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Novel procedure for the synthesis of 1,3,4-oxadiazoles from 1,2-diacylhydrazines using polymer-supported Burgess reagent under microwave conditions

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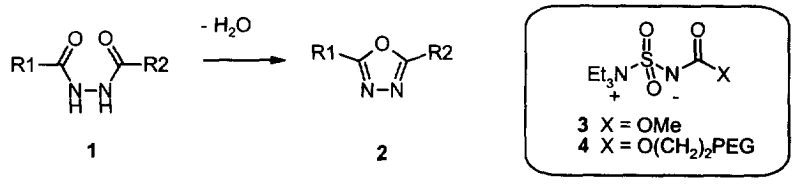
Abstract: A novel and efficient means of effecting the cyclodehydration of 1,2-diacylhydrazines to provide 1,3,4-oxadiazoles is reported. Polymer supported Burgess reagent was utilised in combination with single-mode microwave heating.

Keywords 1,3,4-oxadiazoles; supported reagents; microwave heating.

The development of high throughput and combinatorial technologies has stimulated demand for new synthetic methods that rapidly deliver compounds in high yields and purities, are compatible with a broad range of functionality and are suited to automated synthesis. One emerging approach towards meeting this need involves the use of polymer-supported reagents to effect synthetic transformations in solution [1-4]. The polymer-supported reagent is conveniently removed from the reaction mixture by filtration and reactions may be monitored by conventional analytical techniques. In recent years the use of microwave irradiation to promote reactions has received considerable attention and dramatic rate enhancements have been reported [5]. We provide herein an efficient means of preparing 1,3,4-oxadiazoles, which combines polymer-supported reagent and microwave methods.



Figure

1,3,4-Oxadiazoles **2** have attracted interest in medicinal chemistry as surrogates of carboxylic acids, esters and carboxamides [6-10]. We recently required a mild procedure for the synthesis of 1,3,4-oxadiazoles **2** by cyclodehydration of 1,2-diacylhydrazines **1** as shown in the **Figure.** This transformation usually involves harsh reagents, *e.g.* $SOCl_2$ [6,11], $POCl_3$

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[11], polyphosphoric acid [8] or sulfuric acid [12]. We speculated that Burgess reagent **3** [13] or Wipf's polyethylene glycol supported modification **4** [14] may provide a suitable alternative. Burgess reagent is the reagent of choice for the cyclodehydration of hydroxyamides and thioamides to azoles [14,15]. Additionally, dehydration of primary nitroalkanes to nitrile oxides [16], primary amides to nitriles [17], and formamides to isonitriles [18], have been achieved with Burgess reagent.

In order to ascertain whether Burgess reagent would effect the cyclodehydration of 1,2-diacylhydrazines **1** to provide 1,3,4-oxadiazoles **2**, 1,2-dibenzoylhydrazine was treated with Burgess reagent **3** (1.2 eq.), or with polymer-supported Burgess reagent **4**[1] (1.5 eq.) in THF at reflux. In both cases LC-MS analysis of the crude reaction mixture after 3 h demonstrated *ca.* 40% conversion to 2,5-diphenyl-1,3,4-oxadiazole as confirmed by comparison with authentic material. The reaction with polymer-supported Burgess reagent **4** (1.5 eq.) was repeated under microwave conditions in an attempt to increase the reaction rate: the reaction mixture was irradiated for 2 min at a microwave power of 100 W in a single-mode, continuous wave instrument. After filtration through silica gel to remove the polymer and evaporation of the solvent, the oxadiazole was isolated in 96% yield, 91% purity by HPLC (Entry 1, **Table**).[2]

With these results in hand, cyclodehydration of a range of 1,2-diacylhydrazines[3] using polymer-supported Burgess reagent **4** under single-mode microwave conditions was explored[4] and the results are presented in the **Table**.

1,2-Diacylhydrazines bearing a variety of substituted aromatic rings (Entries 2-7) or heteroaromatic rings (Entries 8-11) readily underwent cyclodehydration by treatment with 1.5 eq. of polymer-supported Burgess reagent **4** in THF. Typically, the reactions were complete after just *2 min* at 100 W irradiation, as indicated by TLC and HPLC analysis, and the 1,3,4-oxadiazoles were obtained in high yields and purities. No significant byproducts were detectable by HPLC or ^{1}H nmr. Apart from filtration through silica gel to remove the polymer, and evaporation of the solvent, no purification was carried out. Cyclodehydration of the 2-furyl compound (Entry 9) proceeded more slowly and required irradation for 2 min at 200 W for efficient conversion. Entries 11 and 12 demonstrate that 1,3,4-oxadiazoles which incorporate a nitrogen substituent at the 2-position are accessible by this method.

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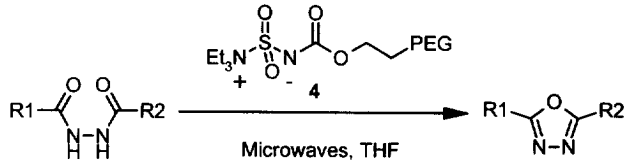
[1] Prepared from Mw 750 polyethylene glycol monomethyl ether [14]. Loading of the polymer was assumed to be quantitative.

[2] No reaction was observed after prolonged microwave heating (in THF or DMF) in the absence of PEG-Burgess reagent.

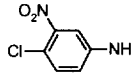
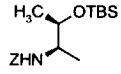
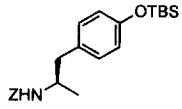
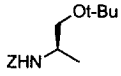
[3] Prepared by acetylation or benzoylation of the appropriate hydrazide, or by treatment with an isocyanate.

[4] Typical procedure: the 1,2-diacylhydrazine **1** (0.25 - 0.5 mmol) and polymer supported Burgess reagent **4** (1.5 eq.) were placed in dry THF (0.5 ml) in a Pyrex tube (16 x 100 mm) equipped with a screw top and PTFE-lined septum. The vial was introduced into the microwave cavity of a *Labwell MW10* instrument and irradiated, CAUTION pressure develops. After cooling to room temperature, residual pressure was relieved by piercing the septum. The crude reaction mixture was filtered through a short column of silica gel, washing with ethyl acetate. Evaporation of the solvent under reduced pressure provided the 1,3,4-oxadiazole **2**.

Table. Data for the synthesis of 1,3,4-oxadiazoles **2** from 1,2-diacylhydrazines **1** using polymer-supported Burgess reagent **4** under single-mode microwave conditions



1 2

Entry	R1	R2	Yield (%)[a]	HPLC Purity (%)[b]
1[c]	Ph	Ph	96	91
2[c]	Ph	Me	75	>99
3[c]	2-Methoxyphenyl	Me	89	>99
4[c]	3-Methoxyphenyl	Me	95	>99
5[c]	4-Methoxyphenyl	Me	86	98
6[c]	2-Chlorophenyl	Me	70	97
7[c]	2-Nitrophenyl	Me	95	>99
8[c]	2-Thiophenyl	Ph	95	97
9[d]	2-Furyl	Ph	86	>99
10[c]	3-Pyridyl	Ph	95	>99
11[c]	4-Pyridyl	NHPh	95	>99
12[c]		Ph	90	92
13[e]	$PhSO_2CH_2$	Me	87	>99
14[f]		Ph	76	98
15[f]		Ph	98	97
16[g]		Ph	79	89

a) Products were identified by ^1H and ^{13}C nmr, MS and IR spectroscopy; where appropriate, data were in agreement with literature values. b) 254 nm detection. **Reaction conditions:** c) 2 min @ 100 W (1.5 eq. PEG-Burgess reagent). d) 2 min @ 200 W (1.5 eq. PEG-Burgess reagent). e) 4 min @ 100W (1.5 eq. PEG-Burgess reagent). f) 2 min @ 100 W (2 eq. PEG-Burgess reagent) then 2 min @ 100 W (+ 1 eq. PEG-Burgess reagent) g) 4 min @ 100 W (3 eq. PEG-Burgess reagent) then 4 min @ 100 W (+ 1 eq. PEG-Burgess reagent).

Interestingly, 1,2-diacetylhydrazine failed to cyclize under these conditions or under conventional thermal heating with **3** or **4**, however the phenylsulfone substituted analogue (Entry 13) cyclized smoothly. Cyclodehydration of the protected threonine, tyrosine and serine derivatives (Entries 14-16) required a larger excess of polymer-supported Burgess reagent **4** and longer irradiation times. These transformations proceeded most efficiently when the reagent **4** was added in two lots with two cycles of microwave irradiation. Analysis by ^{1}H nmr and LC-MS indicated that the Z, TBS and *tert*-butyl protecting groups were stable under these conditions, however 11% (HPLC) of an unidentified byproduct was present in Entry 16. The amino acid-derived oxadiazoles were optically active but their enantiomeric purities were not determined.

In summary, we have devised a rapid and efficient synthesis of 1,3,4-oxadiazoles in high yields and purities by cyclodehydration of 1,2-diacylhydrazines using polymer-supported Burgess reagent under single-mode microwave conditions. The experimental procedure is simple, does not involve tedious purification, and avoids the use of harsh reagents.

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