Specific Solvation as a Tool for the *N*-Chemoselective Arylsulfonylation of Tyrosine and (4-Hydroxyphenyl)glycine Methyl Esters

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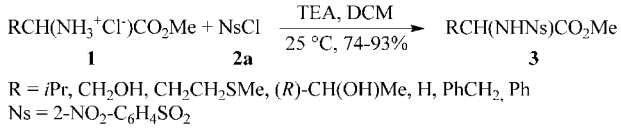
The methyl esters of L-tyrosine and D-(4-hydroxyphenyl)glycine were directly transformed into the corresponding 2-arylsulfonamido esters with arylsulfonyl chlorides, without protecting the phenolic hydroxy group. The reaction is conducted in a THF/DMF (8:1) mixture as solvent, and using lyophilized solid sodium carbonate as base. The *N*-arylsulfonylation takes place with good yields (62–85%) in a chemoselective fashion, without racemization of the stereogenic carbon centers. The DMF (2.6 mol/mol amino ester) specifically solvates the oxygen atom of the formed *N*,*O*-dianion, reducing its nucleophilicity and dramatically increasing the chemoselectivity of the *N*-substitution. In contrast, in the absence of a highly coordinating additive, the phenoxide anion competes unfavorably with the 2-amino group for the nucleophilic attack, and the *N*,*O*-disulfonyl esters are produced with relevant yields.

Introduction

The selective transformation of molecules containing several functional groups that are capable of reacting simultaneously can be realized by protecting one of the reactive centers.[1] Alternatively, to avoid this additional two-step (protection/deprotection) synthetic protocol and the problems connected with the reactivity of the new product, i.e. the protected compound, the appropriate reaction conditions for the specific activation (or deactivation) of a particular group, must be found.

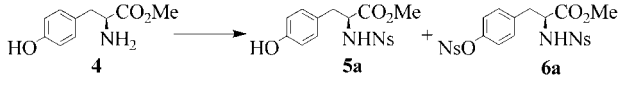
The mono-*N*-alkylated α-amino acids, important intermediates in the preparation of biologically active molecules,[2] have been conveniently prepared from the corresponding *N*-(2-nitrophenyl)sulfonyl-α-amino acid methyl esters **3** by using the Fukuyama protocol.[3]

During our studies on the chemoselective *N*-alkylation of *N*-nosyl esters **3**, under solid-liquid phase-transfer catalysis (SL-PTC) conditions, we prepared several of these *N*-activated compounds **3** (Scheme 1).[4] Esters **1** derived from glycine, or from α-amino acids having in their side chains a phenyl or an alkyl group, gave good yields (74−93%) of the corresponding isolated *N*-nosyl derivatives **3** by reaction with 2-nitrobenzenesulfonyl chloride (NsCl, **2a**) in dichloromethane, and using triethylamine (TEA) as base.



Scheme 1

In contrast, the reaction of L-tyrosine methyl ester (L-Tyr-OMe, **4**) with NsCl (**2a**) under analogous conditions gave a poor yield of the corresponding *N*-nosyl-protected ester **5a** (Scheme 2 and Table 1, Entry 1). The phenolic hydroxy group, due to its acidity, is easily deprotonated and the derived phenoxide anion competes with the α-amino group as a nucleophile, and significant amounts of *N*,*O*-bis[(2-nitrophenyl)sulfonyl]tyrosine methyl ester (**6a**) are produced.



Scheme 2

Results and Discussion

We previously described the effect of specific solvation of the cation−oxido-anion ion pair on the chemoselective *N*-alkylation of 2-hydroxycarbazole,[5] achieved by using a coordinating non-hydrogen-bonding donor (non-HBD) solvent, like DMF, DMSO or diglyme. Moreover, we found

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Table 1. Nosylation of L-Tyr-OMe (**4**)

Entry[a]	Base[b]	Solvent	*T* [°C]	*t* [h][c]	**5a** [%][d]	**6a** [%][d]
1	DIPEA	CH_2Cl_2	25	2.5	35	10
2	pyridine	CH_2Cl_2	0	2.5	27	9
3	−	pyridine	0	2	44	5
4	$KHCO_3$	CH_2Cl_2/H_2O[e]	25	2.5	52	24
5	$KHCO_3$ (S)	DMF	0	1	20	−
6	Na_2CO_3 (L)	DMF	0	1	24	−
7	Na_2CO_3 (L)	DMF	25	1	27	10
8	Na_2CO_3 (L)	THF/DMF[f]	25	2.5	85	6
9	Na_2CO_3 (L)	THF/DMA[f]	25	2.5	72	10
10	K_2CO_3 (S)	THF/DMF[f]	25	6.5	75	11
11	Na_2CO_3 (L)	THF	25	2.5	58	20

[a] Reaction conditions: **4** (10 mmol), NsCl (**2a**; 10 mmol), base (10 mmol), solvent (20 mL). [b] S = solid; L = lyophilized. [c] Time for complete conversion of **4**. [d] Yields of isolated products. [e] Dichloromethane (10 mL) and water (10 mL) were used. [f] A mixture of THF/DMF (or dimethylacetamide, DMA) (8:1, v/v) was used.

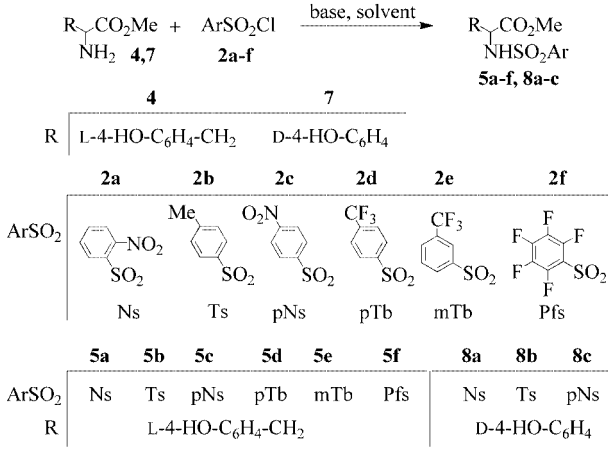
this solvent effect, to some extent, in the alkylation of serine and threonine esters, bearing aliphatic hydroxy groups [Scheme 1, **3**: R = CH_2OH, (*R*)-CH(OH)Me].[4]

In order to verify whether the presence of non-HBD solvents is also beneficial to the chemoselectivity in the *N*-nosylation of L-Tyr-OMe (**4**), a series of screening reactions was conducted (Table 1).

Low yields of the product **5a** (≤ 52%) and a low selectivity were obtained in the presence of tertiary amines, such as diisopropylethylamine (DIPEA) or pyridine (Entries 1−3), or using potassium hydrogencarbonate in a liquid−liquid two-phase system (Entry 4). Weak inorganic solid bases in association with a dipolar aprotic solvent like DMF gave at 0 °C low yields of **5a** (Entries 5 and 6) together with decomposition products, whereas at 25 °C (Entry 7) there was partial *N*,*O*-dinosylation.

A high yield (85%) and high selectivity were obtained by operating in a THF/DMF (8:1, v/v) mixture in the presence of lyophilized sodium carbonate (Entry 8). The reaction was carried out by stirring a solution of **4** and nosyl chloride (**2a**) at 25 °C until 50% conversion of Tyr-OMe (determined by ^1H NMR spectral analysis) was reached, at which time the base was added. When the reaction was stopped before the addition of the base, 50% of **5a** and the hydrochloride salt of the residual amino ester **4** were detected, whereas the dinosylated **6a** was not present. The selective reaction of the amino group is known to be ascribable to the lower nucleophilicity of the phenol group. Sodium carbonate restored the free amino ester **4** and deprotonated the phenolic hydroxy groups. As a consequence, the chemoselectivity of the reaction must be calculated after the formation of the phenoxide anion, which does compete with the amino group for the nosylation. Thus, in Entry 8 the actual chemoselectivity after the addition of the base is 85%, because the 35% yield of **5a** and 41% conversion of the substrate **4** must be taken into account. In contrast, a low yield and only 69% chemoselectivity were obtained employing the THF/dimethylacetamide (8:1, v/v) mixture as solvent (Entry 9). A similar result was obtained when changing the base, sodium carbonate for potassium carbonate (Entry 10). Finally, the chemoselectivity dropped to 29% when carrying out the reaction in THF (Entry 11).

The best reaction conditions found for the *N*-nosylation of L-Tyr-OMe were also applied to the *N*-arylsulfonylation of **4** and D-(4-hydroxyphenyl)glycine methyl ester (D-HPhGly-OMe, **7**) (Scheme 3); the *N*-protected α-amino esters **5** and **8** were isolated in good yields (Table 2).



Scheme 3

Table 2. Selective *N*-arylsulfonylation of methyl esters of L-tyrosine (**4**) and D-(4-hydroxyphenyl)glycine (**7**) with arylsulfonyl chlorides **2**

Substrate[a]	$ArSO_2Cl$	*t* [h]	Yield [%][b]	
4	NsCl (**2a**)	2.5	**5a** [85]	**6a** [6]
4	TsCl (**2b**)	4	**5b** [79]	−
4	*p*NsCl (**2c**)	2.5	**5c** [77]	**6c** [2]
4	*p*TbCl (**2d**)	4	**5d** [75]	−
4	*m*TbCl (**2e**)	4	**5e** [70]	**6e** [7]
4	PfsCl (**2f**)	4	**5f** [62]	−
7	NsCl (**2a**)	4	**8a** [76]	−
7	TsCl (**2b**)	2.5	**8b** [78]	−
7	*p*NsCl (**2c**)	3	**8c** [75]	−

[a] Reaction conditions: α-amino ester **4** or **7** (10 mmol), $ArSO_2Cl$ **2** (10 mmol), lyophilized Na_2CO_3 (10 mmol), anhydrous mixture of THF/DMF (8:1, v/v; 20 mL), 25 °C. [b] Yields of isolated products.

A tentative rationalization for this behaviour is that, in THF, a poor ion-coordinating solvent, the phenoxide anions are present as contact ion pairs, or more complex aggregates.[6] The reactivity of these species is relatively low, due to the strong electrostatic interaction between the ionic counterparts. In THF, the reactivity of the amino group is 1.4 times greater than that of the phenoxide (Table 1, Entry 11), taking into account that the overall yield of the *N*-substitution is 28%, after addition of the base. The addition of a small amount of DMF (2.6 mol/mol of substrate), a highly ion-coordinating solvent, induces the preferential solvation of the ionic center of the substrate, generating solvated contact ion pairs that are most likely in equilibrium

with solvent-shared ion pairs.[6] Under these conditions, the charge on the phenoxide oxygen atom is decreased by both the electrostatic interaction with the cation ($Na^+ > K^+$) and the specific solvation effect. In this case, the reactivity ratio amino group/phenoxide is found to be 6.8 (Table 1, Entry 8), i.e. five times greater than that found in THF. In pure DMF, where the ion pairs dissociate completely, the free phenoxide anion is a reactive species, and therefore the nosylation is not chemoselective.

When the harder sodium cation is involved, the solvation is more extensive than with a potassium cation, and higher chemoselectivities are obtained. Furthermore, with sodium carbonate the reactions are faster, due to the increased solubility in THF of the more solvated ion pair.

Conclusion

These results demonstrate that both the chemoselectivity and the rate of the *N*-arylsulfonylation reaction of amino esters **4** and **7** are influenced by the nature of the solvent and the base used.

This protocol permits the direct synthesis of a series of *N*-arylsulfonyl-protected amino esters of Tyr and HPhGly, and due to the simplicity of the purification, can be used for the preparation of large amounts of product, with no loss of reproducibility. Moreover, the *N*-protection reactions take place without racemization of the stereogenic carbon centers, as proved by ^{1}H NMR spectral analysis of the products **5** and **8**, and of the corresponding racemic amido esters, using $Eu(hfc)_3$ as shift reagent.

A study on the application of specific solvation effects to the *N*-alkylation of sulfonamido esters **5** and **8** is currently under way.

Experimental Section

General Remarks: Melting points were determined with a Büchi 535 apparatus and are corrected. $[\alpha]_D$ values were measured at 589 nm with a Perkin−Elmer 241 polarimeter using a 10 cm × 5 mL cell and *c* is in g/100 mL. ^{1}H NMR spectra were recorded with an AC 300 Bruker spectrometer operating at 300.133 MHz; TMS was used as external reference. ^{19}F NMR spectra were recorded at 282.407 MHz, by using $CFCl_3$ as reference; δ values and calculated chemical shifts υ of ABX systems are reported in ppm and coupling constants *J* in Hz. Reagent-grade commercially available reagents and solvents were used. Petroleum ether (PE) having a b.p. range of 40−60 °C was used. The medium-pressure liquid-chromatographic (MPLC) purifications were performed using a Büchi B681 pump.

Preparation of α-Amino Methyl Esters L-Tyr-OMe (4) and D-HPhGly-OMe (7): Hydrogen chloride was bubbled into a stirred suspension of L-tyrosine (10 g) in anhydrous methanol (400 mL), while heated at reflux. After 1 h, the α-amino acid was completely dissolved. The reaction was stopped after 5.5 h, the mixture cooled to room temperature and the solvent was distilled off. The crude material was left for 3 h under vacuum (2×10^{-2} mbar) and the corresponding ester hydrochloride (L-Tyr-OMe·HCl) was isolated in a quantitative yield. L-Tyr-OMe·HCl: M.p. 184−187 °C (dec.) (ref.[7] 189−190 °C). $[\alpha]_D^{25} = +75.6$ (*c* = 3, pyridine) {ref.[1] $[\alpha]_D^{20} = +78.1$ (*c* = 3, pyridine)}. By using the same procedure, D-HPhGly-OMe·HCl was prepared in a quantitative yield from D-(4-hydroxyphenyl)glycine. D-HPhGly-OMe·HCl: M.p. 156 °C (dec.). $[\alpha]_D^{25} = -125.7$ (*c* = 1, aq. 2 N HCl) {ref.[8] $[\alpha]_D^{25} = -121.1$ (*c* = 1, aq. HCl)}. L-Tyr-OMe·HCl (3 g) was dissolved in a saturated aqueous $KHCO_3$ solution (60 mL) and extracted for 4 h with EtOAc (500 mL) in an apparatus for "lower-than-water" liquid/liquid continuous extraction. After the resulting organic solution was concentrated under reduced pressure (drying procedures with $MgSO_4$, etc., must be avoided, due to the low solubility of **4** in dry EtOAc), the free ester **4** was obtained in a 97% yield. By the same protocol **7** was prepared in 85% yield from D-HPhGly-OMe·HCl.

L-Tyr-OMe (4): M.p. 132−134 °C (ref.[9] 135−136 °C). $[\alpha]_D^{20} = +27.0$ (*c* = 1, MeOH) {ref.[10] $[\alpha]_D^{26} = +27.1$ (*c* = 2, MeOH)}.

D-HPhGly-OMe (7): M.p. 189 °C. $[\alpha]_D^{25} = -151.4$ (*c* = 1, aq. 2 N HCl) {only data for L-HPhGly-OMe are known: ref.[5] $[\alpha]_D^{25} = +146$ (*c* = 1, aq. HCl)}. ^{1}H NMR (300 MHz, [D$_6$]DMSO, 25 °C): δ = 3.32 (br. s, 2 H, NH_2), 3.57 (s, 3 H, $COOCH_3$), 4.38 (s, 1 H, 2-H), 6.70 (dd, $^3J_{H,H} = 6.5$, $^4J_{H,H} = 2.0$ Hz, 2 H, 4-H), 7.15 (dd, $^3J_{H,H} = 6.6$, $^4J_{H,H} = 1.97$ Hz, 2 H, 5-H), 9.36 (s, 1 H, OH) ppm. $C_9H_{11}NO_3$ (181.07): calcd. C 59.66, H 6.12, N 7.73; found C 59.55, H 6.01, N 7.82.

Typical Procedure for the *N*-Arylsulfonylation of the Amino Esters 4 and 7. Synthesis of L-*N*-(2-Nitrophenyl)sulfonyl Tyrosine Methyl Ester 5a: A solution of *N*-(2-nitrophenyl)sulfonyl chloride (**2a**) (2.22 g, 10 mmol) in anhydrous THF (6 mL) was added over 30 min at 0 °C to a solution of the amino ester **4** (1.95 g, 10 mmol) in a mixture of anhydrous THF (10 mL) and DMF (2 mL). After the addition, the reaction mixture was stirred at 25 °C. After 1 h, lyophilized Na_2CO_3 (1.06 g, 10 mmol) was added and the resulting suspension was stirred and monitored by TLC (a sample was acidified, extracted with EtOAc and the organic phase was analysed, eluent Et_2O/EtOAc, 6:1) until NsCl was no longer detected (2.5 h). The solvent was distilled off under reduced pressure, and the crude material was dissolved in 2 M HCl (20 mL) and brine (20 mL), and extracted with EtOAc (3 × 20 mL). The organic phase was washed with brine (3 × 10 mL) and dried with $MgSO_4$. After removal of the solvent by distillation, the yellow solid was purified by MPLC on silica gel (240−400 mesh) using EtOAc/PE (1:1) as eluent, and **5a** (3.24 g, 85%) and **6a** (0.51 g, 9%) were isolated. Alternatively, the product **5a** can be isolated in 80% yield from the crude mixture by recrystallization with a hot solution of EtOH/water (4:1). Compounds **5** and **8** were prepared using the same protocol and their physical, spectroscopic and analytical data are as follows.

5a: M.p. 121.1−121.9 °C. $[\alpha]_D^{20} = -98.5$ (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.99 (υ_A-ABX_{system}, $J_{AX} = 6.5$, $J_{AB} = 14.0$ Hz, 1 H, 3-H), 3.10 (υ_B-ABX_{system}, $J_{BX} = 6.8$, $J_{AB} = 14.0$ Hz, 1 H, 3-H), 3.54 (s, 3 H, $COOCH_3$), 4.42 (υ_X-ABX_{system}, 1 H, 2-H), 5.00 (s, 1 H, OH), 5.97 (d, $^3J_{H,H} = 8.7$ Hz, 1 H, NH), 6.64 (d, $^3J_{H,H} = 8.4$ Hz, 2 H, 6-H), 6.96 (d, $^3J_{H,H} = 8.4$ Hz, 2 H, 5-H), 7.65−7.71 [m, 2 H, C(*p*-SO_2)−H, and C(*p*-NO_2)−H], 7.81−8.02 [m, 2 H, C(*o*-NO_2)−H and C(*o*-SO_2)−H] ppm. $C_{16}H_{16}N_2O_7S$ (380.07): calcd. C 50.52, H 4.24, N 7.36; found C 50.41, H 4.18, N 7.46.

6a: M.p. 54−56 °C. $[\alpha]_D^{20} = -80.0$ (*c* = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.04 (υ_A-ABX_{system}, $J_{AX} = 7.6$, $J_{AB} = 14.0$ Hz, 1 H, 3-H), 3.18 (υ_B-ABX_{system}, $J_{BX} = 5.2$, $J_{AB} = 14.0$ Hz, 1 H, 3-H), 3.53 (s, 3 H, $COOCH_3$), 4.38 (υ_X-ABX_{system}, 1 H, 2-H), 5.97 (d, $^3J_{H,H} = 8.7$ Hz, 1 H, NH), 7.01 (d, $^3J_{H,H}$ =

8.7 Hz, 2 H, 6-H), 7.09 (d, $^3J_{H,H}$ = 8.7 Hz, 2 H, 5-H), 7.64−8.02 [m, 8 H, C(nosyl)−H] ppm. $C_{22}H_{19}N_3O_{11}S_2$ (565.05): calcd. C 46.72, H 3.39, N 7.43; found C 46.61, H 3.24, N 7.46.

5b: M.p. 132.5 °C. $[\alpha]_D^{20}$ = +4.1 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.40 [s, 3 H, CH_3(Tol)], 2.94 (υ_A-ABX_{system}, J_{AX} = 6.1, J_{AB} = 14.1 Hz, 1 H, 3-H), 2.96 (υ_B-ABX_{system}, J_{BX} = 5.7, J_{AB} = 14.1 Hz, 1 H, 3-H), 3.48 (s, 3 H, $COOCH_3$), 4.16 (υ_X-ABX_{system}, 1 H, 2-H), 4.93 (s, 1 H, OH), 5.02 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH), 6.69 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 6-H), 6.92 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 5-H), 7.24 [d, $^3J_{H,H}$ = 8.2 Hz, 2 H, C(*m*-SO_2)−H], 7.63 [d, $^3J_{H,H}$ = 8.2 Hz, 2 H, C(*o*-SO_2)−H] ppm. $C_{17}H_{19}NO_5S$ (349.10): calcd. C 58.44, H 5.48, N 4.01; found C 58.31, H 5.35, N 4.08.

5c: M.p. 168.5−170 °C. $[\alpha]_D^{20}$ = −20.7 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.93 (υ_A-ABX_{system}, J_{AX} = 7.3, J_{AB} = 14.1 Hz, 1 H, 3-H), 3.05 (υ_B-ABX_{system}, J_{BX} = 5.3, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.61 (s, 3 H, $COOCH_3$), 4.20 (υ_X-ABX_{system}, 1 H, 2-H), 4.82 (s, 1 H, OH), 5.19 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, NH), 6.66 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 6-H), 6.90 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, 5-H), 7.86 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-SO_2)−H], 8.24 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-NO_2)−H] ppm. $C_{16}H_{16}N_2O_7S$ (380.07): calcd. C 50.52, H 4.24, N 7.36; found C 50.44, H 4.16, N 7.40.

6c: M.p. 161.8−162.7 °C. $[\alpha]_D^{20}$ = +17.2 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.93 (υ_A-ABX_{system}, J_{AX} = 7.3, J_{AB} = 14.1 Hz, 1 H, 3-H), 3.05 (υ_B-ABX_{system}, J_{BX} = 5.3, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.62 (s, 3 H, $COOCH_3$), 4.20 (υ_X-ABX_{system}, 1 H, 2-H), 5.21 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, NH), 6.93 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 6-H), 7.10 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 5-H), 7.93 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-SO_2)−H], 8.02 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-SO_2)−H], 8.32 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-NO_2)−H], 8.39 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-NO_2)−H] ppm. $C_{22}H_{19}N_3O_{11}S_2$ (565.05): calcd. C 46.72, H 3.39, N 7.43; found C 46.85, H 3.50, N 7.18.

5d: M.p. 137−138 °C. $[\alpha]_D^{20}$ = −2.4 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.93 (υ_A-ABX_{system}, J_{AX} = 7.2, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.03 (υ_B-ABX_{system}, J_{BX} = 5.2, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.54 (s, 3 H, $COOCH_3$), 4.16 (υ_X-ABX_{system}, 1 H, 2-H), 5.09 (s, 1 H, OH), 5.26 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH,), 6.65 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 6-H), 6.89 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 5-H), 7.68 [d, $^3J_{H,H}$ = 8.3 Hz, 2 H, C(*o*-CF_3)−H], 7.82 [d, $^3J_{H,H}$ = 8.3 Hz, 2 H, C(*o*-SO_2)−H] ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −63.52 (s, CF_3) ppm. $C_{17}H_{16}F_3NO_5S$ (403.07): calcd. C 50.62, H 4.00, N 3.47; found C 50.50, H 4.11, N 3.28.

5e: Wax. $[\alpha]_D^{20}$ = −7.7 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.94 (υ_A-ABX_{system}, J_{AX} = 6.7, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.01 (υ_B-ABX_{system}, J_{BX} = 5.5, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.51 (s, 3 H, $COOCH_3$), 4.22 (υ_X-ABX_{system}, 1 H, 2-H), 5.51 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, NH), 5.83 (s, 1 H, OH), 6.65 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 6-H), 6.88 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 5-H), 7.56 [t, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(*m*-CF_3)−H], 7.77 [d, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(*p*-SO_2)−H], 7.88 [d, $^3J_{H,H}$ = 7.7 Hz, 1 H, C(*p*-CF_3)−H], 8.01 [s, 1 H, C(*o*-SO_2)−H] ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −63.28 (s, CF_3) ppm. $C_{17}H_{16}F_3NO_5S$ (403.07): calcd. C 50.62, H 4.00, N 3.47; found C 50.48, H 4.14, N 3.31.

6e: Oil. $[\alpha]_D^{20}$ = +11.0 (*c* = 0.82, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.00 (υ_A-ABX_{system}, J_{AX} = 7.2, J_{AB} = 13.9 Hz, 1 H, 3-H), 3.09 (υ_B-ABX_{system}, J_{BX} = 5.5, J_{AB} = 13.9 Hz, 1 H, 3-H), 3.49 (s, 3 H, $COOCH_3$), 4.19 (υ_X-ABX_{system}, 1 H, 2-H), 5.21 (d, $^3J_{H,H}$ = 9.3 Hz, 1 H, NH), 6.87 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 6-H), 7.05 (d, $^3J_{H,H}$ = 8.5 Hz, 2 H, 5-H), 7.61 [t, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*m*-CF_3)−H], 7.70 [t, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*m*-CF_3)−H], 7.81 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*p*-SO_2)−H], 7.91 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*p*-SO_2)−H], 7.93 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*p*-CF_3)−H], 7.97 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, C(*p*-CF_3)−H], 8.01 [s, 1 H, C(*o*-SO_2)−H], 8.08 [s, 1 H, C(*o*-SO_2)−H] ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −63.33 (s, CF_3) ppm. $C_{24}H_{19}F_6NO_7S_2$ (611.05): calcd. C 47.14, H 3.13, N 2.29; found C 47.00, H 3.02, N 2.36.

5f: Oil. $[\alpha]_D^{20}$ = −17.6 (*c* = 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.94 (υ_A-ABX_{system}, J_{AX} = 8.0, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.13 (υ_B-ABX_{system}, J_{BX} = 4.7, J_{AB} = 14.0 Hz, 1 H, 3-H), 3.73 (s, 3 H, $COOCH_3$), 4.45 (υ_X-ABX_{system}, 1 H, 2-H), 5.21 (s, 1 H, OH), 5.69 (d, $^3J_{H,H}$ = 9.4 Hz, 1 H, NH,), 6.66 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 6-H), 6.95 (d, $^3J_{H,H}$ = 8.3 Hz, 2 H, 5-H) ppm. ^{19}F NMR (282 MHz, $CDCl_3$, 25 °C): δ = −136.56 [d, $^3J_{FF}$ = 20.1 Hz, 2 F, C(*o*-SO_2)−F], −146.66 [t, $^3J_{FF}$ = 20.9 Hz, 1 F, C(*p*-SO_2)−F], −150.56 [dd, $^3J_{FF}$ = 20.9, 20.1 Hz, 2 F, C(*m*-SO_2)−F] ppm. $C_{16}H_{12}F_5NO_5S$ (425.33): calcd. C 45.18, H 2.84, N 3.29; found C 45.35, H 2.93, N 3.16.

8a: M.p. 164.1−164.8 °C. $[\alpha]_D^{25}$ = −143.9 (*c* = 0.5, THF). ^{1}H NMR (300 MHz, $CDCl_3$/$[D_6]$DMSO, 10:1, 25 °C): δ = 3.62 (s, 3 H, CO-OCH_3), 5.19 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, 2-H), 5.54 (s, 1 H, OH), 6.60 (d, $^3J_{H,H}$ = 8.2 Hz, 1 H, NH,), 6.65 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 5-H), 7.08 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 4-H), 7.50 [ddd, $^3J_{H,H}$ = 7.6, 7.6, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(*p*-SO_2)−H], 7.62 [ddd, $^3J_{H,H}$ = 7.8, 7.6, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(*p*-NO_2)−H], 7.70 [dd, $^3J_{H,H}$ = 7.6, $^4J_{H,H}$ = 1.6 Hz, 1 H, C(*o*-SO_2)−H], 7.81 [dd, $^3J_{H,H}$ = 7.8, $^4J_{H,H}$ = 1.4 Hz, 1 H, C(*o*-NO_2)−H] ppm. $C_{15}H_{14}N_2O_7S$ (366.05): calcd. C 49.18, H 3.85, N 7.65; found C 49.05, H 3.80, N 7.72.

8b: M.p. 150.0−150.4 °C. $[\alpha]_D^{25}$ = −97.6 (*c* = 1, MeOH). ^{1}H NMR (300 MHz, $[D_6]$DMSO, 25 °C): δ = 2.35 [s, 3 H, CH_3(Tol)], 3.41 (s, 3 H, $COOCH_3$), 4.83 (s, 1 H, 2-H), 6.43 (br. s, 1 H, NH), 6.64 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 5-H), 7.04 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 4-H), 7.30 [d, $^3J_{H,H}$ = 8.2 Hz, 2 H, C(*m*-SO_2)−H], 7.60 [d, $^3J_{H,H}$ = 8.2 Hz, 2 H, C(*o*-SO_2)−H], 8.21 (s, 1 H, OH) ppm. $C_{16}H_{17}NO_5S$ (335.08): calcd. C 57.30, H 5.11, N 4.18; found C 57.41, H 5.19, N 4.09.

8c: M.p. 178−181 °C. $[\alpha]_D^{20}$ = −98.5 (*c* = 1, THF). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.64 (s, 3 H, $COOCH_3$), 4.84 (br. s, 1 H, OH), 5.10 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, 2-H), 5.82 (d, $^3J_{H,H}$ = 6.0 Hz, 1 H, NH), 6.65 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 5-H), 7.01 (d, $^3J_{H,H}$ = 8.6 Hz, 2 H, 4-H), 7.79 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-SO_2)−H], 8.18 [d, $^3J_{H,H}$ = 8.8 Hz, 2 H, C(*o*-NO_2)−H] ppm. $C_{15}H_{14}N_2O_7S$ (366.05): calcd. C 49.18, H 3.85, N 7.65; found C 49.15, H 3.78, N 7.60.

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