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Synthesis of oxadiazoles on solid support

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Abstract

Aliphatic and aromatic nitriles linked to solid support were converted to amide oximes, and cyclized to oxadiazoles using *N*-protected amino acid anhydrides. The amino protecting group was removed and the products acylated or sulfonylated on resin to provide combinatorial libraries of oxadiazoles. © 1999 Elsevier Science Ltd. All rights reserved.

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Oxadiazoles have been the subject of investigation in a number of different therapeutic areas, usually as a replacement for ester or amide functionalities. The examples described have been primarily limited to simple alkyl and aryl derivatives. 1,2,4-Oxadiazoles have been proposed as muscarinic receptor agonists,[1] benzodiazepine receptor agonists,[2] histamine H3 receptor antagonists,[3] and antiviral compounds.[4] The conversion of amide oximes to oxadiazoles is commonly done by treatment with acid chlorides or anhydrides in refluxing pyridine.[5,6] Symmetrical anhydrides generated in situ from carboxylic acids with EDC have also been used.[7] Other recent reports describe the use of CDI for activation of carboxylic acids,[8] and acyl–palladium complexes as the acylating species.[9] This paper describes the preparation of several oxadiazole variants for the preparation of combinatorial libraries with a high level of diversity.

This investigation began by coupling 4-cyanobenzoic acid, cyanoacetic acid and 1-cyano-1-cyclopropane carboxylic acid to MBHA resin to give the cyano amides **1a** (Scheme 1). Cyano aryl ethers **1b** were made by coupling the cyanophenol potassium salts to *p*-alkoxybenzyl bromide resin at 50°C overnight in dimethylacetamide.[10,11]

Treatment of resin bound nitriles **1a** and **1b** with hydroxylamine hydrochloride and DIEA in 2-methoxyethanol at 85°C for 16 h provided the amide oximes **2** in quantitative yield (Scheme 2). The amide oximes were converted to oxadiazoles **4** by reaction with BOC or FMOC protected amino acid anhydrides, generated in situ from the amino acids with DIC in 2-methoxyethyl ether. In the course of the optimization of this reaction on solid phase, it was observed that the purity of the products depended on the exact conditions used. When the amide oximes were treated with anhydrides and heated directly to

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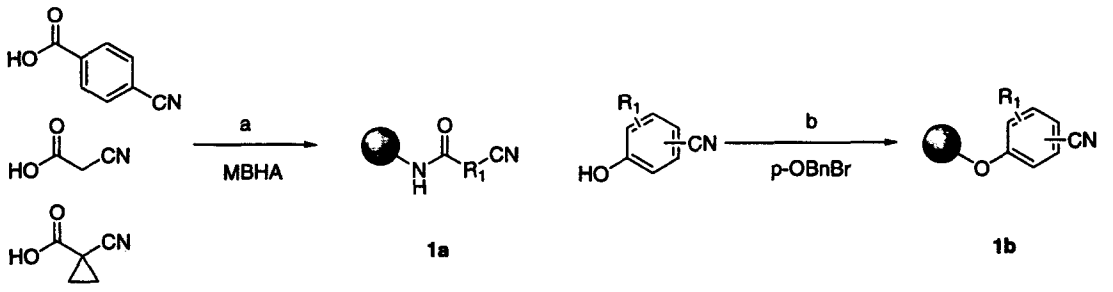
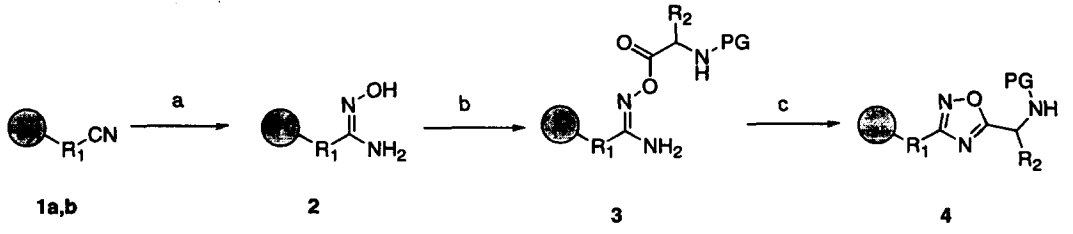


Scheme 1. Conditions: (a) DIC, HOBT, DIEA, DCM; (b) KO*t*Bu, DMA, 50°C, 16 h

85°C, product purity was poor. After 16 h at 65°C followed by cleavage from the resin, only uncyclized *O*-acyl amide oximes **3** were isolated.



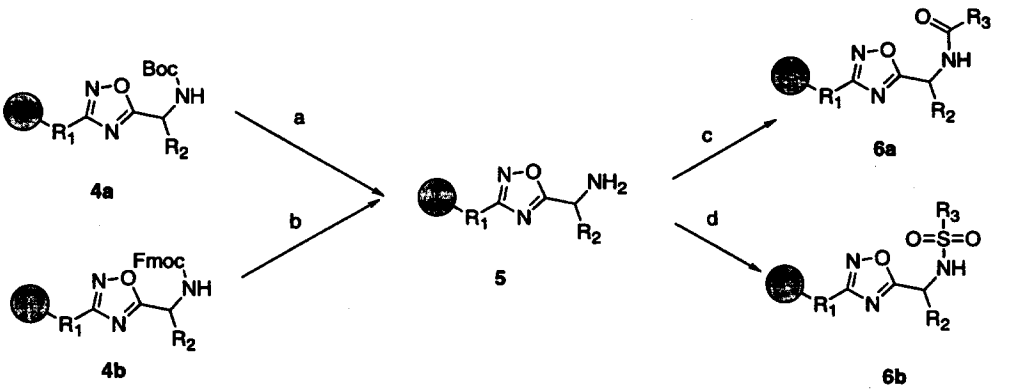
Scheme 2. Conditions: (a) NH_2OH-HCl, DIEA, $CH_3OCH_2CH_2OH$, 85°C, 16 h; (b) Boc-AA-CO_2H or Fmoc-AA-CO_2H, DIC, 2-methoxyethyl ether, rt, 1 h, then 60°C, 16 h; (c) 2-methoxyethyl ether, 85°C, 6 h

The optimized conditions required completing the acylation of the amide oximes at 60°C, washing away the excess anhydride, and heating to 85°C in fresh solvent for 6 h. Washing away the excess amino acid anhydride was necessary to avoid deprotection and addition of another amino acid moiety. The cyclization of *O*-acyl amide oximes does not require a dehydrating agent. Under these conditions, oxadiazole formation gave greater than 95% purity for most amino acid anhydrides used.[12] Extremely hindered amino acids such as 2-methyl-2-aminopropionic acid and other α,α-disubstituted amino acids gave poor yields of the desired product. Glutamine and asparagine derivatives gave multiple products, presumably due to dehydration of the primary carboxamide.

A number of other carboxylic acids were examined. Most aliphatic carboxylic acids tried gave good product purity. In addition, certain cyclic anhydrides such as succinic and glycolic anhydrides were successful. The anhydrides of aromatic carboxylic acids were a notable exception, giving a mixture of oxadiazole and uncyclized products. Prolonged heating or higher temperatures did not improve the yield or product distribution, and the presence of electron donating or withdrawing aromatic substituents had no effect on the yield.

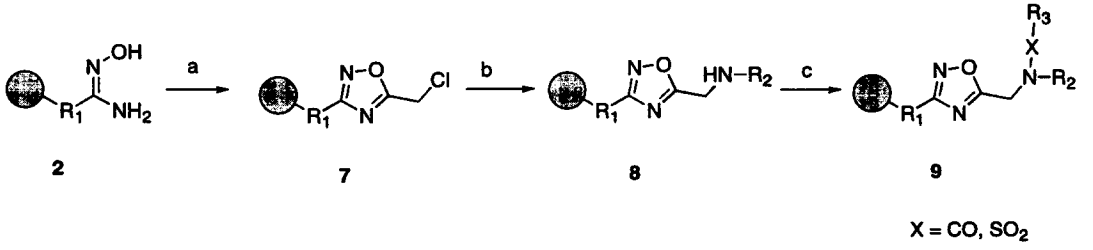
The BOC or FMOC protecting group could be removed from the oxadiazole products **4a** and **4b** using 50% TFA/DCM or 20% piperidine/DMF, respectively, and the resulting amines **5** were derivatized further (Scheme 3). Amide products **6a** were made by acylation with diverse carboxylic acids using either DIC/DMAP or PyBOP activation in the presence of DIEA.[13] Alternatively, sulfonamides **6b** were readily prepared using arylsulfonyl chlorides in acetonitrile or THF in the presence of *N*-methylmorpholine (NMM) and *N*-methylimidazole (NMI).

When amide oximes **2** were treated with chloroacetic anhydride under the optimized conditions described above, the 5-chloromethyl oxadiazoles **7** were obtained. Displacement of the chloride was readily accomplished with primary amines to give a diverse set of 5-aminomethyl oxadiazoles **8** (Scheme 4). These secondary amines were then acylated or sulfonylated to produce tertiary amides and



Scheme 3. Conditions: (a) 50% TFA, DCM; (b) 20% piperidine, DMF; (c) R_3CO_2H, DIC/DMAP or PyBOP, DIEA, DCM/D243MF (2:1); (d) R_3SO_2Cl, NMM, NMI, CH_3CN or THF

sulfonamides **9**. Optimization of the carboxylic acid activation reagent was necessary to achieve complete acylation. HATU gave good results with most carboxylic acids and 5-aminomethyl oxadiazoles, while DIC and PyBOP alone proved ineffective in many cases. It was found that PyBOP with the addition of DMAP gave comparable results to HATU in a much more economical way.



Scheme 4. Conditions: (a) $(ClCH_2CO)_2O$, 2-methoxyethyl ether, 60°C, 16 h, then 85°C, 6 h; (b) R_2NH_2, DMF; (c) R_3CO_2H, PyBOP/DMAP or HATU, DIEA, DCM/DMF (2:1) or R_3SO_2Cl, NMM, NMI, CH_3CN or THF

Readily available reagents (nitriles, amino acids, amines and carboxylic acids) can be utilized to incorporate a wide range of diverse functionality into the final products. With these methods in hand, large diverse combinatorial libraries of 1,2,4-oxadiazoles were prepared using a combination of tea bag and microtiter plate reaction vessels.

Acknowledgements

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12. New products were characterized by HPLC-MS after cleavage from the resin using TFA or HF. Examples: Boc-Ala, Boc-5-aminocaproic acid, Boc-Arg(Tos), Boc-Asp-(OcHex), Boc-cyclohexylalanine, Boc-Glu-(OcHex), Boc-Gly, Boc-His(Tos), Boc-Ile, Boc-isonipecotic acid, Boc-Leu, Boc-Nipecotic Acid, Boc-Phe, Boc-D,L-pipecolinic acid, Boc-Pro, Boc-Ser(OBn), Boc-Thr(OBn), Boc-TIC, Boc-Trp(For), Boc-Tyr(OBn), Boc-Val, *N*-Fmoc-Lys(Boc).
13. Compound **6a**: R1=3-PhCONH$_2$, R2=CH$_2$Ph, R3=CH$_3$; ^{1}H NMR (300 MHz, CDCl$_3$+D$_2$O) δ 8.44 (s, 1H), 8.18 (d, 1H), 7.98 (d, 1H), 7.56 (t, 1H), 7.07–7.28 (5H), 5.71 (t, 1H), 3.32 (d, 2H), 2.06 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$+D$_2$O) 178.9, 169.9, 168.4, 167.4, 134.8, 134.0, 130.7, 130.3, 129.3, 129.2, 128.8, 127.5, 126.9, 126.4, 47.9, 39.5, 23.0; MS (APCI)=351.1 (MH$^+$).