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Parallel synthesis of 4,5-dihydro-1,2,4-oxadiazoles using soluble polymer support

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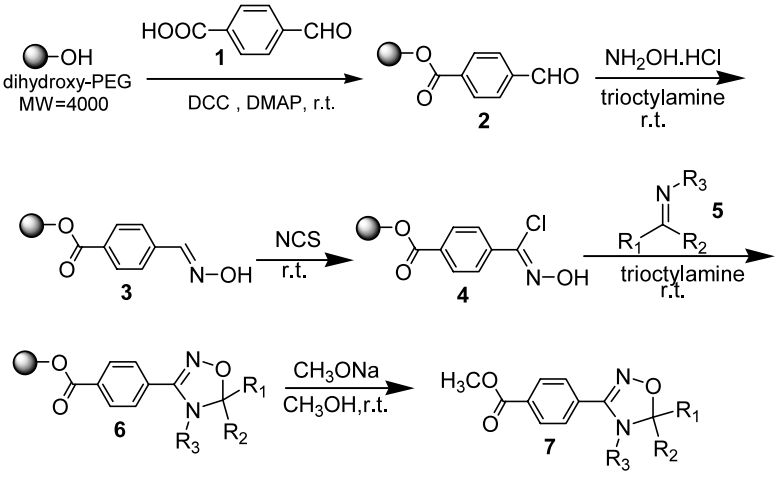
Abstract—1,3-Dipolar cycloadditions of nitrile oxide generated in situ on soluble polymer with a variety of imines provided a library of 4,5-dihydro-1,2,4-oxadiazoles in good yields and purity.

In recent years, the polymer-supported liquid-phase synthesis of small organic molecules has been a subject of intense research activity.[1] It profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena and ease of analysis without following the cleavage-and-check technique) and of solid-phase methods (use of excess reagents and easy isolation and purification of products). Among the various soluble polymers, polyethylene glycol (PEG) is the most useful and promising.[2]

Substituted 4,5-dihydro-1,2,4-oxadiazoles offer a high degree of structure diversity and have proven to be very important in medicinal chemistry.[3] Solution methods for their preparation via 1,3-dipolar cycloaddition of imines with nitrile oxides are well documented.[4] In connection with our research on the PEG-supported liquid-phase synthesis,[5] we wish to report here the parallel synthesis of 4,5-dihydro-1,2,4-oxadiazoles through a 1,3-dipolar cycloaddition of imines with nitrile oxide on PEG support.

As shown in Scheme 1, the aldehyde was attached to the PEG4000 support by esterification of PEG with 4-formyl benzoic acid (**1**) in the presence of DCC and DMAP in anhydrous CH_2Cl_2 at room temperature for 24 h. The conversion of terminal hydroxyl groups on



Scheme 1.

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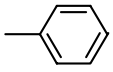
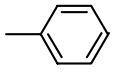
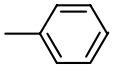
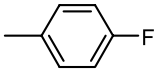
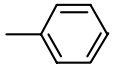
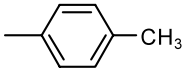
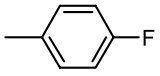
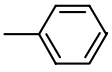
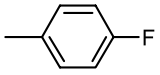
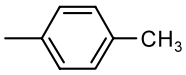
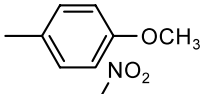
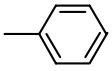
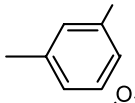
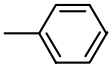
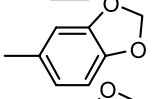
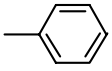
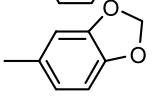
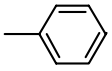
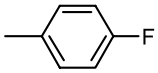
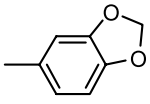
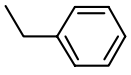
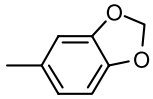
PEG was determined by ^{1}H NMR analysis to be quantitative. The PEG-bound aldehyde **2** was converted to oxime by treating with hydroxylamine hydrochloride in the presence of trioctylamine[6] in CH_2Cl_2 at room temperature. The reaction went to completion over 24 h and gave a high yield of the corresponding PEG-bound aldoxime **3**. Reaction of the aldoxime **3** with *N*-chlorosuccinimide (NCS) in CH_2Cl_2 afforded the PEG-bound chlorooxime **4**,[7] which is a precursor to the nitrile oxide. To this was added excess imines **5** prepared in situ in methylene chloride[8] prior to the generation of the nitrile oxide by slow addition of trioctylamine over a period of 2 h. The resulting mixture was shaken at room temperature overnight. The PEG-bound 4,5-dihydro-1,2,4-oxadiazoles **6** were obtained by precipitation. The target compounds **7** were released from the PEG by treatment of the polymer-bound products **6** with 0.1N MeONa in methanol at room temperature. Normally, cleavage was completed after stirring in 0.1N NaOMe/MeOH for 6 h.[9]

Using this procedure, a variety of substituted 4,5-dihydro-1,2,4-oxadiazoles were synthesized. As shown in Table 1, the yields are good to excellent (79–93%) and the purities are satisfactory ($\geq$89%).

In summary, we have demonstrated that the liquid-phase methodology could be applied efficiently in parallel one-pot synthesis of 4,5-dihydro-1,2,4-oxadiazole library. All reactions involved here are highly efficient in giving the desired compounds at room temperature. Crude products are usually obtained in high purity and high yield just by simple precipitation and washings, providing their direct use in primary biological assays without further purification.

Table 1. Liquid-phase synthesis of 4,5-dihydro-1,2,4-oxadiazoles on PEG support

Compd.	R_1	R_2	R_3	Yield(%)[a]	Purity(%)[b]
7a	H			91	96
7b	H			93	89
7c	H			86	95
7d	H			88	93
7e	H			79	91
7f	H			84	97
7g	H			82	96
7h	H			90	98
7i	H			86	91
7j	-CH_3			83	90
7k	H			87	94
7l	H		-$CH_2CH_2CH_2CH_3$	89	95

[a] Yields refer to product cleaved from PEG.
[b] Purities were determined by HPLC analysis.

Acknowledgements

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9. All the compounds listed in Table 1 give satisfactory ^{1}H, ^{13}C NMR and mass data. For compound **7g** is as follows: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.91 (s, 3H), 6.63 (s, 1H), 6.83 (d, $J=7.6$ Hz, 2H), 7.18–7.23 (m, 3H), 7.67–7.70 (m, 3H), 7.96 (d, $J=7.7$ Hz, 2H), 8.0 (d, $J=8.4$ Hz, 2H), 8.32 (d, $J=7.7$ Hz, 2H), 8.47 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 155.1, 148.9, 141.3, 141.0, 133.4, 132.4, 130.3, 130.2, 130.0, 129.3, 128.3, 127.0, 125.0, 124.9, 122.4, 99.7, 52.6; MS (EI, m/z) 403 (M^+, 18%).