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OXADIAZOLE SYNTHESIS ON SOLID SUPPORTS

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Abstract: Substituted 1,2,4-oxadiazoles were synthesized in good yields on solid supports under basic conditions at room temperature.

Oxadiazoles are frequently used in drug discovery research as an important bioisostere for esters and amides to improve pharmacokinetic properties of drug candidates.[1] After the development of an improved oxadiazole synthesis mediated by peptide coupling reagents,[2] we continued our investigation of oxadiazole synthesis on solid supports. Since acylation reactions on solid supports have been very well studied,[3] we applied the original conditions directly to the solid-phase synthesis in our β3-adrenergic receptor agonist project.[4] A large number of oxadiazole compounds were synthesized in our laboratory, and many functional groups are compatible as previously described.[2,4] However, it is somewhat undesirable that the reaction has to be heated and special equipment is needed for rocking the reaction tubes at elevated temperature.

In the search for conditions under which the cyclization reaction can occur at a reasonable rate at room temperature, we discovered that in solution phase under basic conditions the rate of the cyclization is about the same as the acylation of amidoximes. Simply stirring a carboxylate ester and an amidoxime together with sodium ethoxide at room temperature overnight yielded oxadiazole in good yield, and only small amount of the uncyclized intermediate was isolated. When we applied the same reaction conditions to resin-bound substrates, similar results were obtained. The reaction was somewhat slower, however, and it took several days for completion. Nonetheless, no heating was necessary for the cylization, and oxadiazoles were obtained in good yields and purities. The TentaGel resin (NovaSyn TGA, Novabiochem) was activated by p-nitrophenyl chloroformate, which was then captured by ethyl isonipecotate under similar conditions (Scheme 1). The resin-bound ethyl isonipecotate **1** (100 mg beads, 0.02–0.03 mmol) was first soaked in dichloromethane (1.5 mL) for 10–15 min, and a solution of 4-methyl benzamidoxime (5–10 equiv) and sodium ethoxide (5–10 equiv) in ethanol (1.5 mL) was then added. The reaction tubes were rotated at room temperature for 3 days. Solvents were drained, beads were thoroughly washed. The resin-bound oxadiazole **4** was cleaved from the resin with trifluoroacetic acid and dichloromethane (1:1, 30 min, rt and repeated), and the desired oxadiazole **5** was isolated in 90% yield as its TFA salt.[5] Other conditions were then tested, and the results are summarized in Table 1.

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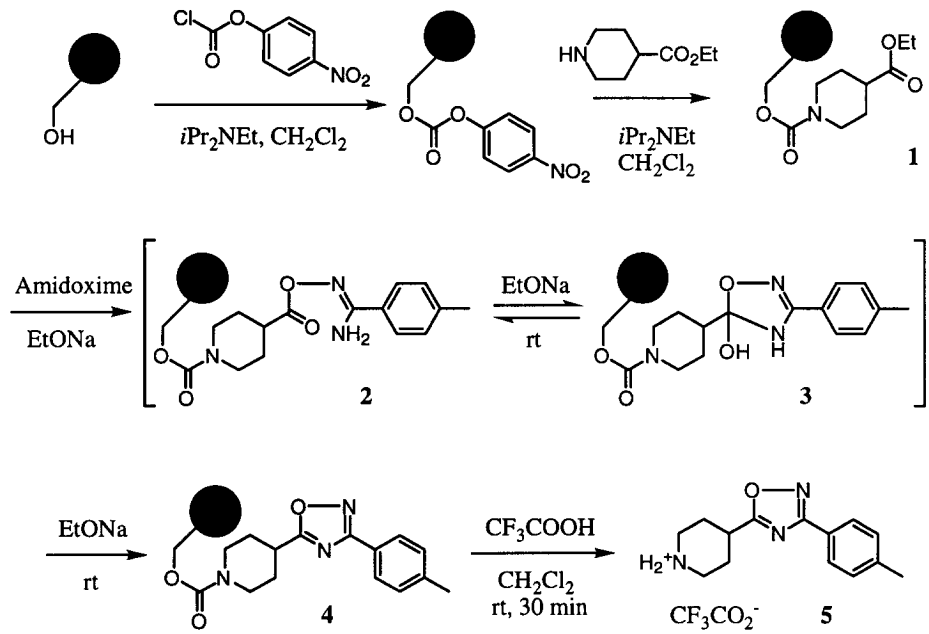


Scheme 1

Table 1. Formation of Oxadiazole **5** under Different Conditions

Entry	Base	Solvent	Time (day)	Isolated Yield
1	Triethylamine	THF	3	No Reaction
2	DBU	THF	3	No Reaction
3	NaOEt	CH_2Cl_2/EtOH	2	Incomplete*
4	NaOEt	CH_2Cl_2/EtOH	3	90%
5	NaOEt	DMF	3	83%
6	NaOEt	THF/EtOH	3	87%
7**	NaOEt	THF/EtOH	3	85%

* No attempts were made to purify the product and to determine the yield.

**Wang Resin linked substrate.

It was found that a variety of solvent and solvent mixtures can be used for the reaction, and yields are very similar as long as the substrates are soluble. Other milder bases, such as triethylamine and DBU, do not work under these conditions and starting material was recovered. These results suggest that deprotonation of amidoxime is necessary for the acylation step. Our previous study[2] has shown that in solution phase the cyclization is very slow at room temperature under neutral conditions. Therefore, base is also required for oxadiazole formation by either (or both) deprotonation of the precusor **2** to promote the cyclization, or (and) more likely deprotonation of the cyclized intermediate **3** to speed up the dehydration. HPLC analysis showed that the purity of oxadiazole **5** was high (typically >90%), and major impurities were the uncyclized intermediate **2** and the unreacted ester **1**. Using these conditions, we set up parallel syntheses of oxadiazoles on a semi-automated synthesizer Quest 210 (by Argonaut Technologies). Some examples[6] are shown in Figure 1.

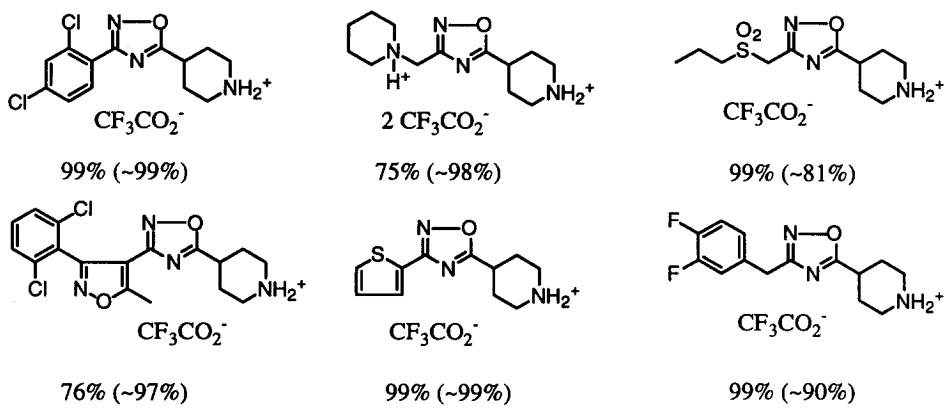
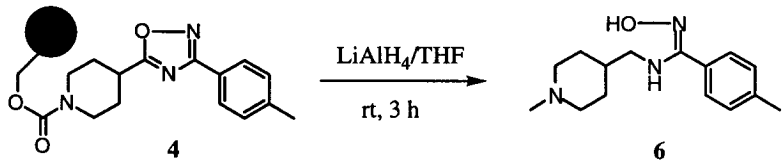


Figure 1. Yield (and Purity determined by HPLC)

To expand the scope of the solid-phase synthesis, we tested a new cleavage method for benzylcarbamate linked piperidine sand tried to obtain N-alkylated amidoximes. When TentaGel resin-bound oxadiazole **4** was treated with a solution of $LiAlH_4$ in THF at room temperature, we expected to see a reductive ring-opening of the oxadiazole[7] and a reductive cleavage of the benzylcarbamate linker to the resin (Scheme 2). Although the desired product was detected, neither yield nor purity was acceptable. We then switched to the more robust Wang (Novabiochem) resin-bound substrate **4**. The reaction was carried out with 5 equiv $LiAlH_4$ (1 M solution in THF) at room temperature for 3 h under nitrogen with occasional agitation, and then was carefully quenched with dropwise addition of aq sat Na_2SO_4 until bubbling ceased. Beads and inorganic salts were filtered through a layer of silica gel, and *N*-alkylated amidoxime **6**[8] was obtained in its free-base form in excellent yield (~95%) and purity.



4 6

Scheme 2

We have successfully developed oxadiazole synthesis on solid supports under both neutral conditions with heating[4] and basic conditions at room temperature. These conditions are complementary to each other and can be used over a wide range of substrates bearing different functional groups. The reductive cleavage of both the carbamate linker and oxadiazole ring offers new ways to access *N*-methyl piperidine derivatives and *N*-alkylated amidoxime derivatives on solid supports. These new developments have largely facilitated our drug discovery research and will be more important as we move toward automated synthesis in the future.

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References and Notes

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4. Biftu, T.; Feng, D.; Liang, G.-B.; Kuo, H.; Qian, X.; Naylor, E. M.; Colandrea, V. J.; Candelore, M. R.; Cascieri, M. A.; Colwell, Jr., L. F.; Deng, L.; Feeney, W. P.; Forrest, M. J.; Hom, G. J.; MacIntyre, D. E.; Miller, R. R.; Stearns, R. A.; Strader, C.; Tota, L; Wang, P.-R.; Wyvratt, M. J.; Fisher, M. H.; Weber, A. E. *Abstracts of presentations*, 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21-25, 1999; Division of Medicinal Chemistry, Abstract # 138.
5. ^{1}H NMR (CD_3OD, ppm): 2.1 (m, 2H), 2.4 (s, 3H), 2.4 (m, 2H), 3.2 (m, 2H), 3.5 (m, 2H+1H), 7.32 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 2H). LC/MS: M^++1 = 244.
6. All new compounds were characterized by ^{1}H NMR and MS.
7. Tavella, M.; Strani, G. *Ann. Chim. (Rome)* **1961**, *51*, 361.
8. ^{1}H NMR ($CDCl_3$, ppm): 1.2 (m, 2H), 1.3 (m, 1H), 1.7 (m, 2H), 1.9 (m, 2H), 2.26 (s, 3H), 2.39 (s, 3H), 2.8 (m, 2H), 2.9 (m, 2H), 5.3 (broad, 1H), 7.21 (d, J = 8 Hz, 2H), 7.34 (d, J = 8 Hz, 2H). LC/MS: M^++1 = 262.