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Synthesis of Aryl Esters of Protected Amino Acids from Aryl Sulfonates

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Abstract : Aryl esters of Boc- and Fmoc-protected amino acids derived from electron-deficient phenols have been prepared in good yields from aryl 4-nitrobenzenesulfonates in the presence of 1-hydroxy-benzotriazole as catalyst.

Keywords : Amino acids and derivatives, Catalysis, Esters, Esterifications

Aryl esters of *N*-protected amino acids derived from phenols bearing electron withdrawing substituents are very useful in peptide synthesis since they are reasonably stable crystalline solids yet very reactive as acylating agents in the presence of a suitable catalyst such as 1*H*-hydroxybenzotriazole (HOBt).[1,2] Synthesis of these compounds by conventional DCC mediated coupling with the corresponding phenols[3] is not always satisfactory due to purification problems. Alternative methods reported to date involve the use of mixed anhydride activation,[4] carboxylic esters such as aryl trifluoroacetate[5] or trichloroacetate[6] and phosphorus (III) derivatives.[7] Many of these reagents still possess undesirable properties such as availability and long-term stability. Here we wish to report that aryl 4-nitrobenzenesulfonates are useful reagents for synthesis of aryl esters from *N*-protected amino acids.

Aryl sulfonates are stable crystalline compounds and are extensively used in synthetic chemistry involving palladium and nickel-catalyzed cross-coupling reactions.[8] Sulfonate esters of strongly acidic compounds such as 1-hydroxybenzotriazole have been reported to be efficient peptide and oligonucleotide coupling agents *via* formation of active esters.[9,10] This was believed to result from nucleophilic substitution by the carboxylate ion at the sulfur atom to form a mixed carboxylic – sulfonic acid anhydride[11] which was further attacked by the anion of the strongly acidic compound liberated from the previous step (**Scheme 1**).

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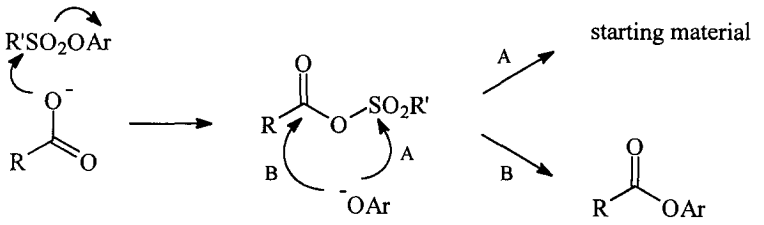
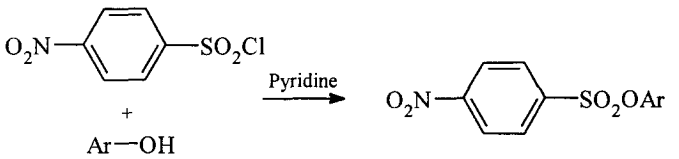


Scheme 1

Although it was previously noted that methanesulfonates of strongly acidic phenols were unreactive towards displacement by carboxylate ions,[9] we found that formation of aryl esters of carboxylic acids from aryl sulfonates was possible in the presence of 1-hydroxybenzotriazole (HOBt) as catalyst. The aryl sulfonates were synthesized from electron-deficient phenols and 4-nitrobenzenesulfonyl chloride in pyridine (**Scheme 2**).[12] These compounds are stable crystalline solids which can be stored at room temperature for prolonged periods of time without deterioration.



1a Ar = 4-nitrophenyl (86 %, m.p.156-157 °C) **1b** Ar = 2,4,5-trichlorophenyl (81 %, m.p.143-144 °C)
1c Ar = pentafluorophenyl (83 %, m.p.108-109 °C) **1d** Ar = pentachlorophenyl (86 %, m.p.195-196 °C)

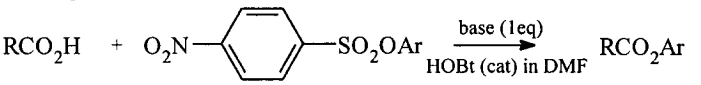
Scheme 2

When a DMF solution of benzoic acid was treated with 1 eq of 4-nitrophenyl 4-nitrobenzenesulfonate (NsONp, **1a**) in the presence of 1 eq of triethylamine and 0.1 eq of HOBt at room temperature, starting materials were completely consumed within 30 minutes and practically pure 4-nitrophenyl benzoate was obtained in 92 % yield after simple aqueous work-up.[13] 4-Nitrophenyl toluenesulfonate (TsONp) reacted with benzoic acid under similar conditions to give the same product in 90 % yield but the reaction was considerably slower. Other aryl 4-nitrobenzenesulfonates (**1b-1d**) reacted similarly with benzoic acid giving the corresponding aryl benzoates in 90, 97 and 87 % yield respectively. No reaction took place in the absence of HOBt. 4-Dimethylaminopyridine (DMAP) was totally ineffective in catalyzing this reaction.

HOBt is a well known acylation catalyst in peptide synthesis.[14] Only in one case was it shown that HOBt induced cleavage of a tosyl group from imidazole ring of histidine *via* formation of benzotriazol-1-yl tosylate.[15] The HOBt probably catalyzed this reaction in the same way by first reacting with the aryl sulfonate to give the corresponding benzotriazol-1-yl

sulfonate as a reactive intermediate. Such compounds were known to react with carboxylate ions to give mixed sulfonic-carboxylic anhydrides,[9] which could react further with phenoxide ions generated in the first step to form aryl esters as previously described.

Table 1 Aryl esters of protected amino acids from aryl 4-nitrobenzenesulfonates[a]



amino acid	reagent	% yield[b]	$[\alpha]_D^{26}$ ($CHCl_3$)	lit[c] $[\alpha]_D^{25}$ ($CHCl_3$)	m.p. (°C)	lit[c] m.p. (°C)
Boc-Gly	**1b**	91	-	-	104-105	106-107
	1c	93	-	-	74-75	79-80
Boc-L-Leu	**1b**	90	-23.9 *c*=1.42		62-63	oil
	1c	80	-16.4 *c*=2.34		oil	48-50
Fmoc-Gly	**1b**	98	-	-	143-144	146
	1c	87	-	-	154-156	157-158
Fmoc-L-Ser	**1b**	87 (99)	-16.2 *c*=3.28		oil	oil
(O^{t}Bu)	**1c**	80 (94)	-11.1 *c*=2.66	-10.5 *c*=5.0	oil	oil
Fmoc-D-Ser	**1b**	83 (97)	+16.0 *c*=1.76		oil	oil
(O^{t}Bu)	**1c**	65 (87)	+11.4 *c*=1.84		oil	oil
Fmoc-L-Phe	**1b**	93 (97)	-29.4 *c*=1.15	-29.3 *c*=1.6[d]	184-185	186.5
	1c	91 (94)	-20.7 *c*=1.42	-20.8 *c*=1.0	148-149	150-153
Fmoc-L-Met	**1b**	88 (90)	-15.7 *c*=1.36		152-153	
	1c	93 (95)	-11.9 *c*=1.32	-12.6 *c*=1.0	110-111	102-104
Fmoc-L-Lys	**1b**	93	-17.7 *c*=1.37		109-110	
(Boc)	**1c**	88 (90)	-15.0 *c*=1.41	-14.1 *c*=1.0	103-104	102-105
Fmoc-L-Val	**1b**	96	-30.2 *c*=1.32	-30.2 *c*=1.0[d]	145-146	150-151[e]
	1c	80 (95)	-22.4 *c*=1.32	-21.9 *c*=1.0	119-121	122-123
Fmoc-L-Glu	**1b**	79 (95)	-18.5 *c*=1.05		140-141	
(O^{t}Bu)	**1c**	61 (93)	-17.7 *c*=1.06	-18.4 *c*=5.0	116-117	119-120

[a] all products gave clean ^{1}H nmr spectra and provided satisfactory elemental analysis (C,H,N)
[b] yield after purification by passing through a short silica gel column (crude yield in parenthesis)
[c] data from ref. 1-5 [d] data for the same compound made by DCC-coupling method [e] D-isomer

Reagents **1b** and **1c** were employed to synthesize 2,4,5-trichlorophenyl and pentafluorophenyl esters of a variety of Boc- and Fmoc-protected amino acids (**Table 1**). In most cases the reaction proceeded as expected under similar conditions except that diisopropylethylamine (DIEA) was used in place of triethylamine when Fmoc-amino acids were employed.[16] All products have been characterized by ^{1}H NMR and microanalysis (C,H,N). Other physical data including melting point and optical rotation are also consistent with literature values,[1-5] suggesting that no significant racemization took place during the reaction. Application of these reagents in peptide synthesis without prior isolation of the active ester intermediate is being explored.

In conclusion, aryl esters of protected amino acids were prepared in good yield from the reaction between carboxylic acids and aryl sulfonates in the presence of a tertiary organic base

and a catalytic amount of 1-hydroxybenzotriazole. The generality of the reactions, simplicity of product purification and availability of starting materials renders this reaction a potentially useful alternative to classical methods for the preparation of this type of compound.

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12. To a cooled (ice bath) solution of the phenol (10 mmol) in dry pyridine (10 mL) was slowly added 4-nitrobenzenesulfonyl chloride (10 mmol) portionwise. The reaction mixture was left at 4 °C overnight. The reaction mixture was diluted with dichloromethane, extracted with 5% HCl, 5% $NaHCO_3$, H_2O and brine. It was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give the crude aryl sulfonate which was recrystallized from ethyl acetate/hexane.
13. A mixture of the carboxylic acid (0.3 mmol), aryl 4-nitrobenzenesulfonate (0.3 mmol) and 1-hydroxybenzotriazole hydrate (0.03 mmol) in DMF was stirred at room temperature. Triethylamine or diisopropylamine (DIEA) (0.3 mmol) was then added and the stirring continued for 20-30 min. The reaction mixture was diluted with dichloromethane and extracted with 5% HCl and 5% $NaHCO_3$, H_2O and brine. The organic phase was dried ($MgSO_4$), filtered and concentrated under reduced pressure to give practically pure product which, if required, could be further purified by column chromatography (SiO_2, CH_2Cl_2:Hexane).
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