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# A SIMPLE PROCEDURE FOR THE SOLID PHASE SYNTHESIS OF UNSYMMETRICALLY FUNCTIONALISED DIAMIDES FROM SYMMETRIC DIACIDS

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**Abstract**

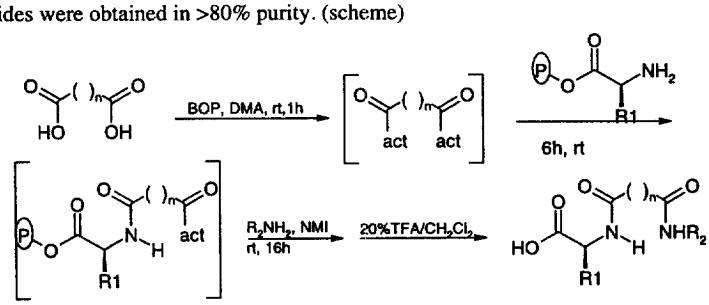
The solid phase synthesis of unsymmetrically substituted diamides from symmetric dicarboxylic acids is described. The process was conducted following these steps: (1) preactivation of the dicarboxylic acid with BOP, (2) addition to amine resin, (3) reaction with a second amine, and (4) TFA cleavage to afford the desired diamide. Most of the unsymmetric diamides were obtained in >80% purity. 

## Introduction

There is an increasing demand for simple templates for use in combinatorial organic synthesis of structurally diverse chemical libraries.[1] One group of templates recently outlined in the literature for use in library synthesis for both solid phase and solution phase methods is carboxylic acid anhydrides.[2] In this case, the acid anhydrides may be treated with an amine, and the resultant free carboxylic acid then converted to an active ester and reacted with a second amine to produce unsymmetrically substituted diamides. In cases where the anhydride cannot be formed, monoallylesters of diacids have been used for the initial reaction ; following deprotection the second amide bond is formed *via* an activated ester[3]. Unfortunately, both of these methods have their limitations: only a small number of carboxylic acid anhydrides are available, whilst the synthesis of monoallylesters from dicarboxylic acid is time-consuming.

Nastri and coworkers used a dicarboxylic acid scaffold for the synthesis of heme-peptide conjugates.[4] However, their method involves isolation and purification of the initially formed monoamide followed by activation of the acid and coupling to a resin bound amine, making such procedure very laborious for library production. As an alternative method, we persued the preparation of unsymmetric diamides employing dicarboxylic acids and resin bound amines for the first acylation.

We found that preactivation of a dicarboxylic acid with BOP; followed by treatment with a resin bound compound possessing a free amine; followed by further reaction with a second amine cleanly yields resin-bound unsymmetrically substituted diamides. Following cleavage from the resin using 20%TFA in dichloromethane, most of the diamides were obtained in >80% purity. (scheme)




$( )_n$ = acyclic, cyclic alkyl, alkenyl, or aromatic.
act= activated; BOP= benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphoniumhexafluorophosphate; NMI= N-methylimidazole; DMA= dimethylacetamide.

R1= -H, $-CH_3$, $-CH(CH_3)_2$, $-CH_2$-Ph, $-CH_2$-O-tBu, $-CH_2-(CH_2)_3$-NH-BOC.

**Scheme**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Amino acids bound to Wang resin, or diamines bound to a trityl or a carbamide[5] resin can serve as the source of the first amine. Whilst, the formation of the first amide bond is fast, the reaction of the second amine proceeds slowly with the major impurity being the mono amide product.[6] The formation of the first amide bond does not require the addition of a base, however, the second acylation proceeds faster in the presence of NMI.It is also important to note that the chemistry is robust and does not require an inert atmosphere.

This simple procedure is amenable to library synthesis, and we have used this methodology to prepare one library of 576 members, for which representative diacids and amines used are listed in Figs **1**, and **2** respectively. Resin bound amines were prepared according to the procedure of Corbett *et al.*[7] Robbins blocks were used for the production of libraries.[8]

**Fig. 1**

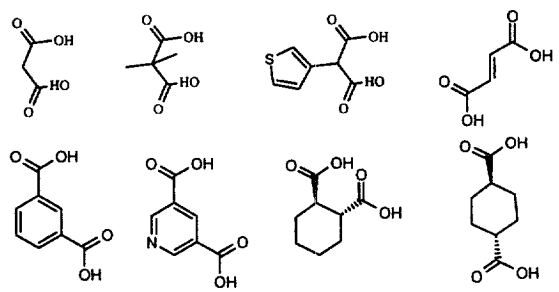
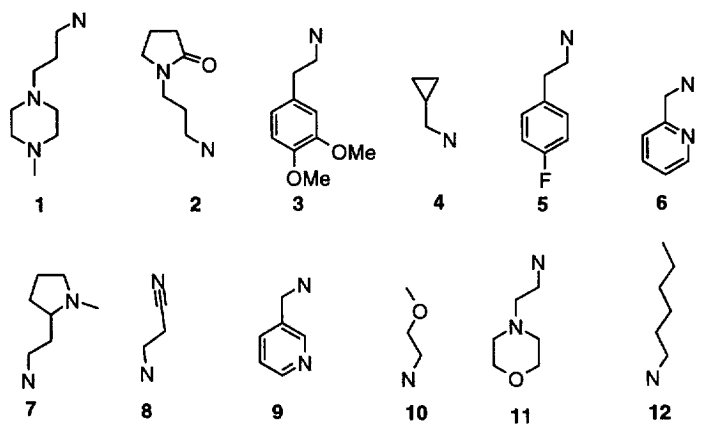


**Fig. 2**




The yields and purities of a subset of a diamide array is given in table below. The reaction is general and most diamides were obtained in >80% purities. Crude yields range from 50 to 100%. Aromatic, olefinic, cyclic and acyclic diacids can be used in this reaction, fig 1. All the resin bound amino acids used behaved normally, whereas, the free amines employed for the formation of the second amide bond reacted as predicted with the exception of 3,4-dimethoxyphenethylamine and 3-aminopropionitrile, entries 3 and 8. From LC/MS, the product from 3-aminopropionitrile, entry 8, is a 1:1 mixture of the nitrile and the acid due to hydrolysis during cleavage from the resin. It is unclear why 3,4-dimethoxyphenethylamine failed to give clean products.

Table : Yields and purity of a subset of a diamide array using fumaric acid.

| entry | compound[a] | yield[b] | purity[g] |
|---|---|---|---|
| **1** | Phe-F-**1**[c] | 57% | 80% |
| **2** | Phe-F-**2**[c] | 56% | 85% |
| **3** | Phe-F-**3**[c] | 74% | 40% |
| **4** | Lys-F-**4**[d] | 100% | 80% |
| **5** | Lys-F-**5**[d] | 75% | 90% |
| **6** | Lys-F-**6**[d] | 100% | >95% |
| **7** | Ala-F-**7**[e] | 90% | >95% |
| **8** | Ala-F-**8**[e] | 67% | 90%[h] |
| **9** | Ala-F-**9**[e] | 60% | 90% |
| **10** | Gly-F-**10**[f] | 71% | >95% |
| **11** | Gly-F-**11**[f] | 100% | >95% |
| **12** | Gly-F-**12**[f] | 65% | 80% |

a. Acylating amines in bold are given in Fig. 2

b. Yields are % mass recovery based on theoretical recovery of products starting from the loading of the resin.

c. Phenyl alanine on Wang resin, Phe.

d. Lysine-NH-BOC on Wang resin, Lys.

e. Alanine on Wang resin, Ala.

f. Glycine on Wang resin, Gly.

g. From LC/MS and HPLC.

h. 1:1 mix. of nitrile and acid.

We are applying this methodology to construct larger libraries using commercially available building blocks. Use of functionalized amines or diacarboxylic acids would offer additional points of structural diversity for the production of libraries from libraries.[9]

**Acknowledgments**

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**References and Notes**

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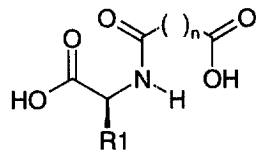


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8. Preparation of a 1x4x12 array of discrete diamides (diacid, amino acid, amine respectively) : BOP (6.27 g, 14.17 mmol) was added to the dicarboxylic acid (7.08 mmol) in dry DMA (48 ml) under nitrogen. After an activation period of 1h, the resulting solution (1.1 ml per well) was added to resin bound amines (50 mg per well, 0.05 mmol). After 6h, 12 different amines were added, followed by NMI (100 µl per well) and the reaction block was agitated at room temperature for 16h. The resin was filtered and washed exhaustively with DMF, $CH_2Cl_2$, MeOH, and $CH_2Cl_2$. Trifluoroacetic acid (20% in $CH_2Cl_2$) was added to each well (1 ml/well) and the reaction block was agitated at room temperature for 3h after which the cleavage products were collected in a deep well plate and the resin was washed with 20% TFA/ $CH_2Cl_2$. The filtrate was concentrated under reduced presure leaving the desired products. Each product was transfered into a tared vial and after drying the net weight of each compound was registered. LC/MS results were consistent with the proposed products. $^1H$ NMR of selected compounds were consistent with the proposed structures.
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