

Video Article

# Solid-phase Synthesis of [4.4] Spirocyclic Oximes

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## Abstract

A convenient synthetic route for spirocyclic heterocycles is well sought after due to the molecule's potential use in biological systems. By means of solid-phase synthesis, regenerating Michael (REM) linker strategies, and 1,3-dipolar cycloaddition, a library of structurally similar heterocycles, both with and without a spirocyclic center, can be constructed. The main advantages of the solid-support synthesis are as follows: first, each reaction step can be driven to completion using a large excess of reagents resulting in high yields; next, the use of commercially available starting materials and reagents keep the costs low; finally, the reaction steps are easy to purify *via* simple filtration. The REM linker strategy is attractive because of its recyclability and traceless nature. Once a reaction scheme is completed, the linker can be reused multiple times. In a typical solid-phase synthesis, the product contains either a part of or the whole linker, which can prove undesirable. The REM linker is "traceless" and the point of attachment between the product and the polymer is indistinguishable. The high diastereoselectivity of the intramolecular 1,3-dipolar cycloaddition is well documented. Limited by the insolubility of the solid support, the reaction progression can only be monitored by a change in the functional groups (if any) *via* infrared (IR) spectroscopy. Thus, the structural identification of intermediates cannot be characterized by conventional nuclear magnetic resonance (NMR) spectroscopy. Other limitations to this method stem from the compatibilities of the polymer/linker to the desired chemical reaction scheme. Herein we report a protocol that allows for the convenient production of spirocyclic heterocycles that, with simple modifications, can be automated with high-throughput techniques.

## Introduction

Despite recent discoveries using highly-functionalized spirocyclic heterocycles in a number of biological systems<sup>1</sup>, a convenient pathway is still necessary for their easy manufacture. Such systems and uses for these heterocycles include: MDM2 inhibition and other anticancer activities<sup>2,3,4,5</sup>, enzyme inhibition<sup>6,7,8</sup>, antibiotic activity<sup>9,10</sup>, fluorescent tagging<sup>10,11,12</sup>, enantioselective binding for DNA probes<sup>13,14,15</sup> and RNA targeting<sup>16</sup>, along with numerous potential applications to therapeutics<sup>17,18,19</sup>. With an increasing demand for these heterocycles, current literature remains divided about which synthetic pathway is best. Modern synthetic approaches to this problem use isatin and isatin derivatives as starting materials for a variety of heterocycles<sup>20,21</sup>, complicated intramolecular rearrangements<sup>22,23,24,25</sup>, Lewis acid<sup>1,26,27</sup> or transition metal catalysis<sup>17,28,29,30</sup>, or asymmetric processes<sup>31</sup>. While these procedures have had success in producing specific spirocyclic oximes with limited functionality, a synthetic strategy for producing a library of molecules with high diastereoselectivity has been explored relatively less<sup>32</sup>.

The technique presented here shows that these molecules of interest can be generated using a number of well-understood synthetic techniques in tandem. Starting with the synthesis of the molecule on a solid support using a REM linker and intramolecular silyl nitronate-olefin cycloaddition (ISOC), the proposed pathway deploys a nonlinear route, characterized by bond severing in a tricyclic system, leaving a highly functionalized heterocycle. REM linkers, known for their convenience and recyclability, utilize a solid support to synthesize tertiary amines<sup>33</sup>. Due to the ease of purification accredited to the REM linker *via* simple filtration, this solid-phase synthesis technique provides scientists with a recyclable and traceless linker, which has been used here. Once the reaction is complete, the REM linker is regenerated and can be reused multiple times. The REM linker is also traceless because, unlike many solid-phase linkers, the point of attachment between the product and the polymer is indistinguishable<sup>34,35</sup>. Also well-studied and understood is the ISOC reaction, useful in the synthesis of pyrrolidine oximes<sup>36,37</sup>. Perhaps better known as a 1,3-dipolar cycloaddition, these reactions form a number of heterocycles with high diastereoselectivity<sup>38,39,40,41,42,43,44,45</sup>. Using the modified REM-coupled-ISOC technique for the synthesis of spirocyclic molecules yields a highly diastereoselective product. Herein, we report on the efficient production of spirocyclic oximes using a new synthetic approach, combining two well-understood pathways and readily available starting materials.

## Protocol

**CAUTION:** Please consult all relevant material safety data sheets (MSDS) before use. Several of the chemicals used in these syntheses are acutely toxic and carcinogenic. Please use all appropriate safety practices when performing the following reactions, including the use of engineering controls (fume hood and IR and NMR spectrometers) and personal protective equipment (safety goggles, gloves, lab coat, full-length pants, and closed-toe shoes).

## 1. Michael Addition of Furfurylamine to the REM Linker

NOTE: The duration of this step is 25 min for the set-up and 24 h of reaction time.

1. Add 1 g (1 equiv.) of REM resin, 20 mL (20 equiv.) of dimethylformamide (DMF), and 2.4 mL of furfurylamine to a 25 mL solid-phase reaction vessel.
2. Agitate the reaction vessel for 24 h at room temperature using a shaker following the reaction initiation. The vessel is capped during the reaction.  
NOTE: Ensure that the resin does not sit at the bottom of the vessel and mixes thoroughly.
3. Drain the solution and wash the resin 1x with 5 mL of DMF after the reaction is complete.
  1. Then, wash the resin 4x, alternating between 5 mL of dichloromethane (DCM) and 5 mL of methanol.
  2. Following the washes, dry the resin thoroughly with compressed air in the reaction vessel for 30 min.
  3. Monitor the reaction progress for a change in IR stretching frequencies, as shown in **Table 1**.

## 2. Tandem Michael Addition/1,3-dipolar Cycloaddition

NOTE: The duration of this step is 25 min for the set-up and 48 h of reaction time.

1. Take the dry resin and add 1.48 mL (5 equiv.) of triethylamine (TEA), 10 mL of dry toluene, and 0.637 g (2 equiv.) of nitro-olefin to the reaction vessel.
2. Add 1 mL (4 equiv.) of trimethylsilyl chloride (TMSCl) to the reaction vessel in a well-ventilated fume hood.  
CAUTION: This reaction will form HCl gas. Do not cap the reaction vessel until the gas has been released under a fume hood.
3. Securely cap the reaction vessel and agitate using a shaker for 48 h at room temperature. Ensure that the resin mixes thoroughly with the reagents.
4. Quench the reaction with 5 mL of methanol.
  1. Drain the solution from the vessel and, then, wash the resin 4x, alternating between 5 mL of DCM and 5 mL of methanol.
  2. Following the washes, dry the resin thoroughly with compressed air in the reaction vessel for 30 min.
  3. Monitor the reaction progress by observing a change in the IR stretching frequencies, as shown in **Table 1**.

## 3. Ring Opening of Resin-bound Isoxazole by Tetra-n-butylammonium Fluoride

NOTE: The duration of this step is 10 min for the set-up and 12 h of reaction time.

1. Place 1 mL of dry tetrahydrofuran (THF) in the reaction vessel with the dry resin. Then, add 1.24 mL (2 equiv.) of 1 M tetra-n-butylammonium fluoride (TBAF) in THF to the reaction vessel.
2. Using a shaker, agitate the solution for 12 h at room temperature and ensure that the resin thoroughly mixes with the solution.
3. Drain the solution and wash the resin 1x with 5 mL of THF after the reaction is complete.
  1. Then, wash the resin 4x, alternating between 5 mL of DCM and 5 mL of methanol.
  2. Following the washes, dry the resin thoroughly with compressed air in the reaction vessel for 30 min.
  3. Monitor the reaction progress by observing a change in the IR stretching frequencies, as shown in **Table 1**.

## 4. N-alkylation of the Resin-bound Heterocycle to Form Quaternary Amine

NOTE: The duration of this step is 10 min for the set-up and 24 h of reaction time.

1. Take the dry resin in the reaction vessel and add 5 mL of DMF.
  1. Then, add 1 mL of alkyl halide (10 equiv.) to the vessel and agitate using a shaker for 24 h at room temperature. Ensure the thorough mixing of the resin with the reagents.
2. Drain the solution and wash the resin 1x with 5 mL of DMF after the reaction is complete.
  1. Then, wash the resin 4x, alternating between 5 mL of DCM and 5 mL of methanol.
  2. Following the washes, dry the resin thoroughly with compressed air in the reaction vessel for 30 min.
  3. Monitor the reaction progress by observing a change in IR stretching frequencies as shown in **Table 1**.

## 5. $\beta$ -elimination of the Quaternary Amine from the Polymer Support

NOTE: The duration of this step is 15 min for the set-up and 24 h of reaction time.

1. Take the dry resin and add 3 mL of DCM to the reaction vessel.
  1. Then, add 1.5 mL (5 equiv.) of TEA to the reaction vessel to cleave the heterocycle from the polymer support.
  2. Agitate using a shaker for 24 h, ensuring the thorough mixing of the resin with the solution. Drain the solution from the resin.  
NOTE: Do not discard since the cleaved product is in the TEA/DCM solution.
2. Wash the resin 4x, alternating between 5 mL of DCM and 5 mL of methanol.

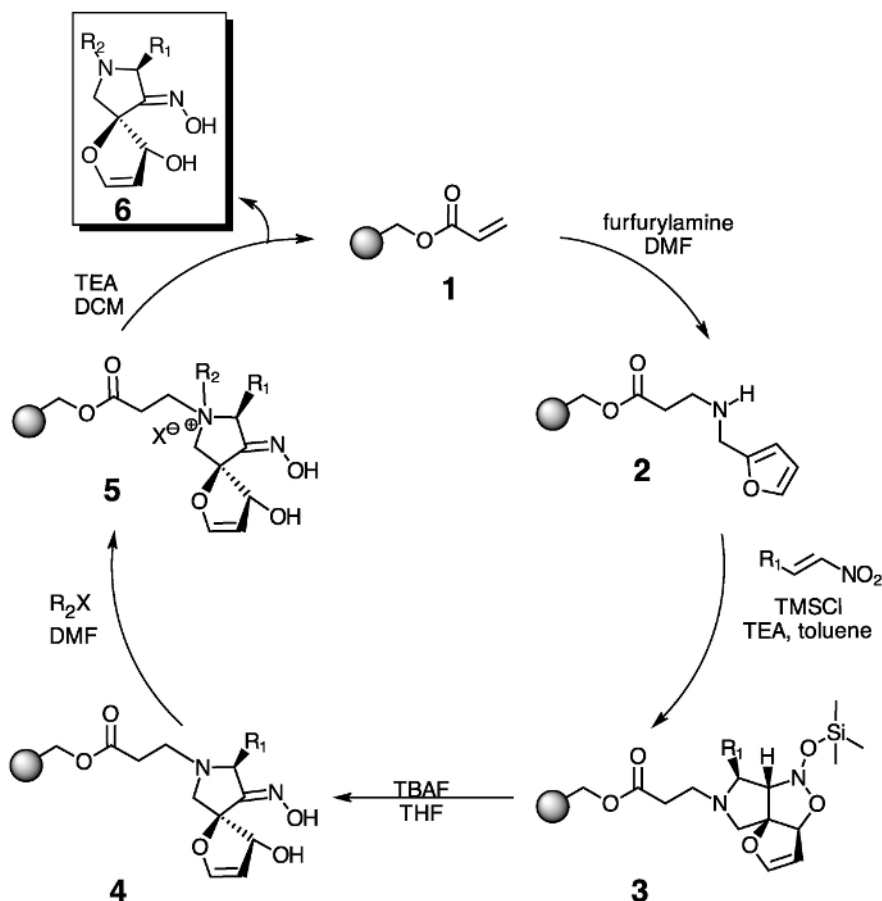
NOTE: Do not discard.

1. Combine the elution from all washes in steps 5.1.2 and 5.2 and concentrate it *via* rotatory evaporation.
  2. Purify the spirocyclic oxime by trituration: add 0.5 mL of hot methanol to dissolve any impurities. The pure product will crash out of the solution and is collected *via* gravity filtration.
3. Following two washes with 5 mL of DCM for reuse in future experiments, thoroughly dry the resin with compressed air in the reaction vessel for 30 min.
    1. Monitor the reaction progress by observing a change in the IR stretching frequencies, as shown in **Table 1**.

## Representative Results

As outlined in the procedure above, the synthetic route to spirocyclic oximes (see **Figure 1**) begins with the Michael addition of furfurylamine to compound **1**, the REM linker, to afford **2**. A subsequent Michael addition and 1,3-dipolar cycloaddition of the support **2** using various  $\beta$ -nitrostyrene derivatives yield the tricyclic compound **3**, an *N*-silyloxy isoxazolidine with four unique stereogenic centers. Desilylation of **3** with TBAF produces the spirocyclic oxime **4**, still bound to the solid-phase linker. Following the desilylation of **3**, polymer-bound **4** is *N*-alkylated with various electrophiles of choice yielding an ammonium salt, as seen with compound **5**. Finally, using  $\beta$ -elimination for the cleavage from the polymer support, compound **6** is generated, along with the fully intact REM linker **1**. A library of spirocyclic molecules can be created and purified with ease based on the choice of  $R_1$ , the  $\beta$ -nitrostyrene, and  $R_2$ , the electrophiles used in *N*-alkylation.

For monitoring the progress of each reaction step shown in **Figure 1**, IR spectroscopy was done on the starting REM resin **1** and on each of the polymer-bound intermediates **2** - **5** to determine whether or not each step had proceeded to completion. These could be classified with a change in the functional group, including conjugated or unconjugated esters, trimethylsilyls, hydroxyls, and oximes, corresponding to a change in wavenumbers as shown in **Table 1**. NMR analysis was not used to monitor the progress of each step since the intermediates formed are bound to the insoluble polymer support. Corresponding diastereoselective ratios (dr) and yields of the six products **6a** - **6f** are depicted in **Table 2**. The yields between 40% and 53% are the overall yields which highlight an average, high yield of between 80% and 88% per step in this five-step route.  $^1\text{H}$  NMR analysis of the crude product mixture provided the dr values reported.



**Figure 1:** REM-coupled-ISOC technique for the synthesis of spirocyclic oximes through a tricyclic system intermediate. Customizable  $R_1$  and  $R_2$  groups using commercially available  $\beta$ -nitrostyrene derivatives and different alkylating reagents, respectively, allow for a library of molecules with a common, spirocyclic backbone to be created, as shown in molecule **6**. [Please click here to view a larger version of this figure.](#)

Starting material and intermediate	IR stretching frequency (cm <sup>-1</sup> )	IR Detectable Functional Groups
1	1722	Conjugated Ester
2	1731	Unconjugated Ester
3	1731	Unconjugated Ester
	1214	Trimethylsilyl
4	3600	Hydroxyl
	1731	Unconjugated Ester
	1655	Oxime
5	3600	Hydroxyl
	1731	Unconjugated Ester
	1655	Oxime

**Table 1: Monitoring solid-phase reactions by infrared spectroscopy.** A reaction progression determination of each step was conducted by tracking the changes in the IR stretching frequencies of the starting REM resin **1** and the intermediates **2** - **5**.

Product	R <sub>1</sub>	R <sub>2</sub>	dr <sup>a</sup>	yield (%) <sup>b</sup>
6a	phenyl	octyl	>99:1	40%
6b	phenyl	methyl	95:5	50%
6c	4-bromophenyl	methyl	96:4	53%
6d	4-bromophenyl	allyl	96:4	45%
6e	3,4-dimethoxyphenyl	benzyl	97:3	45%
6f	2,4-dichlorophenyl	methyl	>99:1	40%

**Table 2: Solid-phase synthesis of *N*-octyl, -methyl, -allyl, and -benzyl, spirocyclic oximes (products **6a** - **6f**).** (a) The diastereoselective ratio was determined by <sup>1</sup>H NMR spectroscopy. (b) The reported yield of the five-step synthesis was determined based on the loading of the REM resin. The overall yield of 40% - 53% indicates an average of 80% - 88% yield for each step.

## Discussion

In a typical REM linker/solid-phase synthetic strategy, prior to the release of an amine from the solid support, it is critical to form a quaternary ammonium salt, as described in section 4 of the protocol<sup>39</sup>. Due to the steric hindrance of the tricyclic system and bulky R<sub>2</sub> groups (benzyl and octyl halides), only small alkylating reagents (methyl and allyl halides) could be utilized in this reaction<sup>46</sup>. With a simple modification, allowing for the addition and use of larger, steric reagents, the rigidity of the tricyclic structure was decreased before the *N*-alkylation step by opening the isoxazoline ring first<sup>32</sup>. This is illustrated in **Figure 1**. The ring opening of the tricyclic intermediate **3** relieves the steric hindrance which allows for the addition of virtually any primary alkyl halide desired.

This method was successful in reporting some of the highest dr values in the synthesis of spirocyclic compounds<sup>30,47,48</sup>. Success in the diastereoselectivity is attributed to the ISOC reaction, which takes the furfurylamine moiety of **2** and creates the rigid, tricyclic system of **3**<sup>38,39,40</sup>. Further steps, such as the breaking of the tricyclic system, conserve the diastereoselective nature of the molecule, affording the scientist, in the end, with compounds at or above diastereoselective ratios of 95:5. Equally important is the customizability of the method: with modified β-nitrostyrene derivatives and other electrophiles for *N*-alkylation, a large library of molecules can be made with relative ease.

To conclude, a highly diastereoselective protocol for the construction of highly functionalized, spirocyclic molecules using a new REM-coupled-ISOC pathway has been developed. This pathway yields a rigid, tricyclic scaffold from the ISOC reaction, from which diastereoselectivity is conserved throughout the remaining reactions. The availability of β-nitrostyrene derivatives and alkylating reagents makes the route convenient and cost-effective. However, should they not be available for purchase, the synthesis of such reagents would be required. This is one such limitation of the method, another being the size of the cycles. As of now, the proposed method is suitable for the construction of a [4.4] spirocyclic framework. Limitations in the 1,3-dipolar cycloaddition method prevent the formation of other ring sizes.

We are in the process of testing the recyclability of the REM linker used in the protocol presented here and will report this shortly. In addition, future applications of the proposed method will be put to use in a number of biological assays. A high-throughput combinatorial synthesis of these spirocyclic molecules using this method can afford a large number of spirocyclic derivatives, which can be tested for anticancer activities in human cancer cells. Such tests will involve cytotoxicity assays, pull-down experiments, and cell culture viability.

## Disclosures

The authors have nothing to disclose.

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