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Solid-Phase Synthesis of Isoxazoles Using Vinyl Ethers as Chameleon Catches

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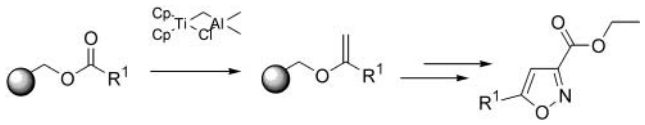
ABSTRACT

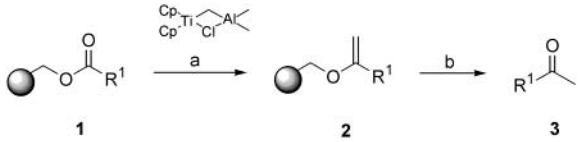


Regioselective 1,3-dipolar cycloadditions of supported vinyl ethers $R^1C(=CH_2)O\text{-}CH_2$-polymer, prepared by the Tebbe olefination of $R^1CO_2\text{-}CH_2$-polymer, with ethyl cyanoformate *N*-oxide gave supported isoxazoline derivatives. Release from the support under mild acidic conditions gave the isoxazoles ethyl 5-R^1-isoxazole-3-carboxylates. Alternatively, further on-resin functionalization of the R^1 substituent using Suzuki coupling reactions and release from the support under acidic conditions gave more structurally diverse isoxazoles.

The application of solid-phase organic synthesis (SPOS) in the preparation of small compound libraries is of considerable significance in the discovery and development of new drug compounds.[1] An important aspect of any solid-phase methodology is the choice of the linker, which is crucial for the attachment and detachment of the requisite substrates to and from the resin.[2] Many solid-phase syntheses rely on the release of carboxylic acids, esters, or amides from an ester- or amide-bound substrate.[2b] Alternative methods that allow the cleavage of resin-bound carboxylate derivatives, yet with access to more variable functionalities, are extremely desirable. Previous work in the group[3] has shown that carboxylic esters **1** supported on Wang or Merrifield resin underwent smooth methylenation using the Tebbe reagent to produce supported vinyl ethers **2** (Scheme 1). These vinyl ethers are convenient substrates for further on-resin functionalization or cleavage with additional chemical change. They could be released from the resin under mildly acidic conditions to produce methyl ketones **3** or be subjected to further on-resin transformations followed by release as amines, thiazoles, or cyclohexanone derivatives. As such the vinyl ethers **2** represent examples of Chameleon Catches for combinatorial chemistry.[4]

Isoxazole moieties represent a class of unique pharmacophores that are constituent units of diverse therapeutic agents.[5] Therefore, they are interesting targets in the devel-

Scheme 1[a]



[a] Reagents and conditions: (a) Tebbe reagent (Aldrich), THF, 25 °C, 16 h; (b) 3% TFA, CH_2Cl_2, 25 °C, 30 min.

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opment of new drug leads in solid-phase combinatorial chemistry. Several authors have studied the synthesis of isoxazoles using solid-phase chemistry.[6] These include the condensation of 1,3-dicarbonyl compounds with hydroxylamine,[7] the addition of nitrile oxides to supported alkynes,[8] or the anchoring of a nitrile oxide precursor onto the solid phase.[9] However, all methods suffer from a lack of regioselectivity, and the linker remains unchanged in the released product. Herein we report a regioselective 1,3-dipolar cycloaddition reaction of nitrile oxides to vinyl ethers for the synthesis of supported isoxazolines and their subsequent transformation to isoxazoles by elimination and release from the support. This strategy, in combination with Suzuki couplings to enhance diversity, allows a rapid synthesis of a wide range of isoxazoles. Effectively, the linker remains traceless in the product of cleavage. In addition, [3 + 2] cycloadditions of nitrile oxides in solution are known to suffer from many side reactions including dimerization as a result of their high reactivity.[10] Therefore it is synthetically interesting to carry out these reactions on the solid phase, which makes isolation of the product easier.

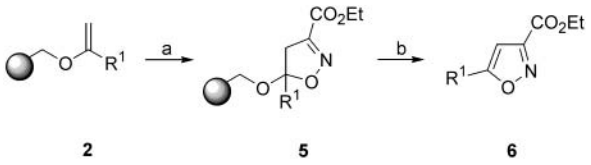
Methylenation of the resin bound esters **1** with the commercially available Tebbe reagent (Aldrich) in THF at room temperature gave the corresponding vinyl ethers **2** (Scheme 1). The reaction mixtures were quenched with 10% aqueous sodium hydroxide, and the resin was washed consecutively with THF, H_2O, EtOAc, and MeOH followed by removal of the solvent in vacuo. The transformation could easily be monitored by using single bead microscope IR spectroscopy for the disappearance of the carbonyl stretch (ν_{max}, 1720−1740 cm^{-1}). Acid-catalyzed cleavage of ethers **2** with trifluoroacetic acid in dichloromethane brought about cleavage from the resin and gave the corresponding ketones **3** in good yields (51−77%) and excellent purities (>95%, ^1H NMR).

Nitrile oxides can be generated in situ by dehydration of primary nitroalkanes using a base and phenyl isocyanate[11] following the Mukaiyama method or by base-induced elimination of HCl from hydroximinoyl chlorides.[9,12] Preliminary model studies in solution showed that heating in the presence of a base, which is usually required in the Mukaiyama method, would lead to premature cleavage of the supported isoxazoline **5**. Thus, the more convenient procedure for the synthesis of reactive nitrile oxides was dehalogenation of hydroximinoyl chlorides, which can be purchased or be obtained by chlorination of the corresponding aldoximes with *N*-chlorosuccinimide. We concentrated our work on the application of commercially available ethyl chlorooximidoacetate to obtain supported ethyl isoxazoline-3-carboxylates **5** and ethyl isoxazole-3-carboxylates **6**, respectively (Scheme 2).

Vinyl ethers **2** were allowed to react with ethyl chlorooximidoacetate **4** (3 equiv) and triethylamine (10 equiv) in THF. The addition of the reagent was carried out incrementally over 1 h, and then the resin was consecutively washed with THF, H_2O, EtOAc, and MeOH. The formation of the

(4) Other Chameleon Catches in SPOS: Gowravram, M. R.; Gallop, M. A. *Tetrahedron Lett.* **1997**, *38*, 6973−6976.

Scheme 2[a]



[a] Reagents and conditions: (a) 3 equiv of ethyl chlorooximidoacetate **4**, Et_3N, THF, 1 h, four times; (b) 5% TFA, CH_2Cl_2, 25 °C, 30 min.

supported isoxazolines was again easily monitored by IR spectroscopy for the appearance of a new carbonyl stretch (ν_{max}, 1724 cm^{-1}). The products were cleaved from the resin by treatment with 5% trifluoroacetic acid in dichloromethane. As a result of the rapid dimerization of the nitrile oxide, incomplete cycloaddition was observed, resulting in a mixture of the desired heterocycle **6** and the ketone **3** after the acidic cleavage. This could be optimized by repeating the [3 + 2] cycloaddition step four times prior to cleavage. Remaining traces of ketone were removed by using a polystyrene-supported phenyl sulfonylhydrazine as scavenger. Isoxazoles **6 a**−**h** (Figure 1) were obtained as single regioisomers in

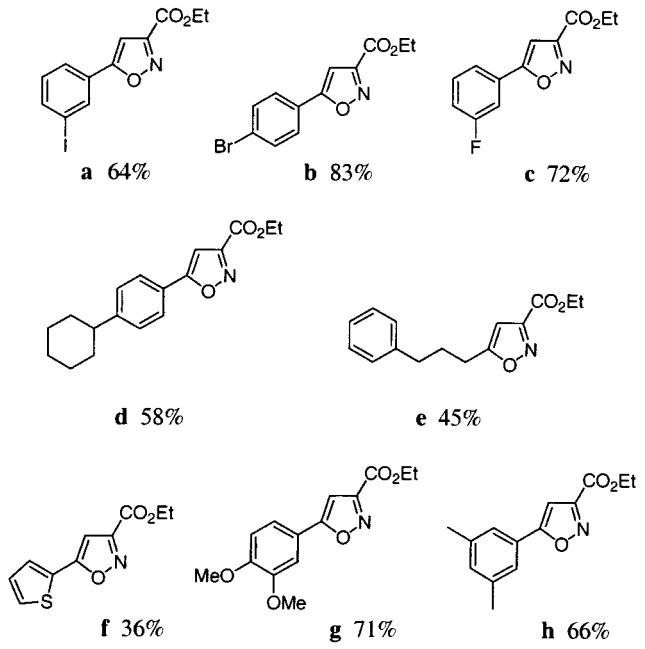
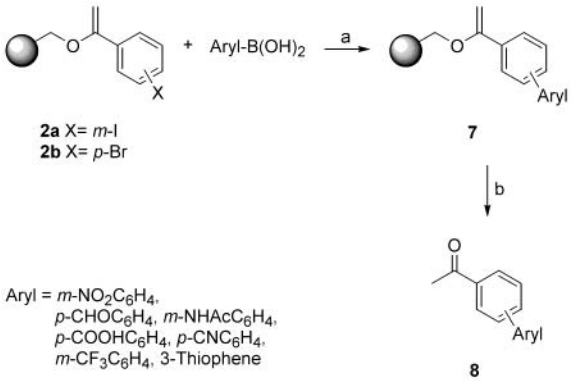


Figure 1. Synthesis of isoxazoles **6** via [3 + 2] cycloaddition of nitrile oxide **4** onto vinyl ether **2**.

good purity (>93% by HPLC) and with 36−83% yield based on the loading of the Wang resin (1.2 mmol g^{-1}) to which the acids had been attached.

Because the Tebbe reagent is not compatible with a range of functional groups, Suzuki coupling reactions[13] after the formation of **2** were examined in order to increase the diversity of the isoxazoles formed (Scheme 3).

Scheme 3[a]



[a] Reagents and conditions: (a) 10 mol % $Pd(OAc)_2$, 20 mol % dppf, 10 equiv of K_2CO_3, DMF, 90 °C, 16 h; (b) 3% TFA, CH_2Cl_2, 25 °C, 30 min.

Best results for the Suzuki coupling on solid support were achieved using $Pd(OAc)_2$ (10 mol %), dppf (20 mol %), and K_2CO_3 (10 equiv) at 90 °C in degassed DMF. Subsequent washing of the resin with DMF, THF, H_2O, EtOAc, and MeOH and treatment of the supported biaryl vinyl ether **7** with 3% trifluoroacetic acid in dichloromethane gave the corresponding ketones **8** (Figure 2) in good yields (60−79%)

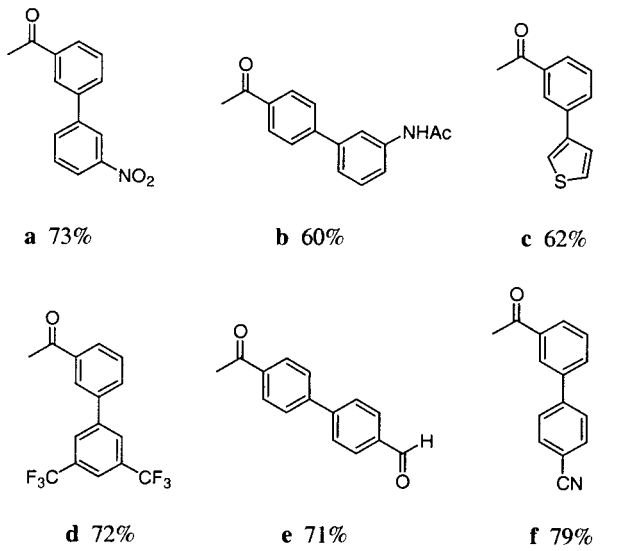
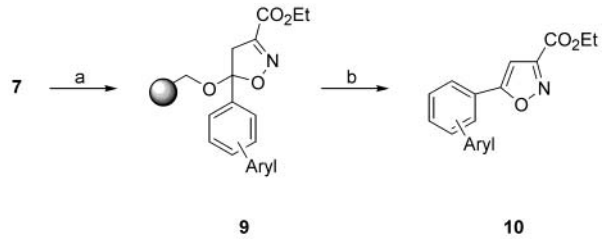


Figure 2. Synthesis of biarylic ketones **8** via Suzuki couplings onto vinyl ether **2**.

and excellent purities (>95% by NMR). Traces of phenyl methyl ketone as a result of hydrolysis of an aryl-palladium-halide species were observed after cleavage but could easily be evaporated under vacuo. Palladium-containing side products, which were soluble under the cleavage conditions, were removed by filtration of the crude products in dichloromethane or acetone through silica gel.

Alternatively, the solid-supported vinyl ether intermediates **7** were further treated with ethyl chlorooximidoacetate **4** as described for **6** to produce isoxazoles **10** (Scheme 4). Thus,

Scheme 4[a]



[a] Reagents and conditions: (a) 3 equiv of ethyl chlorooximidoacetate **4**, Et_3N, THF, 1 h, four times; (b) 5% TFA, CH_2Cl_2, 25 °C, 30 min.

several ethyl 5-biphenyl-3-yl-isoxazole-3-carboxylates **10 a**−**g** could be synthesized in good purities (∼90%) and reasonable yields (38−80%, Figure 3). 1,3-Dipolar cycloadditions as well as the Suzuki coupling reactions were carried

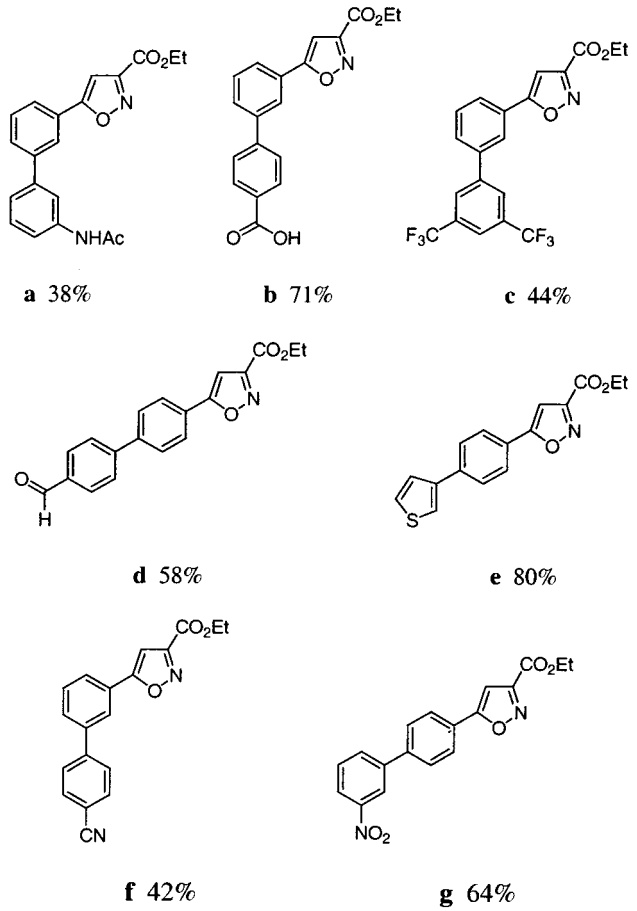


Figure 3. Synthesis of isoxazoles **10** via Suzuki coupling and [3 + 2] cycloaddition of nitrile oxides onto vinyl ether **2**.

out using the Quest Synthesizer from Argonaut Technologies Inc.

In conclusion, Tebbe olefination of supported esters gave the corresponding vinyl ethers, which are convenient substrates for further on-resin functionalization or cleavage with additional chemical change. 1,3-Dipolar cycloaddition of nitrile oxide onto these vinyl ethers results in the formation of supported isoxazolines, which were released under acidic conditions to produce isoxazoles. Suzuki coupling reactions were applied to introduce further functionalities and enhanced diversity. So, starting with easily accessible solid-supported carboxylic esters, a small library of diverse isoxazoles could be synthesized. Further reactions of the supported enol ethers will be reported in due course.

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Supporting Information Available: Detailed experimental data and proton and carbon NMR spectra for compounds **6a**−**h**, **8a**−**f**, and **10a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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