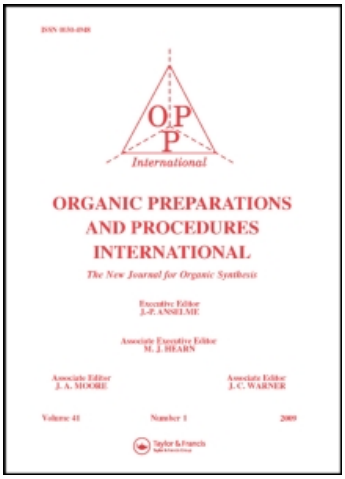

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SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES USING DRY MEDIA

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SYNTHESIS OF 2,5-DISUBSTITUTED 1,3,4-OXADIAZOLES USING DRY MEDIA

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(06/06/02)

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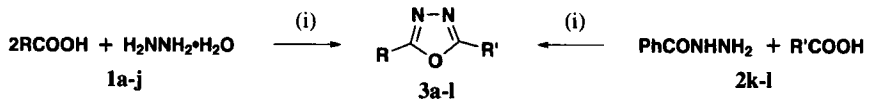
The emergence of microwave assisted solid phase synthesis[1] has facilitated organic processes by providing high yields of pure products and eliminating or minimizing the use of organic solvents.[2] The absence of solvent[3] coupled with high yields and short reaction time makes this methodology very attractive for synthesis.[4] Since 1,3,4-oxadiazoles have been used as corrosion[5] and procollagen C-proteinase[6] inhibitors, it was thought worthwhile to synthesize substituted 1,3,4-oxadiazoles in dry media under microwave irradiation.

1,3,4-Oxadiazoles have long been prepared from dihydrazides using various reagents such as thionyl chloride[7], phosphorus pentoxide[8] and phosphorus oxychloride;[9] other methods that effect the reaction require heat and the use of acidic reagents.[10] The present communication reports the synthesis of 2,5-disubstituted 1,3,4-oxadiazole from acids and hydrazine hydrate using acidic alumina/montmorillonite K_{10} clay[11] as solid supports under MWI. In comparison to reaction over montmorillonite clay the product was obtained in less time when acidic alumina was used as solid support (Table 1). Moreover the conversion of aromatic acids to 1,3,4-oxadiazoles required more time while aliphatic acids react readily with hydrazine hydrate at room temperature[12] to give 1,2-diacylhydrazines, which on cyclization under acidic media yield 1,3,4-oxadiazoles. Unsymmetrical 1,3,4-oxadiazoles were also obtained by reacting benzhydrazide with carboxylic acids under the same conditions. The products were obtained in good yield in contrast to the low yields reported[13] for heterocyclic or *o*-substituted phenyl derivatives.



i) acidic alumina or Montmorillonite K_{10} Clay/MWI

a) R = R'= C_6H_5 b) R = R' = 4-ClC_6H_4 ; c) R = R'= 2-ClC_6H_4; d) R = R'= 4-HOC_6H_4 ; e) R = R'= 4-$CH_3OC_6H_4$; f) R = R' = $C_6H_5OCH_2$; g) R = R'= $CH_3(CH_2)_{14}$; h) R = R'= $CH_3(CH_2)_{10}$; i) R = R' = $CH_3(CH_2)_8$; j) R = R' = $CH_3(CH_2)_6$; k) R = C_6H_5, R' = 2-HOC_6H_4; l) R = C_6H_5, R' = 4-pyridyl

The formation of products was confirmed using spectroscopic data and elemental analysis of new compounds. In conclusion we have developed a facile and economical methodology for preparation of 1,3,4-oxadiazoles using microwave assisted solid phase technology.

Table 1. 1,3,4-Oxadiazoles **3a-l** by Microwave Irradiation using Solid Support[a]

Cmpd.	Yield[b] (%)	Time[b] (min.)	Yield[c] (%)	Time[c] (min.)	mp. (°C)	lit. mp. (°C)
3a	85	2.0	84	2.5	138-139	137-138.5[14]
3b	86	2.5	85	3.0	240-241	241-242[15]
3c	85	2.5	86	3.0	95-96	94-94.5[15]
3d	86	3.0	85	3.5	350-352	350-351[16]
3e	86	3.0	86	3.5	162-163	163-164[14]
3f	88	2.5	88	3.0	82-84	(d)
3g	88	2.0	89	2.5	70-72	72[17]
3h	87	2.0	88	2.5	57-58	56[17]
3i	87	2.0	88	2.5	85-87	(e)
3j	87	2.0	88	2.5	149-150	(f)
3k	85	2.0	87	2.5	165-166	164-165[18]
3l	86	3.0	87	3.5	146-147	145-147[19]

(a) Total time of irradiation at 800 watts (b) Acidic alumina (c) Montmorillonite K10 clay
(d) *Anal.* Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.05; H, 4.98; N, 9.95. Found : C, 68.08; H, 4.96; N, 9.93
(e) *Anal.* Calcd. for $C_{20}H_{38}N_2O$: C, 74.55; H, 11.83; N, 8.70. Found : C, 74.53; H, 11.80; N, 8.69
(f) *Anal.* Calcd. for $C_{16}H_{30}N_2O$: C, 72.20; H, 11.25; N, 10.55. Found : C, 72.18; H, 11.27; N, 10.52

EXPERIMENTAL SECTION

Mps were determined on a Thomas Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer FTIR-1710 spectrophotometer. ^{1}H NMR spectra were recorded on FT NMR Hitachi R-600 (60 MHz) instrument using TMS as internal reference. EI mass spectra were recorded on a JEOL NMS-DX303 mass spectrometer. Microwave irradiation were carried out in Kenstar microwave oven, Model No. 0M9925E (2450MHz, 800watts). Elemental analysis were performed by means of Heraeus CHN-Rapid Analyzer and their results agreed satisfactorily with the calculated values. The purity of the compounds were checked on silica gel coated Al plates (Merck). The approximate bulk temperature (approx 90-120°C, 800W) of the reaction vessel immediately after taking it out from microwave oven.

2,5-Disubstituted-1,3,4-oxadiazoles (3a-l). Typical Procedure.- To a solution of acid (0.02 mol) in a minimum quantity of ethanol, hydrazine hydrate (0.01 mol) was added. The reactants were adsorbed over acidic alumina (20 g) or montmorillonite K_{10} clay (20 g). The reaction mixture was mixed well and allowed to dry in air. The reactants were subjected to microwave irradiation for 2-3.5 minutes. After completion of reaction, as monitored by TLC (at an interval of 30 sec.), product was extracted (3 x 15 mL) using ethanol and the product obtained was washed with $NaHCO_3$ solution, dried and recrystallized. Similarly for the preparation of mixed oxadiazoles, acidic alumina (20g) or montmorillonite clay (20g) was added to a solution of acid (0.01 mol) and benzhydrazide (0.01 mol) in ethanol (15 mL) at room temperature. The reaction

mixture was thoroughly mixed and dried in air. It was then subjected to microwave irradiation intermittently at 30 sec. intervals for the specified time (*Table 1*). On completion of reaction as monitored by TLC, the reaction mixture was cooled to room temperature and the product was extracted using ethanol (3 x 15 mL). Removal of solvent under reduced pressure yielded the product which was washed with $NaHCO_3$ solution and recrystallized from ethanol.

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11. (a)Aluminium oxide, acidic, Brockmann I, ~150 mesh, 58 CAMAG 506-C-1 Surface area 155 m^2/g pH=6 (b) Montmorillonite K 10 : K- catalyst, 69866 Fluka, Surface; 200 ± 20 m^2/g
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A NEW APPROACH TO THE SYNTHESIS OF 1,3-AMINOALCOHOLS FROM *MESO* CYCLIC ACID ANHYDRIDE

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1,3-Aminoalcohols and their derivatives play important roles in the synthesis of various compounds with biological activity.[1] For example, the naturally occurring amino sugars are important components of several antibiotics.[2] Carbocyclic nucleosides containing an amino cyclanol moiety exhibit potent antiviral activity.[3] Chiral 1,3-aminoalcohols can be obtained from their racemic mixtures through enzymatic resolution and have been used as chiral auxiliaries in asymmetric syntheses.[4] Although several synthetic methods of 1,3-aminoalcohols have been described,[5] to our knowledge only Fülöp and coworkers have reported a route to 1,3-aminoalcohols from *meso* cyclic acid anhydrides. In Fülöp's method, the β-amino acid was prepared by a Hofmann rearrangement of the carboxamide, obtained by ammonolysis of cyclic anhydride. Lithium aluminium hydride (LAH) reduction of the amino acid gave 1,3-aminoalcohols.[6, 7] We now report a new route to 1,3-aminoalcohols from *meso* cyclic acid anhydrides.

Treatment of lactones **2a,b** prepared from the readily available Diels-Alder adducts **1a,b**, with ammonia gave amido alcohols **3a,b**. While the Hofmann rearrangement of the amidoalcohols **3** with sodium hypochlorite did not occur, the reaction of alcohol **3a** with bis(acetoxy)iodobenzene under mild conditions led to the **4a** and **5a** (9:1 ratio); only cyclic carbamate **4b** was obtained from **3b** under the same conditions. Hydrolysis of carbamates **4a,b** in the presence of $Ba(OH)_2 \cdot 8H_2O$ in a mixture of dioxane and water afforded 1,3-aminoalcohols **6a,b**. The reduction of **4a,b** and of **5a** with LAH led to the N-methyl-1,3-aminoalcohols **7a,b**. This method may be useful for the synthesis of chiral 1,3-aminoalcohols from *meso* cyclic acid anhydrides without resolution of the racemic mixtures.[8]