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A suitable 1,2,4-oxadiazoles synthesis by microwave irradiation

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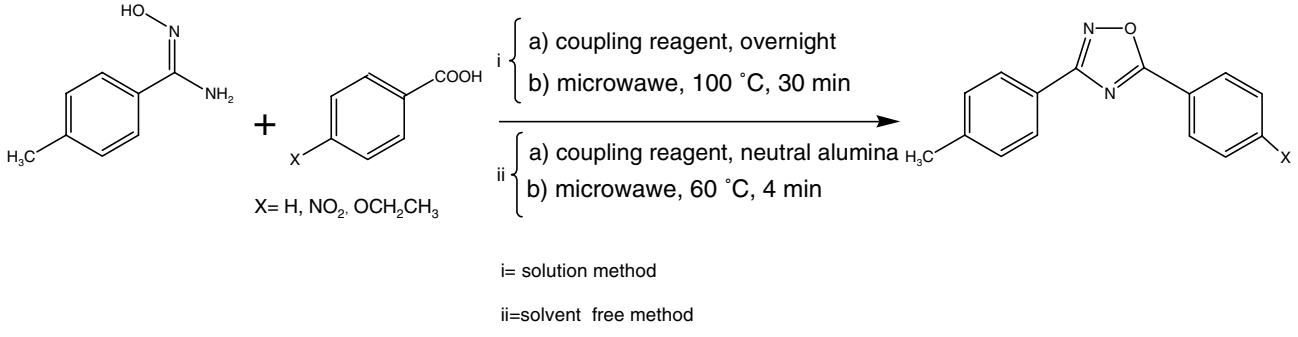
Abstract—One pot microwave-assisted synthesis of substituted 1,2,4-oxadiazoles in solvent and under solvent free condition was performed exploring the importance of some coupling reagents. Good yields and short reaction times were the main aspects of the methods.

Bioisosteric replacements for the amide moiety represent an area that is currently the centre of focus because of its implications in peptide chemistry and the development of peptidomimetics. Peptide linkages have been replaced with a wide variety of structural moieties in an attempt to create chemically stable and orally available molecules. Heterocyclic rings such as 1,2,4-oxadiazoles and 1,3,4-oxadiazoles have been used as replacements for the amide functionality in biologically active compounds.[1] These compounds contain reactive intermediate functionality, thus allowing easy incorporation into the parent molecule by a variety of synthetic transformations. Moreover, the oxadiazole nucleus is a well studied traditional pharmacophoric scaffold that has emerged as a core structural unit of various muscarinic agonists,[2a] benzodiazepine receptor partial agonists,[2b] growth hormone secretagogous.[2c] 1,2,4-Oxadiazoles can be formed by the reaction of an amidoximes with a carboxylic acid or acid chloride. A wide variety of reaction conditions have been published for the synthesis of 1,2,4-oxadiazoles in solution, on solid phase or under solvent free conditions.[3] Knowing the importance of the 1,2,4-oxadiazole ring as pharmacophoric scaffold, our attention has turned to improve the synthesis of this important nucleus bearing in mind new synthetic methodologies. The application of microwave energy to organic compounds for conducting synthetic reactions at highly accelerated rates is an emerging technique.[4,5] In fact in later years, microwaves have become popular among synthetic organic chemists both to improve classical organic reactions, shortening reaction times and/or improving yields, as well as to promote



Scheme 1. General synthetic procedure of 1,2,4-oxadiazole derivatives.

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new reactions. This paper describes a facile synthesis of 1,2,4-oxadiazole derivatives by application of microwave energy in the presence of solvents and under solvent free condition. At first we investigated, in the presence of solvent, the O-acylation of an amidoxime with a few carboxylic acids mediated by some peptide coupling reagents and the subsequent cyclization reaction (Scheme 1, i).

Conventional heating (oil bath) and microwave irradiation of the reactions were compared (Table 1). The synthetic procedure, summarized in Scheme 1, was performed using a microwave oven (ETHOS 1600, Milestone) especially designed for organic synthesis. The experimental conditions used during microwave application were similar, with the same concentration of starting material and volume of solvent, to those used by conventional heating. All reactions were performed in standard Pyrex glassware and were performed by microwave program, which was composed by appropriate ramping and holding steps. Identification of the optimum profile power/time and temperature for the synthesis was reported in Table 1. The temperature of the stirred reaction mixture was monitored directly by a microwave-transparent fluoroptic probe inserted into the solution. The general procedure for the synthesis of 1,2,4-oxadiazole derivatives in solution, reported in Scheme 1, is as follows:[6] *p*-toluene amidoxime and the carboxylic acid were dissolved in the solvent in the presence of the coupling reagents. The reaction mixture was stirred overnight and then transferred, according to our procedure, in the microwave oven. A starting temperature of 50 °C for the acylation step was used with EDC in order to facilitate the dissolution of this coupling reagent in diglyme or in DMF; both these conditions are necessary in the conventional synthetic method than in the microwave procedure proposed by us. The main advantage to this synthetic route is that a short time of irradiation of the mixture reaction provided the 1,2,4-oxadiazole derivatives as the major product. If the application of microwave energy was performed for a longer time (>30 min, Table 1) the reagents were not completely transformed in the corresponding 1,2,4-oxadiazole derivatives. The results obtained with the considered coupling reagents are summarized in Table 1. For compounds **4**–**9** we obtained higher yields (68–94%) using TBTU/HOBt and DCC/HOBt, while with DCC, EDC and CDI the yields were lower (27–50%, compd **1**–**3**). Instead, reactions performed under conventional heating always gave the desired 1,2,4-oxadiazoles in lower yields. We have also investigated the electronic effects on the overall reaction using different substituted benzoic acids. Compounds **8** and **9**, with electron donor substituent (OEt) gave lower yields (75–68%) with respect to compounds **6** and **7**, characterized by electronic withdraw substituent (NO_2, 94–91%), or unsubstituted acid **4** and **5** (93–88%).

When the reactions were performed under solvent free conditions,[7] in the presence of neutral alumina as support, (Scheme 1, ii) the time of reaction was greatly reduced (4 min). Yields were always lower respect the solution microwave method except for compound **2**

Table 1. Conventional heating versus microwave irradiation of 1,2,4-oxadiazole derivatives

Compd	X	Coupling reagent	Solvent[d]	Conventional heating[b]			Microwave irradiation[e]			Solvent free microwave irradiation[e]		
				Temp (°C)	Yield[a] (%)	Time (h)	Temp (°C)	Yield[a] (%)	Time (min)	Solid support	Time (min)	Temp (°C)	Yield (%)
1	H	DCC	Diglyme	110	28[c]	3	110	50	30	Neutral alumina	4	60	37
2	H	EDC	Diglyme	110	12[c]	3	110	27	30	Neutral alumina	4	60	27
3	H	CDI	Diglyme	100	15[c]	2	100	46	30	Neutral alumina	4	60	32
4	H	TBTU/HOBT	Diglyme	100	75	2	100	93	30	Neutral alumina	4	60	21
5	H	DCC/HOBT	Diglyme	100	68	2	100	88	30	Neutral alumina	4	60	55
6	NO_2	TBTU/HOBT	Diglyme	100	91	2	100	94	30	Neutral alumina	4	60	31
7	NO_2	DCC/HOBT	Diglyme	100	78	2	100	91	30	Neutral alumina	4	60	58
8	OEt	TBTU/HOBT	Diglyme	100	63	2	100	75	30	Neutral alumina	4	60	22
9	OEt	DCC/HOBT	Diglyme	100	52	2	100	68	30	Neutral alumina	4	60	46

[a] All the reactions were performed three times and the reaction time and yields given are the average values.
[b] Oil-bath.
[c] The yields reported in literature were higher of those obtained by us.[2a]
[d] All the reactions have been performed also in DMF and the obtained yields were comparable.
[e] The power used with solvent was 300 W while it was 600 W in solvent free experiments.

(EDC activation), while were comparable (compd **9**) or higher (compd **1**–**3**) respect the conventional heating (Table 1). Even in the solvent free method the presence of a withdrawing group provided higher reaction yields. In contrast to that observed in both the solution methods, the activation by DCC/HOBt represents the optimal condition. No further yield increasing was evidenced when the irradiation time was prolonged for over 4 min; this is related to the decomposition of the starting materials. Finally, neat reaction was not successful (we did not noticed the presence of the final compound even if heating was prolonged for over 30 min).

In conclusion, we have shown that the application of microwave irradiation in to the solution method in presence of a peptide coupling reagent improves the yields of 1,2,4-oxadiazole derivatives and significantly reduces reaction times. Furthermore, when the cyclization was performed under solvent free condition, reaction times were strongly reduced although yields were not so satisfactory.

Abbreviations and symbols. We have followed the recommendations of the IUPAC-IUB Joint Commission on Biochemical Nomenclature (*Eur. J. Biochem.* **1984**, *138*, 9). In addition the following abbreviations are used: TBTU, *O*-(1*H*-benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate; HOBt, 1,2,3-benzotriazole-1-hydroxide; DCC, dicyclohexyl-carbodiimide; EDC, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride; CDI, 1,1′-carbonyldiimidazole.

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6. General procedure of 1,2,4-oxadiazole derivatives in solution: Commercially available (Aldrich) *p*-toluene amidoxime (1 mmol) and 1 equiv of carboxylic acid were dissolved in 10 mL of the solvent (diglyme or DMF) in the presence of the coupling reagents (1 equiv). An opportune quantity of base (*N*-ethyldiisopropylamine) was added when TBTU/HOBt was used. The reaction mixture was kept at room temperature, under nitrogen atmosphere, overnight. Then the vessel containing reaction mixture was transferred in the microwave oven and was heated at 100 °C by application of microwave energy for 30 min. The desired parameters (microwave power, temperature and time) were set as reported in Table 1. The reaction was monitored by TLC. After irradiation, the solvent was removed and the crude residue was purified by silica gel chromatography. 1,2,4-Oxadiazole derivatives were characterized by ^{1}H NMR and MS and the data were consistent with the considered structures. NMR spectra were recorded on a Bruker WM 500 spectrometer using tetramethylsilane as an internal standard. For the H-substituted derivatives (**1**–**5**): mp 98–100 °C, ESI: calcd for $C_{15}H_{12}N_2O$ 237.26, found 237.27 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.21 (d, 2H), δ 8.08 (d, 2H), δ 7.64 (dd, 1H), δ 7.58 (d, 2H), δ 7.37 (d, 2H), δ 2.42 (s, 3H). NO_2-substituted derivatives (**6**,**7**): mp 167–169 °C, ESI: calcd for $C_{15}H_{11}N_3O_3$ 282.27, found 287.26 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.41 (d, 4H), δ 8.07 (d, 2H), δ 7.34 (d, 2H), δ 2.44 (s, 3H); OEt-substituted derivatives (**8**,**9**): mp 119–121 °C, ESI: calcd for $C_{17}H_{16}N_2O_2$ 281.31, found 281.32 (MH^+); ^{1}H NMR ($CDCl_3$): δ 8.13 (d, 2H), δ 8.05 (d, 2H), δ 7.31 (d, 2H), δ 7.02 (d, 2H), δ 4.11 (q, 2H), δ 2.42 (s, 3H), δ 1.46 (t, 3H).
7. Synthesis of 1,2,4-oxadiazole derivatives under solvent free conditions: *p*-Toluene amidoxime (1 mmol), benzoic substituted acid (1 equiv) and coupling reagents (1 equiv) were mixed with the neutral alumina in a 4:1 ratio. The mixture was shacked for 5 min. To have a complete mixing in the powder, dichloromethane was added in small quantity to solubilize the reagents and then the solvent was evaporated. The reaction mixture was then irradiated by microwave for 4 min. The desired parameters (microwave power, temperature and time) were set as reported in Table 1. After irradiation the solid was extracted in dichloromethane and purified by silica gel chromatography. ^{1}H NMR spectra and MS data were consistent with the considered structures.