Pergamon

*Tetrahedron Letters*, Vol. 37, No. 37, pp. 6627-6630, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01492-X

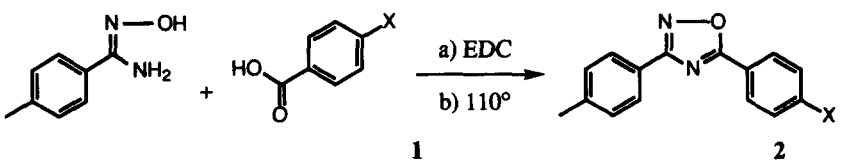
# An Improved Oxadiazole Synthesis Using Peptide Coupling Reagents

Gui-Bai Liang* and Danqing D. Feng

Department of Medicinal Chemistry, Merck Research Laboratories, P. O. Box 2000, Rahway, NJ 07065

**Abstract:** Substituted 1,2,4-oxadiazoles were synthesized in good yields in a one pot procedure by condensation of the corresponding amidoxime with carboxylic acids in the presence of a peptide coupling reagent in diglyme, followed by heating the reaction mixture to 100°C for several hours. 

Oxadiazoles are often considered as ester and amide bioisosteres in drug discovery research.[1] They have been incorporated into muscarinic agonists,[2,3] benzodiazepine receptor agonists,[4] and antirhinovirus agents.[5] Oxadiazoles have also been used as dipeptidomimetics, and their electrostatic and hydrogen bonding properties have been studied.[1] Synthesis of oxadiazoles usually involves *O*-acylation of an amidoxime with an acid chloride[5] or an anhydride[1] followed by cyclization in refluxing pyridine. This method, although it works well on relatively simple substrates, is incompatible with many functional groups. For example, hydroxyl groups have to be protected prior to the reaction.[5] In our current research project we need to assemble oxadiazole rings from starting materials that have other functional groups. Encouraged by an early report[6] that *O*-acylation of amidoximes can be achieved under mild conditions with acetic anhydride, we investigated the *O*-acylation of amidoximes with carboxylic acids mediated by peptide coupling reagents and the subsequent cyclization reaction.




1 2

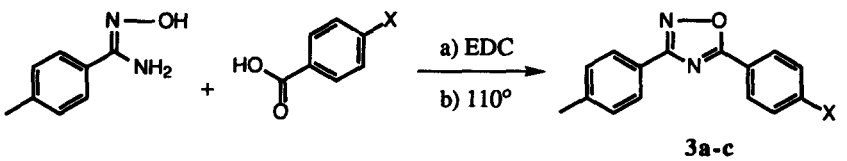
Scheme 1

Commercially available *p*-toluene amidoxime (1.0 mmol) was treated with 1 equiv of butyric acid in the presence of EDC in diglyme (2-3 mL) at 50°C under nitrogen overnight, and the reaction mixture was then heated to 110°C for 3 hr (Scheme 1). After removal of solvent under vacuum, the reaction mixture was purified on a silica gel column eluting with 1-5% methanol in dichloromethane. The desired 1,2,4-oxadiazole **2** was isolated in 60% yield.[7] Other solvents and peptide coupling reagents were then tested, and results are summarized in Table 1. It was found that a variety of peptide coupling reagents can be used for the acylation step, and the intermediate **1** can be isolated by silica gel chromatography. The 50°C temperature for the acylation step was used in our initial study to solubilize EDC in diglyme, but was later found to be unnecessary in other cases. A trace of the cyclized product **2** can be detected by TLC if the reaction is stirred

Table 1. Formation of Oxadiazole **2** under Different Conditions

| Entry | Reagent[a] | Solvent | Condensation | Cyclization | Yield[b] |
|---|---|---|---|---|---|
| 1 | 0.5 eq EDC | diglyme | 50°, overnight | 110°, 3 hr | 30% |
| 2 | 1 eq EDC | diglyme | 50°, overnight | 110°, 3 hr | 60% |
| 3 | 2 eq EDC | diglyme | 50°, overnight | 110°, 3 hr | 63% |
| 4 | 1 eq EDC | dioxane | 50°, overnight | 110°, 3 hr | 45% |
| 5 | 1 eq EDC | DMF | 50°, overnight | 110°, 3 hr | 30% |
| 6 | 1 eq DCC | diglyme | r.t., overnight | 110°, 3 hr | 54% |
| 7 | 2 eq DCC | dioxane | r.t., overnight | 110°, 3.5 hr | 50% |
| 8 | 1 eq BOP-Cl | diglyme | r.t., overnight | 110°, 3 hr | 47% |
| 9 | 2 eq BOP-Cl | diglyme | r.t., overnight | 110°, 5 hr | 64% |
| 10 | 1 eq CDI | THF, diglyme[c] | r.t., overnight | 100°, 2 hr | 62% |
| 11 | 1 eq CDI | diglyme | r.t., overnight | 100°, 2 hr | 57% |

a) EDC: 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DCC: 1,3-Dicyclohexylcarbodiimide; BOP-Cl: Bis(2-oxo-3-oxazolidinyl)phosphinic chloride; CDI: 1,1'-Carbonyldiimidazole; b) Isolated yields; c) THF for condensation, and diglyme for cyclization.




**3a-c**

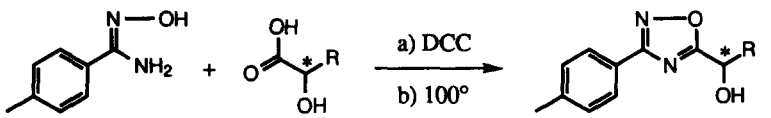
**3a**, X=H; **3b**, X=OMe; **3c**, X=$NO_2$

Scheme 2

at room temperature for several days. The cyclization is very slow in refluxing THF; however, it proceeds rapidly at 100°C in diglyme. *O*-Acylamidoxime **1** is stable and can be isolated (in ~70% yield[8]). No evidence was observed for *cis*- or *trans*-isomers of *O*-acylamidoxime **1** by $^1$H NMR. Oxadiazole **2** is obtained in very high yield (>90%) if purified *O*-acylamidoxime **1** is used instead of heating the reaction mixture directly. No reagents are needed for the cyclization. Depending on the substrates, the cyclization may be complete in 2 hr

at 90°C. In other cases, however, starting materials can still be detected after 3 hr at 110°C. Prolonged heating usually does not increase the yield, and in some cases tends to produce new by-products which can be detected by TLC. Electronic effects on the overall reaction are not significant since similar yields of **3a-c** (50-60%) were obtained from substituted benzoic acids under the same reaction conditions (Scheme 2). A recent study shown that microwave irradiation may accelerate the cyclization.[9]

The most obvious advantage of this improved method for oxadiazole synthesis compared to the aforementioned acid chloride method[5] is the ready availability of a large number of carboxylic acids. The symmetrical anhydride method,[1] which also uses carboxylic acids as starting material, is not economical because half of the acid is wasted. The use of refluxing pyridine as solvent for cyclization,[1,5] which is not desirable for large scale operations, is also eliminated in our improved oxadiazole synthesis. More importantly this improved method is compatible with many functional groups. For example, mandelic acid derivatives can be used directly without protection of the hydroxyl group (Scheme 3). Thus, racemic 4-fluoro-mandelic acid (R=4-fluorophenyl) was treated with amidoxime **1** in the presence of 1 equiv of DCC in diglyme followed by heating to 110°C for 3 hr. The desired α-hydroxy oxadiazole **4a** was isolated in 52% yield after silica gel column chromatography. When optically pure (*S*)-(-)-mandelic acid (R=phenyl) was used in the reaction, oxadiazole **4b** was obtained in 40% yield. Analysis of the corresponding Mosher ester **5** by $^{1}H$ and $^{19}F$ NMR indicated that no racemization had occurred. Two other optically pure α-hydroxycarboxylic acids (R=benzyl, and R=isopropyl) were also studied under the same conditions. Comparable yields (40-50%) for **4c** and **4d** were obtained, and no racemization was detected based on NMR studies on their Mosher esters. It is worth mentioning that **5** slowly epimerizes at the benzylic position at room temperature in methanol as determined by $^{1}H$ NMR. This is presumably due to the high acidity of the benzylic proton, which has a chemical shift of 7.28 ppm in methanol-$d_4$.

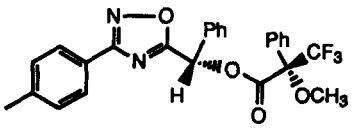



**4a-d**

**4a**, R=4-fluorophenyl; **4b**, R=phenyl; **4c**, R=benzyl; **4d**, R=isopropyl

Scheme 3

We have demonstrated that oxadiazoles can be synthesized in good yields by condensation of a carboxylic acid with an amidoxime in the presence of a peptide coupling reagent at room temperature followed by heating to 100°C for several hours, all in one pot. The reaction proceeds under neutral conditions and can be directly applied to functionalized substrates without modification and functional group protection. A wide range of structurally diverse oxadiazoles can now be readily synthesized.



5

**Acknowledgement**: Authors thank Dr. Tesfaye Biftu, Dr. Ann Weber, and Dr. Mike Fisher for their support, and helpful discussions.

## REFERENCES AND NOTES

1. Borg, S.; Estenne-Bouhtou, G.; Luthman, K.; Csoregh, I.; Hesselink, W.; Hacksell, U. *J. Org. Chem.* **1995**, *60*, 3112-3120, and references therein.
2. Watjen, F.; Baker, R.; Engelstoff, M.; Herbert, R.; MacLeod, A.; Knight, A.; Merchant, K.; Moseley, J.; Saunders, J.; Swain, C. J.; Wong, E.; Springer, J. P. *J. Med. Chem.* **1989**, *32*, 2282-2291.
3. Showell, G. A.; Gibbons, T. L.; Kneen, C. O.; MacLeod, A. M.; Merchant, K; Saunders, J.; Freedman, S. B.; Patel, S.; Baker, R. *J. Med. Chem.* **1991**, *34*, 1086-1094.
4. Orlek, B. S.; Blaney, F. E.; Brown, F.; Clark, M. S. G.; Hadley, M. S.; Hatcher, J.; Riley, G. J.; Rosenberg, H. E.; Wadsworth, H. J.; Wyman, P. *J. Med. Chem.* **1991**, *34*, 2726-2735.
5. Diana, G. D.; Volkots, D. L.; Hitz, T. J.; Bailey, T. R.; Long, M. A.; Vescio, N.; Aldous, S.; Pevear, D. C.; Dutko, F. J. *J. Med. Chem.* **1994**, *37*, 2421-2436.
6. Lenaers, R.; Moussebois, C.; Eloy, F. *Helv. Chim. Acta* **1962**, *45*, 441-446.
7. This compound was characterized by $^1$H NMR [($CDCl_3$, ppm): 1.04 (t, J=7.4 Hz, 3H), 1.88 (sextet, J=7.4 Hz, 2H), 2.40 (s, 3H), 2.90 (t, J=7.5 Hz, 2H), 7.25 (m, 2H), 7.94 (m, 2H)], MS, and elemental analysis. All other new compounds were characterized by $^1$H NMR and MS.
8. $^1$H NMR ($CDCl_3$, ppm): 0.998 (t, J=7.4 Hz, 3H), 1.75 (sextet, J=7.4 Hz, 2H), 2.36 (s, 3H), 2.46 (t, J=7.4 Hz, 2H), 5.00 (broad s, 2H), 7.20 (m, 2H), 7.59 (m, 2H).
9. Oussaid, B.; Moeini, L.; Martin, B,; Villemin, D.; Garrigues, B. *Synth. Commun.* **1995**, *25*, 1451-1459.

(*Received in USA* 5 *June* 1996; *revised* 22 *July* 1996; *accepted* 23 *July* 1996)