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PARALLEL SYNTHESIS OF 1,2,4-OXADIAZOLES USING CDI ACTIVATION

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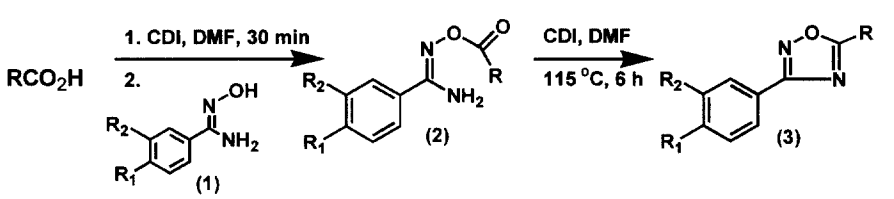
Abstract: 1,2,4-Oxadiazoles have been prepared in parallel using 1,1'-carbonyldiimidazole (CDI) as a reagent for both formation and cyclodehydration of O-acyl benzamidoximes. The use of CDI facilitates parallel purification of the oxadiazole products by simple liquid–liquid extraction and filtration.

Oxadiazoles are important bioisosteres for esters and amides and have been reported to have muscarinic agonist,[1] benzodiazepine receptor agonist,[2] 5-HT agonist,[3] and antirhinoviral activities.[4] 1,2,4-Oxadiazoles have also been used as replacements for peptidal amide bonds.[5] Several methods are available for the synthesis of 1,2,4-oxadiazoles[6] including O-acylation/cyclodehydration[7] and palladium-mediated carbonylative coupling of aryl iodides with amidoximes.[8] A recent publication[7] describing the use of a variety of activating agents for O-acylation of benzamidoximes prompted us to disclose our results on the use of 1,1'-carbonyldiimidazole (CDI)[9] as a reagent for both formation and cyclodehydration of O-acyl benzamidoximes. Use of this activating agent for the synthesis of 1,2,4-oxadiazoles permits the use of a wide range of benzamidoximes and carboxylic acids and also facilitates parallel product purification and isolation.

The general approach to parallel solution-phase synthesis of 1,2,4-oxadiazoles is provided in Scheme 1. Carboxylic acids were activated with CDI in DMF at room temperature and treated with readily available benzamidoximes (**1**) in DMF. Noncommercially available benzamidoximes were readily prepared from benzonitrile derivatives.[10] We have found that the resulting O-acyl benzamidoximes (**2**) may be dehydrated by further treatment with additional CDI in DMF (115 °C, 6 h) in a one-pot procedure.[11] Previous studies reported 57–62% yields of 1,2,4-oxadiazoles with *p*-toluamidoxime, butyric acid, and CDI as a reagent for O-acylation and 50–60% yields with 4-nitrobenzoic acid and EDC.[7] In our hands, we were not able to effect complete and clean cyclodehydration using DCC, EDC, or diethyl cyanophosphate

Scheme 1



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employing electron-deficient benzoic acids. Use of CDI for both activation and subsequent cyclodehydration was successful for all carboxylic acids examined, including electron-deficient benzoic acids, and led to cleaner products. Dilution of reaction mixtures with methylene chloride, aqueous workup, and plug filtration of the products through Florisil afforded the 1,2,4-oxadiazole products (**3**).

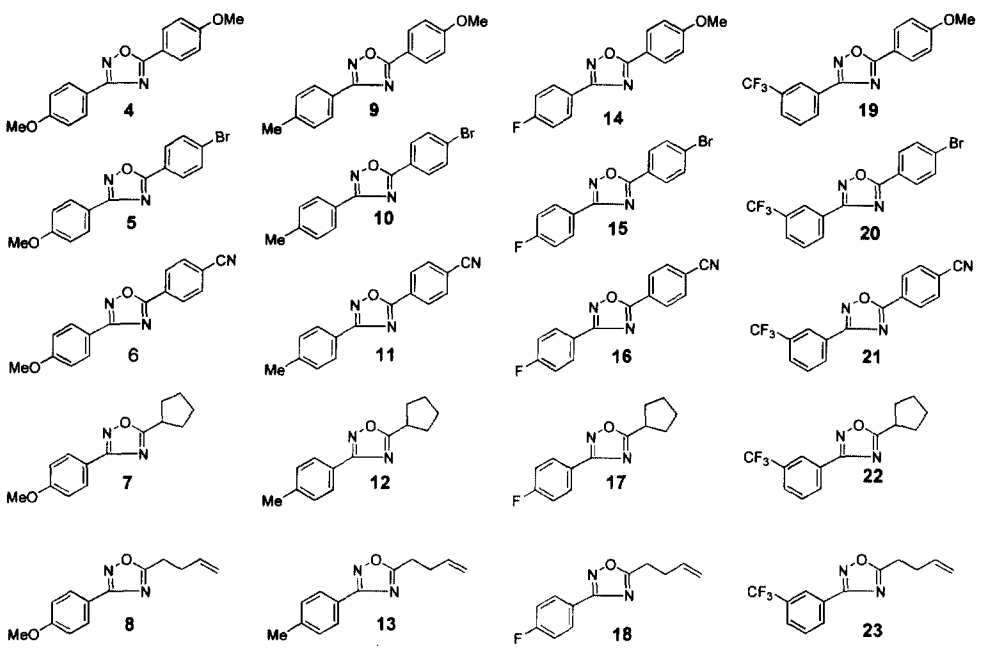
Using these general experimental conditions, a 4 x 5 matrix of benzamidoximes and carboxylic acids were utilized to prepare a focused library of twenty 1,2,4-oxadiazoles and to assess the scope of the synthesis method. A range of electron-rich and electron-poor benzamidoximes (Table 1) and both aromatic and aliphatic carboxylic acids were employed. Parallel synthesis was performed using the Quest 210 Organic Synthesizer (Argonaut Technologies). In a typical experimental procedure, 1 mL of a 0.5 M carboxylic acid solution (0.5 mmol) in DMF was added to 10 mL reaction vessels, followed by addition of 0.55 mL of 1.0 M solution (0.55 mmol) of CDI in DMF. After mixing for 30 min, 1.0 mL of a 0.55 M benzamidoxime solution (0.55 mmol) in DMF was added and the resulting solution was mixed for 4 h at 25 °C. A further 0.55 mL of 1.0 M CDI (0.55 mmol) in DMF was added and the reaction mixtures were heated to 115 °C for 6 h to effect cyclodehydration (*Caution*: gas evolution!). After cooling to room temperature, 7 mL of DCM was added to each vessel, followed by 3 mL of water. After 10 min of agitation, the upper aqueous layers were removed via aspirator needle and the DCM layer further washed with 1 x 3 mL H_2O, 1 x 3 mL 1 N HCl, 1 x 3 mL sat. $NaHCO_3$, and 1 x 3 mL brine. The methylene chloride layers were dried in situ using $MgSO_4$ and filtered through 1 g of Florisil pre-packed into 12 ml

Table 1

Entry	Benzamidoxime	Carboxylic Acid	Oxadiazole	% Wt. Yield	Area % Purity[a]
1	4-methoxybenzamidoxime	*p*-anisic acid	**4**	53	97
2	4-methoxybenzamidoxime	4-bromobenzoic acid	**5**	59	97
3	4-methoxybenzamidoxime	4-cyanobenzoic acid	**6**	60	96
4	4-methoxybenzamidoxime	cyclopentanecarboxylic acid	**7**	61	97
5	4-methoxybenzamidoxime	4-pentanoic acid	**8**	60	98
6	*p*-toluamidoxime	*p*-anisic acid	**9**	60	97
7	*p*-toluamidoxime	4-bromobenzoic acid	**10**	57	97
8	*p*-toluamidoxime	4-cyanobenzoic acid	**11**	61	96
9	*p*-toluamidoxime	cyclopentanecarboxylic acid	**12**	61	99
10	*p*-toluamidoxime	4-pentanoic acid	**13**	64	95
11	4-fluorobenzamidoxime	*p*-anisic acid	**14**	51	97
12	4-fluorobenzamidoxime	4-bromobenzoic acid	**15**	58	97
13	4-fluorobenzamidoxime	4-cyanobenzoic acid	**16**	63	98
14	4-fluorobenzamidoxime	cyclopentanecarboxylic acid	**17**	58	97
15	4-fluorobenzamidoxime	4-pentanoic acid	**18**	60	91
16	3-(CF_3)benzamidoxime	*p*-anisic acid	**19**	50	95
17	3-(CF_3)benzamidoxime	4-bromobenzoic acid	**20**	64	97
18	3-(CF_3)benzamidoxime	4-cyanobenzoic acid	**21**	69	98
19	3-(CF_3)benzamidoxime	cyclopentanecarboxylic acid	**22**	60	98
20	3-(CF_3)benzamidoxime	4-pentanoic acid	**23**	45	84

[a] GC Analysis (HP-5 phenylmethylsilicone column (175 °C, 3 min), 20 °C/min to 300 °C).

Figure 1



SPE cartridges.[12] Concentration of the solutions afforded the 1,2,4-oxadiazole products **4–23** (Figure 1).[13] Many of the oxadiazole products were found to be solids, except those derived from aliphatic acids (entries 4,5,9,10,14,15,19, and 20).[14]

Results from the parallel oxadiazole synthesis are provided in Table 1. In general, chemical yields were in the 50–70% range and GC purities >90%. All products were found to have high purity by ^{1}H NMR and gave the predicted M+1 peaks by mass. spectral analysis (EI). It is noteworthy that final pure compounds were obtained from simple parallel liquid–liquid extractions (tandem acid and base to remove imidazole- and benzamidoxime-derived byproducts, respectively) and final SPE filtration through Florisil, which is a key advantage of employing CDI as an activation/cyclodehydration reagent.

In conclusion, a solution-phase, parallel synthesis protocol for preparation of 1,2,4-oxadiazoles has been developed. The method makes use of a single activating agent, CDI, for both coupling and cyclodehydration of a wide range of O-acyl benzamidoximes, and allows for simple product purification and isolation (byproducts are removable by simple aqueous workup). Parallel synthesis and purification in this series has been facilitated by the use of a benchtop organic synthesizer, the Quest 210. Further studies on the preparation of heterocycles using expedited solution-phase methods are in progress in these laboratories and will be reported in due course.

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References and Notes

1. (a) 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. (b) 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. (c) Macor, J. E.; Ordway, T.; Smith, R. L.; Verhoest, P. R.; Mack, R. A. *J. Org. Chem.* **1996**, *61*, 3228.
2. (a) 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. b) Tully, W. R.; Gardner, C. R.; Gillespie, R. J.; Westwood, R. *J. Med. Chem.* **1991**, *34*, 2060.
3. Chen, C.; Senanayake, C. H.; Bill, T. J.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 3738.
4. Diana, G. D.; Volkots, D. L.; Nitz, T. J.; Bailey, T. R.; Long, M. A.; Niranjan, V.; Aldous, S.; Pevear, D. C.; Dutko, F. J *J. Med. Chem.* **1994**, *37*, 2421.
5. Borg, S.; Luthman, K.; Nyberg, F.; Terenius, L.; Hacksell, U. *Eur. J. Med. Chem.* **1993**, *28*, 801.
6. For a review, see: Clapp, L. B. *Adv. Heterocycl. Chem.* **1976**, *20*, 65.
7. Liang, G-B.; Feng, D. D. *Tetrahedron Lett.* **1996**, *37*, 6627 and references cited therein.
8. Young, J. R.; DeVita, R. J. *Tetrahedron Lett.* **1998**, *39*, 3931.
9. *Abbreviations*: CDI: 1,1'-carbonyldiimidazole; DMF: dimethylformamide; DCM: dichloromethane; SPE: solid phase extraction. EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; DCC: 1,3-dicyclohexylcarbodiimide.
10. Benzamidoximes were prepared according to a modification of the reported procedure: Eloy, F.; Lenaeres, R. *Chem. Rev.* **1961**, *62*, 155. *Representative preparation of p-toluamidoxime*: To a 250 mL round-bottom flask was added 10.2 g (87.0 mmol, 1.0 equiv) of *p*-tolunitrile, 12.4 g (191.5 mmol, 2.2 equiv) of hydroxylamine hydrochloride, and the solids dissolved in 150 mL of 95 % ethanol. 27.9 mL (200.2 mmol, 2.3 equiv) of triethylamine was added, and the reaction mixture stirred at 75 °C for 12 h. After cooling to rt, the mixture was filtered, diluted with 200 mL distilled water, and neutralized to pH 7 with conc HCl. The solution was placed on a rotovap at 40 °C bath temperature to remove the ethanol and precipitate the product. The solid product was filtered, washed three times with water, and dried in vacuo to afford 10.4 g (80 %) of *p*-toluamidoxime.
11. For a discussion of the cyclodehydration mechanism, see: Ooi, N. S.; Wilson, D. S.; *J. Chem. Soc. Perkin Trans. II* **1980**, 1792.
12. Jones Chromatography, Lakewood, Colorado, USA. We have found that Florisil is also particularly effective at removing trace amounts of DMF that are contained in crude products.
13. Characterization for oxadiazole **9** (3-[4'-methylphenyl]-5-[4'-methoxyphenyl]-1,2,4-oxadiazole): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, J = 6.9 Hz, 2H), 8.04 (d, J = 8.7 Hz, 2H), 7.30 (d, J = 8.7 Hz, 2H), 7.03 (d, J = 6.9 Hz, 2H), 3.87 (s, 3H, -OMe), 2.42 (s, 3H, -Me) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.4, 168.8, 163.1, 141.2, 129.9, 129.4, 127.3, 124.2, 116.9, 114.3, 55.2, 21.2 ppm. MS (EI): 266 (M+, base), 133, 118, 104, 92, 77. Calcd for $C_{16}H_{14}N_2O_2$: 266.25.
14. Initial attempts were made to precipitate the products in parallel using water. However, oxadiazoles derived from aliphatic acids were found to be non-crystalline which required us to utilize a liquid–liquid extraction procedure.