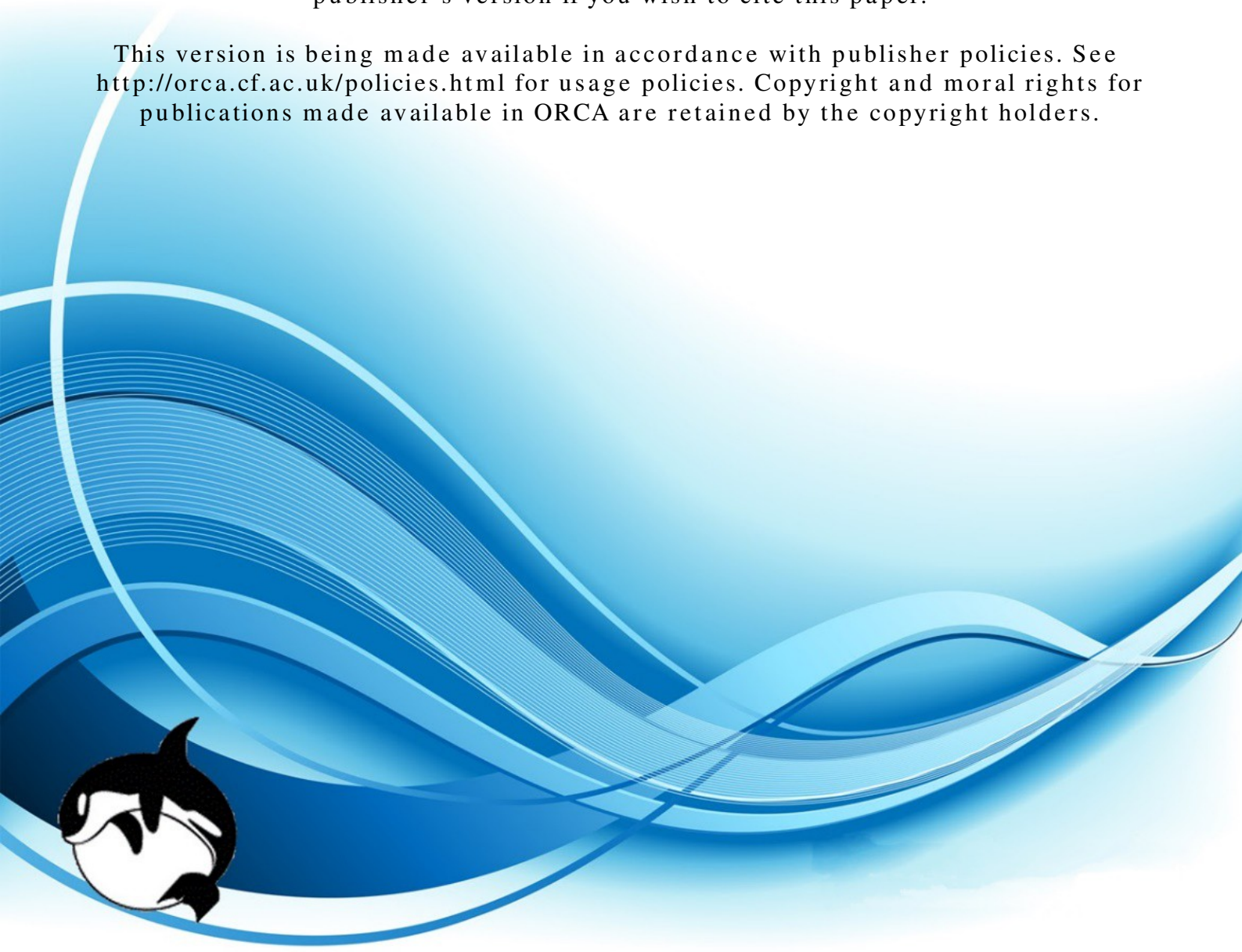

Acid-catalyzed Tandem Process for the One-Pot Synthesis of Oxazolidines

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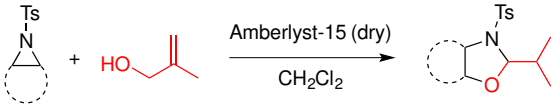
Dedicated to Prof. Victor Snieckus on the occasion of his 80th birthday

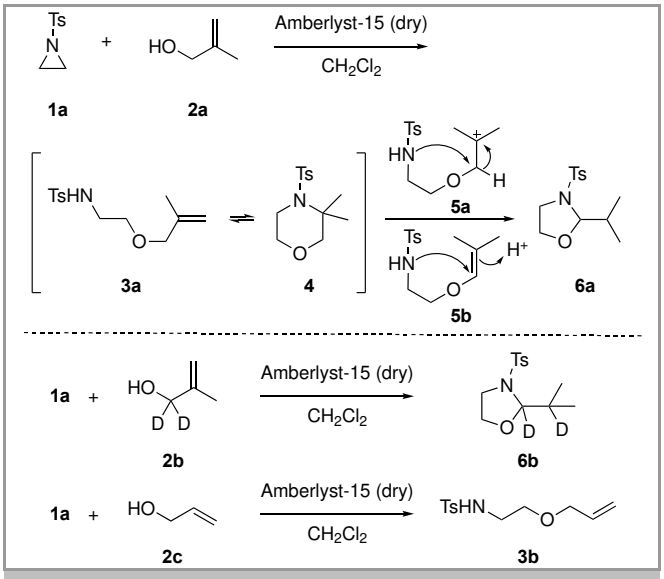


Abstract A simple protocol for the synthesis of oxazolidines from aziridines and allylic alcohols is reported. The solid-supported sulfonic acid catalyst can be easily removed after the reaction by a simple filtration leading to the oxazolidine reaction products in good to excellent yields.

Key words aziridines, cyclization, oxazolidines, rearrangement, ring-opening

Aziridines are important key intermediates in synthesis and many routes for their synthesis have been described. Aziridines can be ring-opened through different processes and allow the facile introduction of C_2N building blocks.[1] The ring opening with oxygen nucleophiles leads to 1,2-aminoalcohol derivatives which are valuable compounds. We describe herein the ring opening of aziridines with 2-methylallyl alcohol followed by a subsequent cyclization leading to oxazolidines.

Oxazolidines are heterocyclic motifs commonly used as protected aminoalcohols, but also embedded in various natural compounds such as quinocarcin,[2] where the oxazolidine moiety is important for the biological activity. Acid-catalyzed aziridine ring opening reactions using alcohols as nucleophiles have already been reported and proven to be a useful tool for synthesizing aminoalcohol derivatives.[3] The use of allylic alcohols for the ring opening reaction provides substrates which have been used for the preparation of six-membered *N*-heterocycles through oxidative palladium-catalyzed cyclizations.[4] Condensation reactions of aziridines with aldehydes have been reported for the synthesis of oxazolidine derivatives.[5] We have employed 2-substituted allylic alcohols for the ring opening reaction as this substitution pattern allows the formation of stabilized carbocationic intermediates and, hence, the direct formation of heterocyclic reaction products. Treatment of *N*-tosylaziridines **1** with allylic alcohols **2** in the presence of Amberlyst-15 as a sulfonic acid catalyst provided the oxazolidine derivatives **6** in good yields. The reaction between **1a** and **2a** in the presence of Amberlyst-15 led to quantitative yield of oxazolidine **6a**. In order to explore the course of the reaction in more detail, the reaction was carried out at lower temperatures (0 ºC) and stopped after 1 h. In addition to oxazolidine **6a** (~25%), also the addition product **3** (~25%) and the morpholine derivative **4** (~50%) were detected by ^{1}H NMR.[6] If this reaction is continued for another 4 h at 0 ºC, only the oxazolidine derivative **6a** is obtained in quantitative yields. Amberlyst-15 does not only provide the reaction conditions for a facile acid-catalyzed aziridine opening which initially leads to compound **3a**, the protonation of the double bond in **3a** leads to a reversible formation of morpholine **4**. Rearrangement of protonated **3a** (or **4**) is accompanied by a hydride transfer as shown in **5a** resulting in the formation of **6a** as the final product.

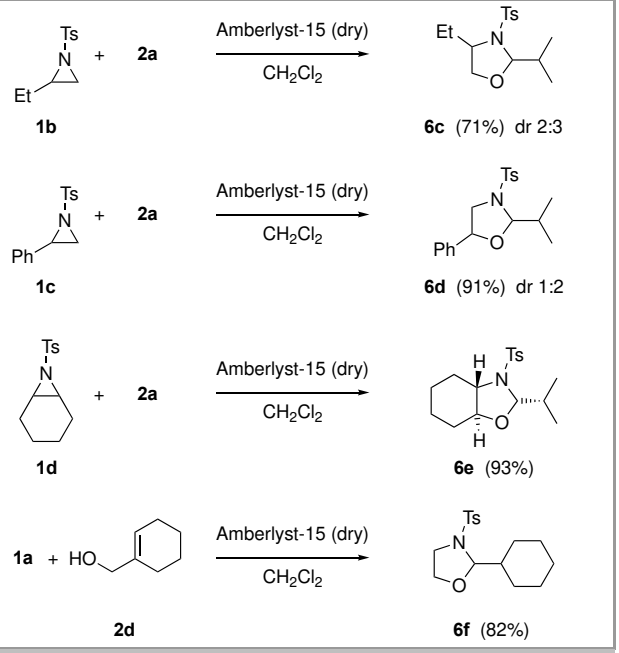


Scheme 1 Synthesis of oxazolidine **6a** from aziridine **1a** and allylic alcohol **2a**.

We recently have reported other cationic rearrangements which were accompanied by hydride transfer.[7] Alternatively, a double

bond isomerization in **3** would lead to an enol ether **5b** which can also cyclize to oxazolidines as has been shown before.[8] The use of the deuterated allylic alcohol **2b** led exclusively to the reaction product **6b** indicating that a hydride / deuteride shift as shown in **5a** is operating in this reaction as otherwise only a partially deuterated product would have been obtained. The subsequent reaction to **6a** achieved with the substituted allylic alcohol **2a** and Amberlyst-15 catalyst is remarkable as allylic alcohol **2c** only forms ring-opened addition product **3b** under acid catalysis. Product **3b** is stable and does not further cyclize.[3a]

Different aziridines can be used in a similar reaction catalyzed by Amberlyst-15. Ethyl-substituted aziridine **1b** is regioselectively ring-opened at the least substituted position providing oxazolidine **6c** in a 2:3 ratio of diastereomers. Phenyl-substitued aziridine **1c** is also regioslectively ring-opened, but exclusively in the benzylic position leading to oxazolidine **6d** in 91% yield. The two diastereomers, obtained in a 1:2 ratio (*trans*:*cis*), could be separated. The configuration of the *cis*-stereoisomer was confirmed by X-ray analysis.[9] With the bicyclic aziridine **1d** as starting material, oxazolidine **6e** is formed as a single diastereomer as confirmed by NMR spectroscopy in 93% yield. The relative stereochemistry of the isopropyl substituent was determined by NOESY NMR experiments (see supporting information). Even substituted allylic alcohols such as **2d** can react efficiently with **1a** forming oxazoldine **6f** as product in 82% yield.[10,11] Amberlyst-15 is a solid-supported sulfonic acid which can be easily removed after the reactions by simple filtration. It is important that dry Amberlyst-15 is used in the process as traces of water can hydrolyze the oxazolidine products to the corresponding aminoalcohols.



Scheme 2 Other oxazolidines **6** prepared by the addition / cyclization sequence.

In summary, we have developed an operationally very simple protocol for the synthesis of oxazolidines from aziridines and allylic alcohols. The reaction is catalyzed by Amberlyst-15, a solid-supported sulfonic acid, which is removed by filtration after the reaction. The oxazolidine reaction products are obtained in good yields.

Acknowledgment

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Supporting Information

Yes.

Primary Data

No.

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(9) Coles, S. J.; Gale, P. A. *Chem. Sci.* **2012**, *3*, 683. CCDC-1576825 (***cis*-6d**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(10) General procedure: A mixture of *N*-tosylaziridine (1 mmol), the allylic alcohol (1.1 mmol) in dry dichloromethane (20 mL) was stirred at 0 ºC for 10 min, then dry Amberlyst-15 (0.5 g) was added. The mixture was left to warm up to room temperature for 2 hours. The reaction mixture was filtered and washed with dichloromethane (2 x 10 mL). The combined organic layers were concentrated in vacuo and purified by column chromatography on silica gel to afford the oxazolidine as a clear oil.

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