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Solid-Phase Synthesis of 3,5-Disubstituted 1,3-Oxazolidin-2-ones by an Activation/Cyclo-elimination Process

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Abstract:

Polymer-supported sulfonyl chloride is used in the solid-phase synthesis of disubstituted 1,3-oxazolidin-2-ones. The target compounds were prepared by attaching 1,2-diols to the solid support, followed by reaction with *p*-toluenesulfonyl isocyanate and subsequent cyclo-elimination with concurrent detachment from the resin. Oxazolidinones of high enantiopurity can be prepared with this method by employing enantiopure 1,2-diols.

Solid-phase organic synthesis (SPOS) has attracted increasing attention over the past several years.[1] Combinatorial application of SPOS enables the preparation of large numbers of (structurally related) molecules in short periods of time, which is of great importance in finding new lead compounds in drug development.[2] We have focused our research efforts on the development of new methodology for the solid-phase chemistry of heterocyclic compounds. Here, we report the convenient preparation of polymer-supported sulfonyl chloride **2**, which was proved to be a useful polymer-bound analogue of *p*-toluenesulfonyl chloride. This polymer-supported reagent was utilized in the solid-phase synthesis of 3,5-disubstituted 1,3-oxazolidin-2-ones from 1,2-diols. In recent years, there has been a considerable interest in 3,5-disubstituted 1,3-oxazolidin-2-ones as they exhibit a broad and powerful antibacterial activity.[3] Therefore, they are interesting targets for SPOS.[4]

The solid-supported reagent **2** was prepared from a commercially available sulfonic acid resin. The solution-phase preparation of sulfonyl chlorides from the corresponding sulfonates is well documented.[5a-d] Recently, some solid-phase preparations of sulfonyl chlorides have been reported.[5e-g] These methods, however, require elevated temperatures and

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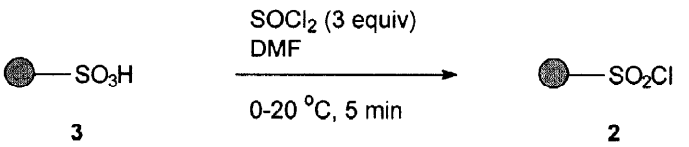
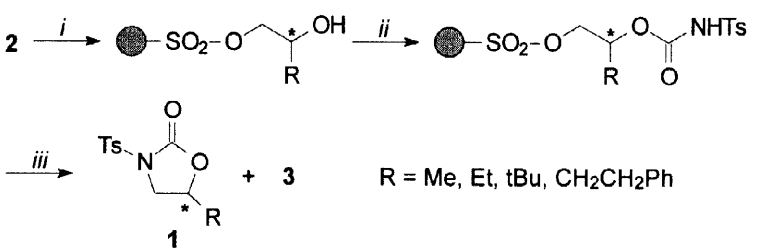
should be avoided because of the thermal instability of sulfonyl chloride **2**.[6] Conversion of sulfonated polystyrene **3** (4.5 mequiv/g, 2% crosslinked polystyrene/divinylbenzene)[7] into **2** was performed within 5 minutes using thionyl chloride in *N*,*N*-dimethylformamide (Scheme 1).

Scheme 1



For the preparation of the target heterocycles, 1,2-diols were selected as the starting material. The primary alcohol functionality of these diols could be selectively attached to the solid support, allowing a selective activation of the secondary alcohol function for the subsequent step in the sequence (Scheme 2). In this manner the primary alcohol function was protected and at the same time converted into a potential leaving group for the cyclo-elimination step. The linking reaction to the solid support was monitored by the infrared absorption band at 1370 cm^{-1} (S-O stretch of $-SO_2Cl$) which was shifted to 1350 cm^{-1} ($-SO_2-O-$) as well as by the appearance of a typical OH absorption at 3500 cm^{-1}.

Scheme 2



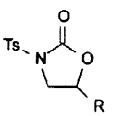
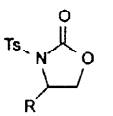
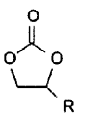
i) 1,2-diol (1.1 equiv), Et_3N (1.0 equiv), CH_2Cl_2, rt, overnight; *ii)* tosyl isocyanate (1.1 equiv), CH_2Cl_2, rt, 5 h; *iii)* 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) (3 equiv), CH_2Cl_2, rt, overnight.

In the next step, the secondary alcohol was reacted with *p*-toluenesulfonyl isocyanate. Formation of the urethane moiety was followed by the appearance of an absorption at 1740 cm^{-1} (which is typical for this unit) and the concurrent disappearance of OH absorption at 3500 cm^{-1}. Arylsulfonyl isocyanates react instantaneously with alcohols without the need of a catalyst.[8] This reagent is highly attractive for our purpose as it provides urethanes, which contain an *N*-activating group allowing an easy cyclo-elimination to give the heterocyclic target.

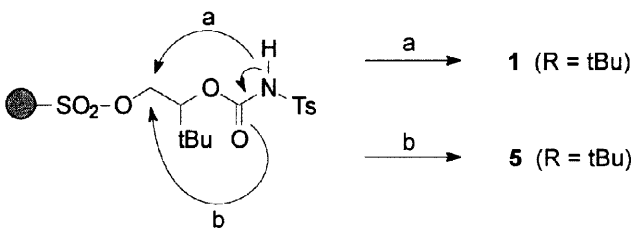
The cyclo-elimination to products **1**, with the polymeric tosylate serving as a leaving group, was accomplished with DBN as the base. After this product-forming step, DBN was removed by filtration through a short plug of silica and the product was obtained in an overall yield of 70%.

GC/MS and ^{1}H-NMR analysis of the product obtained, clearly showed the predominant formation of one compound, namely **1**, along with one minor contaminant (Table 1). For the substrates R = Me and Et, this by-product was regioisomer **4**. For R = tBu, the minor product is the cyclic carbonate **5** probably formed by ring closure *via* the oxygen atom (due to steric hindrance) and subsequent hydrolysis (Scheme 3). *No impurities other than isomers **4** and by-product **5** were detected in any of these syntheses.*

Table 1

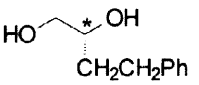
R	 **1** (%)	 **4** (%)	 **5** (%)
Me	>99	<1	0
Et	99	1	0
tBu	79	0	21

Scheme 3



Treatment of the remaining polymer with sulphuric acid (1 N) resulted in regeneration of sulfonic acid **3**; the infrared spectrum of the support obtained was identical with that of starting material **3**. This observation implies that the cyclo-elimination process is complete. Furthermore, conversion of this recycled resin into sulfonyl chloride **2** was easily accomplished, which allows re-use of the polymer support.

The use of enantiomerically pure 1,2-diol **6**[9] as starting material gave enantiopure oxazolidinone **1** (R = CH_2CH_2Ph) after crystallization of the crude product.[10]



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Generally accepted procedures to prepare optically active 1,2-diols, such as the Sharpless asymmetric dihydroxylation,[11] can thus be applied to obtain various building blocks with defined chirality to be used in this sequence. The methodology presented here offers good prospects for the SPOS of a variety of 1,3-oxazolidin-2-ones.

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