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A useful acylation method using trichloroacetonitrile and triphenylphosphine for solid phase organic synthesis

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Abstract—A novel acylation procedure was developed for polymer supported synthesis, with in situ generated acyl chlorides using trichloroacetonitrile and triphenylphosphine. © 2002 Published by Elsevier Science Ltd.

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1. Introduction

In recent years solid phase organic synthesis has become an important technique for the generation of biologically active molecules. Acylation was one of the first reactions performed on solid phase[1] and is used frequently in solid phase organic chemistry. Despite the fact that there are many coupling agents and methods for coupling carboxylic acids and amines,[2] in some cases there is a need to use acyl chlorides for amide synthesis. Steric hindrance or low reactivity can hamper acylation with coupling agents and in those cases using acyl chlorides gives better results. Herein we report a new solid phase acylation method that converts carboxylic acids to the corresponding acyl chlorides in situ, in the acylation step, and can be easily employed similar to other coupling agents.

Trichloroacetonitrile (TCA) and triphenylphosphine (TPP) convert carboxylic acids to acyl chlorides mildly and rapidly under acid free conditions.[3] The application of this method for solid phase chemistry seems advantageous because the excess of reagents and the resulting triphenylphosphine oxide by-product can be easily removed by washing. To investigate the applicability of this method we performed 40 experiments with two different amines attached to two types of solid supports, using the two different acylation methods and ten benzoic acids (Fig. 1).

Two amines were used in the experiments: benzylamine was attached to the sterically hindered bromo-(4-methoxyphenyl)-methyl polystyrene[4] (MAMP[5]) and cyclohexylamine was attached to 2-(4-formyl-3-methoxy)-phenoxyethyl polystyrene[6] (FMPE). The

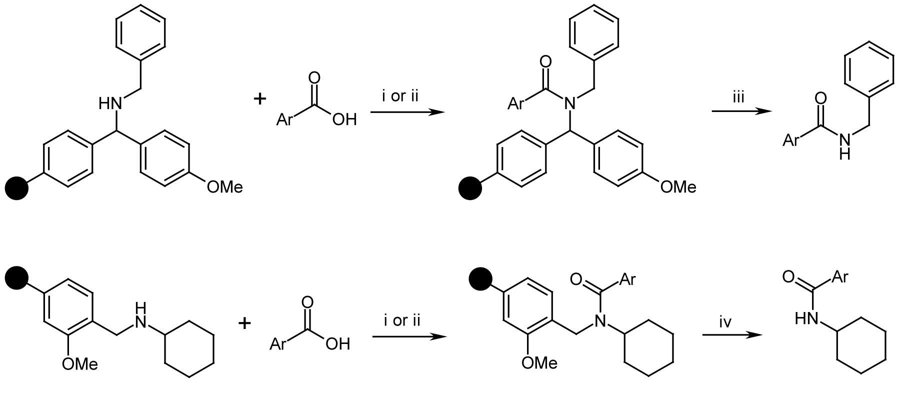

Figure 1. *Reagents and conditions*: (i) 4 equiv. TCA/TPP 10 h, rt; (ii) 4 equiv. HBTU 10 h, rt; (iii) 5% TFA/DCM, 1 h, rt; (iv) 25% TFA/DCM, 1 h, rt.

Keywords: solid phase synthesis; acylation; acyl chloride.

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amines were attached to the polymers using standard procedures.[7,8] The loading of the resins were determined by Kjeldahl nitrogen analysis, and was equal to the substitution data provided by the manufacturer.

Ten commercially available benzoic acid derivatives were chosen for the experiments. Two acylation protocols were used, TCA/TPP in DCM and for comparison the commonly used *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate[9] (HBTU) coupling agent. Subsequent cleavage with acid treatment released the products from the resins. The purity of products were determined by HPLC/MS analysis (Tables 1 and 2).

2. Conclusions

In the case of benzylamine bound to the sterically hindered benzhydryl-type MAMP linker (Table 1), no acylated product could be isolated using HBTU as the coupling agent. On the other hand, with the TCA/TPP method, the desired products were obtained with high to acceptable purity. When steric hindrance has no effect on acylation, as in the case of cyclohexylamine bound to the FMPE linker, the TCA/TPP and HBTU methods gave comparable results in terms of purity and isolated yields (Table 2).

3. Experimental

3.1. General procedure for acylation with TCA/TPP

To a mixture of 0.1 mmole of resin bound amine, 0.4 mmole of benzoic acid, 125 µl of triethylamine and 90 µl of trichloroacetonitrile in 1.5 ml of THF was added 0.25 g of triphenylphosphine in 1.5 ml of THF. The suspension was shaken for 10 hours at room temperature. The resin was washed sequentially with 2×2 ml of THF, MeOH, DMF, MeOH, and DCM.

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Table 1. Results of acylation of benzylamine bound to MAMP resin

Entry	Carboxylic acid	HBTU		TCA/TPP	
		Yield[a] (%)	Purity[b] (%)	Yield[a] (%)	Purity[b] (%)
1	Benzoic	0	–	59	87
2	2,3-Dichlorobenzoic	0	–	19	84
3	2,4-Dichlorobenzoic	0	–	46	97
4	2,5-Dichlorobenzoic	0	–	24	92
5	2,6-Difluorobenzoic	0	–	16	81
6	3-Chloro-6-methoxybenzoic	0	–	57	99
7	2-(2-Cyanophenylthio)benzoic	0	–	15	87
8	2-Bromo-5-methoxybenzoic	0	–	43	74
9	3-Cyanobenzoic	0	–	84	88
10	2-Chloro-5-methylthiobenzoic	0	–	41	98

[a] Isolated yields, without further purification.

[b] Determined by HPLC/MS.

Table 2. Results of acylation of cyclohexylamine bound to FMPE resin

Entry	Carboxylic acid	HBTU		TCA/TPP	
		Yield[a] (%)	Purity[b] (%)	Yield[a] (%)	Purity[b] (%)
1	Benzoic	65	99	98	99
2	2,3-Dichlorobenzoic	50	99	33	99
3	2,4-Dichlorobenzoic	65	95	26	83
4	2,5-Dichlorobenzoic	66	100	95	94
5	2,6-Difluorobenzoic	57	81	77	91
6	3-Chloro-6-methoxybenzoic	50	99	63	99
7	2-(2-Cyanophenylthio)benzoic	70	93	60	99
8	2-Bromo-5-methoxybenzoic	66	81	22	98
9	3-Cyanobenzoic	40	99	100	92
10	2-Chloro-5-methylthiobenzoic	78	99	94	95

[a] Isolated yields, without further purification.

[b] Determined by HPLC/MS.

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