solvation by Non-Hydrogen Bonding Donor Solvents

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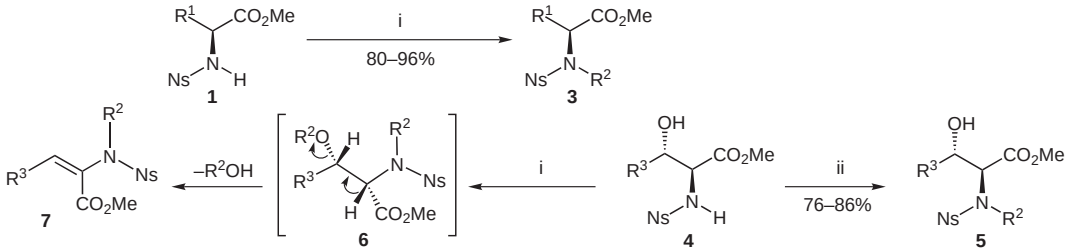
Abstract: *N*-(2-Nitro-benzenesulfonyl) activated L-tyrosine methyl ester has been directly N-alkylated under solid–liquid phase-transfer catalysis (SL-PTC) conditions and in a coordinating non-hydrogen bonding donor (non-HBD) solvent, which reduces through specific solvation the nucleophilicity of the oxy-anionic center of the N,O-dianion formed by action of an anhydrous inorganic carbonate.

Key words: solvent effects, chemoselectivity, alkylations, amino acids, phase-transfer catalysis

Mono-N-alkylated α-amino acid derivatives are a class of exciting products, both as pharmacologically active compounds[1] and as starting materials for the construction of peptidomimetics.[2] Among the *N*-alkyl-α-amino acids preparations,[3] Fukuyama's amine protocol stands out for its mild reaction conditions, simplicity and broad range of applications.[4] Bowman and Coghlan[5] utilized this procedure for the N-alkylation–deprotection of a limited number of 2-(2-nitro-benzenesulfonylamino) carboxylic esters, using organic bases under homogeneous conditions. In a subsequent paper,[6] we reported that solid–liquid phase-transfer catalysis (SL-PTC)[7] permitted remarkable improvements on both times and yields of the N-alkylation reactions for a wider series of α-nosylamido esters (Scheme 1). In particular, esters **1** derived from glycine or amino acids bearing in their side chain either a phenyl or an alkyl group (R^1 = Ph, Alkyl), reacted in a chemo- and stereoselective fashion with alkyl halides **2** under SL-PTC conditions, using acetonitrile as a solvent (Scheme 1), and the corresponding *N*-alkyl-α-nosylamido esters **3** were obtained in excellent yields (80–96%). The alkylation reactions of α-nosylamido-β-hydroxy esters **4** (Scheme 1), derived from serine (R^3 = H) and threonine (R^3 = Me), were less chemoselective. In fact, the aliphatic hydroxy group under these conditions competes with the nosylamide for the nucleophilic attack, and significant amounts of the corresponding substituted α-nosylamido acrylic esters **7** were formed by 1,2-elimination of an alcohol unit (R^2OH) from the unstable di-N,O-alkylated intermediates **6**. The substitution of DMF for acetonitrile improved the N-alkylation chemoselectivity of compounds **4**, and products **5** were isolated in good yields (76–86%).[5]

In view of these results, we guessed that the alkylation reactions of sulfonamido esters derived from α-amino acids containing a phenol unit (10^5–10^6 times more acidic than an aliphatic OH) in their side chain would be knottier. In fact, due to the close acidity values of the aromatic hydroxy group and of the nosylamido group[8] (pk_a ca. 10–11, relative to water),[9] the simultaneous deprotonation of both these functions, and the consequent competition between the two nucleophilic centers of the formed N,O-dianion, are expected. With the aim of investigating the behavior of these compounds in the nucleophilic substitution reactions and producing *N*-alkyl-tyrosine derivatives, an interesting class of new multifunctionalized molecules, we have chosen as a model the methyl ester of L-*N*-(2-nitrobenzenesulfonyl)tyrosine (**9**, Scheme 2).



Scheme 1 N-Alkylation of α-nosylamido esters **1** and **4** under SL-PTC conditions. *Reagents and conditions*: *i*) R_2X (**2**), $K_2CO_{3\ (anhyd)}$, $Et_3BnN^+Cl^-_{(cat.)}$, MeCN, 25–80 °C; *ii*) R^2X (**2**), $K_2CO_{3\ (anhyd)}$, $Et_3BnN^+Cl^-_{(cat.)}$, DMF, 25 °C, R^3 = H, Ns = 2-NO_2–C_6H_4–SO_2.

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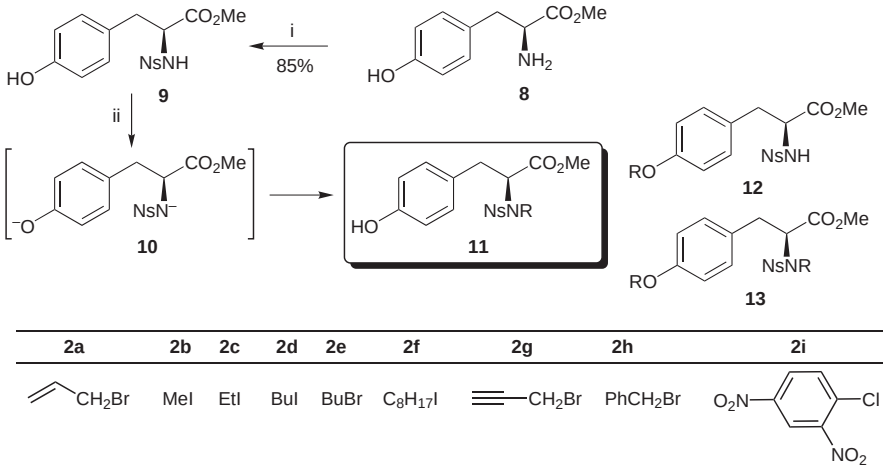

Scheme 2 N-Chemoselective arylsulfonylation–alkylation of methyl tyrosinate. *Reagents and conditions*: *i*) NsCl, $Na_2CO_{3\ (lyoph)}$, THF–DMF (8:1), 25 °C; *ii*) RX (**2a**–**i**), base, solvent, $Q^+X^-_{(cat.)}$.

The nosylamido ester **9** and several arylsulfonamido esters of tyrosine were prepared from the corresponding α-amino acid esters under SL-PTC conditions without protecting the phenolic hydroxy group.[10] As a representative example (Scheme 2), the methyl tyrosinate **8** was made to react with nosyl chloride, in the presence of lyophilized sodium carbonate, by using a THF–DMF mixture as solvent. The highest chemoselectivity of N-arylsulfonylation and sulfonamido ester **9** yield were reached in the presence of a small amount of DMF (2.6 mol/mol of substrate), because this highly ion-coordinating solvent preferentially solvates the [phenoxide/sodium] ion pairs and decreases the charge and hence the nucleophilicity of the oxy-anion.

The reaction of **9** with allyl bromide **2a**, in anhydrous acetonitrile (Table 1) and under the PTC conditions applied to the nosylamido esters **1** (entries 2 and 3), gave only partial conversion of the substrate and produced a mixture of all the possible allylation products **11a**–**13a**, that were separated and identified. Similar results were obtained by operating in THF–DMF and MeCN–DMF mixtures (entries 4–6). Complete conversion of **9** and an interesting N-chemoselectivity were reached in anhydrous DMF at 30 °C (entry 7) and **11a** was isolated in 60% yield, whereas at 80 °C the di-N,O-substituted **13a** (entry 8) was the major product. Substituting lyophilized sodium carbonate for potassium carbonate, even if the reaction times are longer, resulted in higher N-chemoselectivity (79%, entry 9), while Cs_2CO_3 was ineffective also at 30 °C (entry 11) and large amounts of **12a** and **13a** were produced.

Table 1 N-Alkylation of **9** with Allyl Bromide **2a** under SL-PTC Conditions[a]

Entry	Solvent	Base	Temp (°C)	Time (h)	Isolated yields (%)			
					9	**11a**	**12a**	**13a**
1	THF	$K_2CO_{3\ anhyd}$	80	120	63	11	10	9
2	MeCN	$K_2CO_{3\ anhyd}$	30	144	22	38	13	27
3	MeCN	$K_2CO_{3\ anhyd}$	80	4	35	22	21	22
4	THF–DMF (8:1)	$K_2CO_{3\ anhyd}$	30	120	18	36	15	24
5	THF–DMF (1:2)	$K_2CO_{3\ anhyd}$	30	54	35	35	18	12
6	MeCN–DMF (1:2)	$K_2CO_{3\ anhyd}$	30	54	30	35	17	18
7	DMF	$K_2CO_{3\ anhyd}$	30	54	–	60	25	15
8	DMF	$K_2CO_{3\ anhyd}$	80	4	–	20	38	42
9	DMF	$Na_2CO_{3\ lyoph}$[b]	30	96	15	66	–	18
10	DMF	$Na_2CO_{3\ lyoph}$	50	76	–	53	–	35
11	DMF	$Cs_2CO_{3\ anhyd}$	30	54	–	34	18	48

[a] Nosylamido ester **9** (1 mmol), **2a** (2 mmol), base (4 mmol), TEBA (0.1 mmol), anhyd solvent (2.5 mL).
[b] Without PTC agent, 26% of **11a** was isolated after 120 h.

Lyophilized sodium carbonate, which gave the best results in the alkylation of **9**, was employed as a base in a series of reactions carried out in DMF or dimethylacetamide (DMA) by changing the PTC agent (Table 2). Under these conditions, the lipophilic tetrabutylammonium salts (entries 2 and 5) were more efficient than TEBA (entry 1) or than a tetraalkylphosphonium salt (entry 3). In particular, good yields of **11a** and selectivities (≥88%) were obtained with tetrabutylammonium hydrogensulfate in both DMA and DMF (entries 4 and 5). The screening of several aprotic dipolar solvents (entries 4–8), in the presence of catalytic amounts of TBA–HSO_4 indicated that the best results were reached in DMSO (entry 6), which permitted also a simple and rapid separation of the product by aqueous workup.[11] The use of *N*,*N*′-dimethylpropylene urea (DMPU, entry 7) or *N*-methyl-pyrrolidin-2-one (NMP, entry 8) as solvents gave good yields in acceptable reaction times but, conversely, these solvents generated more problems in the workup step than DMSO, due to their higher solubility in organic media. The effect of non-HBD solvents on the alkylation of **9** with a series of activated and non-activated alkyl halides **2b**–**i** was also investigated and the best results are reported in Table 3. The activated alkylating agents **2a**,**b**,**g**–**i** gave very good yields (80–98%) under mild reaction conditions, whereas, as expected, the less activated **2c**–**f** required more drastic conditions, i.e. a higher temperature and longer reaction times. In general, dimethylsulfoxide was found to be the solvent of choice for these alkylations, with the exception of butyl and benzyl bromide (entries 5 and 8) that prefer less polar non-HBD solvents, such as DMPU and DMA.

In conclusion, methyl L-*N*-(2-nitro-benzenelsulfonyl)tyrosinate (**9**) has been chemoselectively N-alkylated under SL-PTC conditions, without protecting the phenolic hydroxy group through deprotonation to the corresponding N,O-dianion in the presence of a non-HBD solvent, which dissociates the ion pairs and specifically solvates the oxyanion, decreasing its nucleophility.[12] This alkylation reactions proceed without racemization of the stereogenic carbon atom and the N-alkylated derivatives **11** produced are easily transformed into the enantiomerically pure *N*-alkyl α-amino esters (or acids) by simple and mild removal of the nosyl protecting group.[3–5] This straightforward synthetic protocol can be favorably applied to the preparation of a new class of multifunctionalized α-amino acid derivatives containing, besides an alkylated amino group, a free phenolic unit that is a site for further modifications of the molecule backbone.

Table 2 N-Allylation of **9**[a] and Effect of the PTC Agent (Q^+X^-) and of the Non-HBD Solvent

Entry	Solvent	Q^+X^-[b]	Time (h)	Yield of **11a** (%)[c]	C (%)[d]
1	DMA[e]	TEBA	54	70	82
2	DMA	TBAB	25	84	96
3	DMA	$C_{16}H_{33}P^+Bu_3Br^-$	54	68	80
4	DMF	TBA–HSO_4	37	75	88
5	DMA	TBA–HSO_4	25	90	95
6	DMSO	TBA–HSO_4	6	98	98
7	DMPU	TBA–HSO_4	13	93	93
8	NMP	TBA–HSO_4	13	91	91

[a] Nosylamido ester **9** (1 mmol), allyl bromide (**2a**, 2 mmol), lyophilized Na_2CO_3 (4 mmol), Q^+X^- (0.1 mmol), anhyd solvent (2.5 mL), 30 °C.
[b] TEBA: triethylbenzylammonium chloride; TBA–HSO_4: tetrabutylammonium hydrogensulfate; TBAB: tetrabutylammonium bromide.
[c] Isolated yields.
[d] C: chemoselectivity expressed as: 100 × (mol **11a**)/(mol reacted **9**).
[e] In DMF 66% of **11a** was isolated (see entry 9 of Table 1).

Table 3 N-Alkylation of **9** Using a Series of Alkylating Agents RX under SL-PTC Conditions[a]

Entry	RX		Solvent	Temp (°C)	Time (h)	Product	Yield (%)[b]	ee (%)[c]	$[\alpha]_D^{20}$	*c*
1	CH_2=CH–CH_2Br	**2a**	DMSO	30	6	**11a**	98	100 (**A**)	–23.6	0.83
2	MeI	**2b**	DMSO	30	1	**11b**	98	100 (**A**)	+101.5	0.60
3	EtI	**2c**	DMSO	50	1.5	**11c**	86	100 (**B**)	–17.7	0.84
4	BuI	**2d**	DMSO	50	22	**11d**	74	92 (**B**)	–21.0	1.00
5	BuBr	**2e**	DMPU	50	48	**11e**	64	69(**B**)	–15.7	1.00
6	$C_8H_{17}I$	**2f**	DMSO	50	20	**11f**	68	93 (**B**)	–24.2	1.00
7	HC≡C–CH_2Br	**2g**	DMSO	30	8	**11g**	86	95 (**B**)	–58.7	0.79
8	$PhCH_2Br$	**2h**	DMA	30	8	**11h**	96	100 (**B**)	–32.1	0.90
9	2,4-$(NO_2)_2C_6H_3Cl$	**2i**	DMSO	50	0.5	**11i**	80	100[d]	–98.2	0.56

[a] Nosylamido ester **9** (1 mmol), **2** (2 mmol), lyophilized Na_2CO_3 (4 mmol), TBA–HSO_4 (0.1 mmol), anhyd solvent (2.5 mL).
[b] Isolated yields.
[c] Determined by HPLC analysis on Daicel columns (**A**, CHIRALPAK® AD; **B**, CHIRALCEL® OD), using *i*-PrOH–hexane mixtures as eluant.
[d] Determined by ^1H NMR analysis, using (*R*)-(–)-Pirkle shift reagent.

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(11) **Typical Procedure for the N-Alkylation: Synthesis of L-*N*-Allyl-*N*-(2-nitrophenyl)sulfonyl Tyrosine Methyl Ester (11a).**
In a dried flask, lyophilized sodium carbonate (424 mg, 4 mmol) was added to a solution of **9** (380 mg, 1 mmol), allyl bromide (**2a**, 242 mg, 2 mmol) and tetrabutylammonium hydrogensulfate (34 mg, 0.1 mmol) in anhyd DMSO (2.5 mL). The heterogeneous mixture was stirred at 30 °C for 6 h, controlling by TLC analysis (EtOAc–hexane, 2:3), then the crude was diluted with EtOAc (10 mL), washed with an aq sat. solution of NH_4Cl (2.5 mL), then with brine (2 × 5 mL). The aqueous phases were extracted with EtOAc (5 × 5 mL); the organic phases were collected and washed with H_2O (5 mL), brine (2 × 5 mL) and dried over $MgSO_4$. The solvent was distilled under vacuum and the residue was purified by flash chromatography (EtOAc–hexane, 2:3). *N*-Allyl derivative **11a**, pale yellow oil (412 mg, 98%); ee 100% [HPLC: column CHIRALPAK® AD (Daicel); 25 °C; *i*-PrOH–hexane (15:85); flow 0.8 mL/min; λ = 266.8 nm; t_R 27.575 min]; $[\alpha]_D^{20}$ –23.6 (*c* 0.83, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ = 7.84 (d, 1 H, *J* = 7.6 Hz), 7.64 (d, 1 H, *J* = 7.6 Hz), 7.58–7.54 (m, 2 H), 7.07 (d, 2 H, *J* = 8.1 Hz), 6.68 (d, 2 H, *J* = 8.4 Hz), 5.85–5.71 (m, 1 H), 5.35 (br s, 1 H), 5.20 (dd, 1 H, *J* = 17.3, 1.3 Hz), 5.11 (dd, 1 H, *J* = 9.9, 1.8 Hz), 4.85 (t, 1 H, *J* = 7.4 Hz), 4.13–3.98 (m, 2 H), 3.56 (s, 3 H), 3.27 (dd, 1 H, *J* = 14.3, 7.7 Hz), 2.96 (dd, 1 H, *J* = 14.3, 7.6 Hz). ^{13}C NMR-APT ($CDCl_3$): δ = 170.8 (CO), 154.7 (COH), 148.0 (CNO_2), 134.2 (CH=), 133.6 (CH), 133.2 (CSO_2), 131.6 (CH), 131.0 (CH), 130.4 (2 CH), 128.0 (C_{Ph}), 124.0 (CH), 118.5 (CH_2=), 115.4 (2 CH), 61.4 (CH-N), 52.2 (OCH_3), 48.8 (CH_2N), 35.5 (CH_2Ph). Anal. Calcd for $C_{19}H_{20}N_2O_7S$ (420.44): C, 54.28; H, 4.79; N, 6.66. Found: C, 54.37; H, 4.76; N, 6.69.
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