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Chemoselective *O*-methylation of *N*-acylated/sulfonylated tyrosine derivatives

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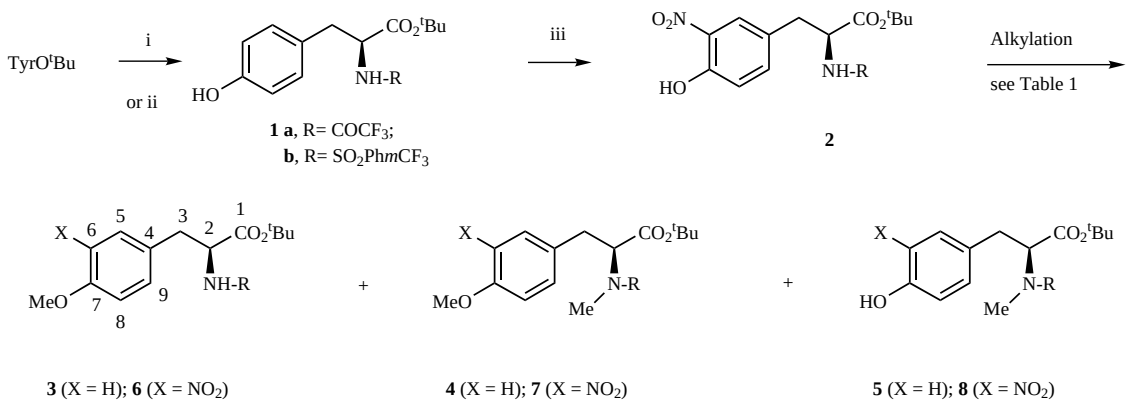
Abstract—Methyl ethers (**6a** and **6b**) of *N*-trifluoroacetyl- and *N*-(*m*-trifluoromethyl) phenylsulfonyl-6-nitro-tyrosine *t*-butyl ester were readily prepared by modified Mitsunobu reaction (DPPE, DIAD, MeOH). Williamson (MeI, K_2CO_3 or Li_2CO_3 or NaOH under phase transfer) and classical Mitsunobu conditions (PPh_3, DEAD, MeOH) gave *O*,*N*-dimethylated derivatives (**7a** and **7b**) as side or main products. *O*- versus *N*-selectivity in tyrosine methylation reactions depends on both pK_a values and steric factors.

O-Alkylation of tyrosine derivatives is usually performed by the Williamson reaction.[1] However, depending on the acidity of the *N*-protected function, *N*-alkylation can occur in competition with the formation of phenolic ether.[2] The Mitsunobu reaction has been scarcely applied in this case.[3]

During the search of RGD peptidomimetic compounds,[4] we were interested in the preparation of methyl ethers of *N*-trifluoroacetyl- and *N*-(*m*-trifluoromethyl)phenylsulfonyl-6-nitro-tyrosine *t*-butyl ester **6a** and **6b** (Scheme 1), respectively.

The required precursors **2a** and **2b** were obtained in two steps from tyrosine *t*-butyl ester (TyrO^{t}Bu).[4] Williamson etherification of **2a** with methyl iodide in the presence of potassium carbonate led to a mixture of *O*-methyl and *O*,*N*-dimethyl derivatives **6a** and **7a** (Table 1, entry 1). Similar reaction of methyl iodide and lithium carbonate applied to precursor **2b** gave exclusively *O*,*N*-dimethyl derivative **7b** (entry 2). Under phase transfer conditions, the same result was obtained (entry 3). Therefore, we turned to the Mitsunobu reaction and systematically examined the *O*/*N* chemoselectivity of precursors **1**–**2**. The reactions were performed



Scheme 1. *O*/*N*-Methylation of tyrosine derivatives. *Reagents and conditions*: (i) trifluoroacetic anhydride (1 equiv.), CH_2Cl_2, 20°C, 2 h, 95% yield; (ii) *m*CF_3PhSO_2Cl (1.1 equiv.), pyridine (1.2 equiv.), CH_2Cl_2, 20°C, 5 h, 48% yield; (iii) HNO_3 (1.2 equiv.), HOAc, 16°C, 1 h, 95% yield.

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Table 1. *O*/*N* selectivity

Entry	Conditions (conversion ratio of 100%)	Products (ratio)[a]	^{1}H NMR (δ)	
			OMe	NMe
1	**2a**; MeI, K_2CO_3, CH_3CN, reflux	**6a**/**7a** (75/25)	3.93 (**6a**); 3.84 (**7a**)	2.98
2	**2b**; MeI, Li_2CO_3, DMF, 40°C	**7b** (100)	3.95	2.90
3	**2b**; MeI, NaOH, BTBACl, CH_2Cl_2, H_2O, 20°C	**7b** (100)	3.95	2.90
4	**1a**; PPh_3, DEAD, MeOH, 20°C	**3a**/**4a** (84/16)	3.80 (**3a**); 3.79 (**4a**)	2.94
5	**2a**; PPh_3, DEAD, MeOH, 20°C	**6a**/**7a** (86/14)	3.80 (**3a**); 3.79 (**4a**)	2.94
6	**2a**; DPPE, DEAD, MeOH, 20°C	**6a**/**7a** (96/4)	3.80 (**3a**); 3.79 (**4a**)	2.94
7	**2a**; DPPE, DIAD, MeOH, 20°C	**6a** (100)	3.80 (**3a**); 3.79 (**4a**)	2.94
8	**1b**; PPh_3, DEAD, MeOH, 20°C	**4b**/**5b** (65/35)	3.79 (**4b**)	2.90
9	**2b**; PPh_3, DEAD, MeOH, 20°C	**7b** (100)	3.79 (**4b**)	2.90
10	**2b**; DPPE, DEAD, MeOH, 20°C	**6b**/**7b**/**8b** (66/27/7)	3.95 (**6b**)	2.90
11	**2b**; DPPE, DIAD, MeOH, 20°C	**6b**/**7b**/**8b** (51/30/18)	3.95 (**6b**)	2.92

[a] Determined by ^{1}H NMR analysis of the crude mixtures.

in methanol (0.4 M) at 20°C with diethyl azodicarboxylate (DEAD, 1.1 equiv.) and triphenylphosphine (1.1 equiv.).

In the trifluoroacetamide series (**1a**, **2a**), *O*-methylation was always preferred over *O*,*N*-dimethylation (entries 4 and 5); at the end of the reaction, 84:16 and 86:14 mixtures of **3a**:**4a** and **6a**:**7a** were recovered. However, a 98:2 selectivity of **3a**:**4a** and **6a**:**7a** could be observed for conversion ratios of 60 and 80%, respectively. On the other hand, in the *m*-(trifluoromethyl)phenyl sulfonamide series (**1b**, **2b**), *O*-monomethylation was never observed (entries 8 and 9). Due to the high acidity of NH proton, *N*-methylation occurred faster, leading to a 35:65 mixture of *N*-methyl (**5b**) and *O*,*N*-dimethyl (**4b**) derivatives of **1b** at 100% of conversion ratio. When the acidity of the phenol moiety increased, due to the *ortho*-nitro substitution, *O*,*N*-dimethyl (**7b**) derivative of **2b** was the only formed product at the end of the reaction. Indeed, sulfonamides are known to be good substrates of Mitsunobu reaction.[5,6]

Since the differences of pK_a values of the competing functions were not sufficiently marked for complete selectivity,[7] we speculated that steric effects could help. By using 1,2-bis(diphenylphosphino)ethane[8] (DPPE) in replacement of triphenylphosphine, reaction of **2a** (trifluoroacetamide series) furnished a 96:4 mixture of **6a**:**7a** (entry 6). The next replacement of DEAD by diisopropyl azodicarboxylate[9] (DIAD) gave **6a** as single product (entry 7). Application of these modified Mitsunobu conditions to methylation of compound **2b** (sulfonamide series) gave *O*-methyl product **6b** as the major compound (entries 10 and 11), but *N*-methyl- and *O*,*N*-dimethyl derivatives **8b** and **7b** were still present. Nevertheless, the desired methyl ether **6b** could be obtained in about 60% yield, although it was not formed under Williamson or classical Mitsunobu conditions. Thus, steric factors[10] dramatically changed the *O*/*N* selectivities of the methylation reaction.

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