Rapid One-pot Solid-phase Synthesis of 1,2,4-Oxadiazolines

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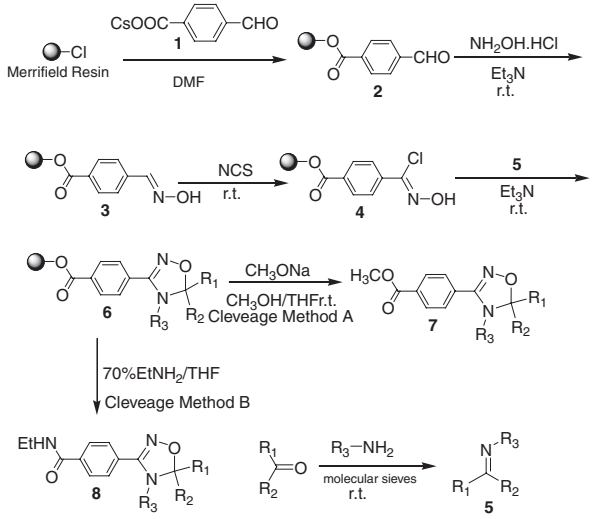
The first solid phase synthesis of 1,2,4-oxadiazolines via 1,3-dipolar cycloaddition of nitrile oxide generated in situ on solid support with a variety of imines is described. The synthetic sequences were performed in parallel one-pot fashion. Cleavage from the support under two different mild conditions afforded a library of 1,2,4-oxadiazolines in good yields and purity.

The polymer-supported synthesis of small heterocyclic molecules is the subject of intense research activity,[1] since it represents one of the most promising ways to generate small molecular libraries in the field of combinatorial chemistry.[2] Substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as therapeutic agents.[3] As a result, an increasing range and number of pharmaceutically useful heterocyclic compounds recently have been prepared using solid phase methodology.[4] This approach permits the rapid synthesis of large numbers of individual compounds, as well as mixture-based combinatorial libraries in a short time period and facilitates their use in high-throughput screening.[5]

Nitrile oxides undergo [3 + 2] cycoladditions with imines to provide 1,2,4-oxadiazolines in solution phase synthesis.[6] These products have proven to be very important in medicinal chemistry.[7] The major limitations of this chemistry are the propensity of nitrile oxide undergoing rapid dimerization to furoxan *N*-oxide[8] and the slow synthesis of large organic compound collections. Solid-phase organic synthesis can overcome these limitations. Accordingly, our plan was to anchor a nitrile oxide precursor onto the solid support, and then generate the reactive species in the presence of multifold excess of imines, preferably all in one pot. Finally, washing off all of the surplus reagents followed by cleavage would provide the cycloadducts. Our efforts to obtain a representative library of 1,2,4-oxadiazolines, which exploited four sites of chemical diversity are presented below.

As show in Scheme 1, cesium salt of 4-formylbenzoic acid **1** was attached on Merrifield resin in standard conditions.[9] The aldehyde functionality of resin **2** was converted to aldoxime by treating with excess hydroxylamine hydrochloride in the presence of triethylamine in $MeOH/CH_2Cl_2$ at room temperature, monitored by Infrared spectroscopy for the disappearance of the aldehyde stretch at 1702 cm^{-1}. The reaction went to completion over 48 h and gave a high yield of the corresponding aldoxime resin **3**.[10] After washing and drying, reaction of the aldoxime resin **3** with excess *N*-chlorosuccinimide (NCS) in CH_2Cl_2 for 6 h to afford chlorooxime resin **4**, which is a precursor to the nitrile oxide. To this was added directly ten folds excess of imines **5** as a methylene chloride solution before generating the nitrile oxide by slow addition of triethylamine. This is one pot procedure. The resulting mixture was shaken at room temperature for 36 h. The resin was then filtered, washed, and dried to provide resin-bound 1,2,4-oxadiazolines **6**. It is worthy to note that imines, prepared by incubating the aldehyde and the amine in dichoromethane overnight at room temperature in the presence of activated 4 Å molecular sieves, was directly used without further purification. This is a crucial method for rapid solid phase synthesis to provide large numbers of 1,2,4-oxadiazolines.



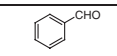
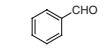
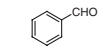
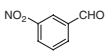
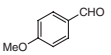
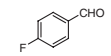
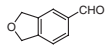
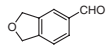
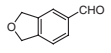
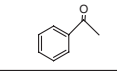
Scheme 1.

The cycloadducts were cleaved off the resin with two different methods to give a 20-member library of 1,2,4-oxadiazolines **7** and **8**. Method A: The target compounds **7** were released from the resin by treatment of the resin **6** with 0.5 M MeONa in MeOH/THF (1:4) at room temperature for 12 h. Method B: Cleavage of the product from the resin was readily achieved with ethylamine (70% ethylamine in water and THF (1:1) at 40 °C overnight, providing the ethyl amides **8**.

A variety of imines reacted well with the resin-bound chlorooxime under similar reaction conditions to afford the corresponding 1,2,4-oxadiazolines in good yields and purity. The ready availability of aldehydes and amines from commercial sources allows the preparation of large heterocyclic compound libraries. Table 1 summarizes some of the initial results we have obtained by application of the above methodology.[11]

In summary, we have first demonstrated that solid-phase methodology can be applied efficiently in parallel synthesis of the 1,2,4-oxadiazoline libraries, which exploited four sites of chemical diversity. This method of synthesis is versatile and produces compounds with known pharmacophoric scaffolds, and which are thus ideally suited for combinatorial library generation. This application to the synthesis of large 1,2,4-oxadiazoline libraries is presently under investigation.

Table 1. One pot solid phase synthesis of 1,2,4-oxadiazolines

Entry	Carbony compound	Amine	Cleavage A Product **7** Yield (Purity)%[a]	Cleavage B Product **8** Yield (Purity)%[a]
a			80 (95)	96 (92)
b			85 (92)	87 (90)
c			73 (85)	91 (85)
d			68 (85)	95 (77)
e			77 (90)	93 (89)
f			81 (80)	80 (88)
g			71 (97)	79 (87)
h			87 (96)	92 (88)
i			64 (89)	83 (89)
j			83 (86)	90 (83)

[a]Yields refer to crude chemical yields and purity was determined by LC-MS analysis.

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11 All the compounds listed in Table 1 give satisfactory ^{1}H NMR, FT-IR, MS and HRMS data. For compound **8a** is as follows: ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (t, $J = 7.2$ Hz, 3H), 3.48 (q, $J = 7.2$ Hz, 2H), 6.35(br, 1H), 6.54 (s, 1H), 6.77(d, $J = 7.5$ Hz, 2H), 7.11–7.18(m, 3H), 7.45 (m, 3H), 7.58–7.64 (m, 4H), 7.72 (d, $J = 8.3$ Hz, 2H); FT–IR (KBr): 1642 (C=O), 1592 (C=N) cm^{-1}; ESI–MS (+): 372.3 ($[M + H]^+$), 394.3 ($[M + Na]^+$); HRMS calcd for $C_{23}H_{21}N_3O_2$ ($[M + H]^+$): 372.1634, found: 372.1645.

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