Synthesis of Imidazolidine-2-(thi)ones via C2-Selective Oxidation and Thionation of 2-Imidazolinium Halides

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Received 11 October 2011

Abstract: This article describes a scope study for the synthesis of imidazolidine-2-(thi)ones by selective oxidation or thionation of 2-imidazolinium halides, which in turn are synthesized by alkylation of 2-imidazolines obtained from an initial multicomponent reaction.

Key words: alkylation, cyclization, heterocycles, imines, multicomponent reactions

In recent years, imidazolidine-2-ones (**A**, Figure 1) and imidazolidine-2-thiones (**B**, Figure 1) have proven important heterocyclic scaffolds. Imidazolidine-2-ones display biological activity as NK1[1] or 5-HT_{2C} receptor antagonists[2] and BACE-1 inhibitors[3] and exhibit retinoidal activity.[4] In addition, they can be used as chiral auxiliaries in asymmetric synthesis.[5] Imidazolidine-2-thiones are valuable intermediates towards biologically active compounds such as antibacterials[6] and (derivatives of) nutlins, which are promising leads for anticancer therapy.[7] Furthermore, imidazolidine-2-thiones are precursors of both cyclic guanidines[8] and N-heterocyclic carbene (NHC) ligands in coordination chemistry and homogeneous catalysis.[9]

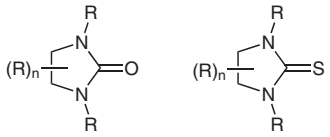
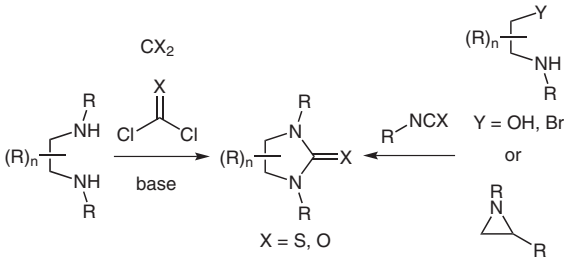


Figure 1 Imidazolidine-2-ones (**A**) and imidazolidine-2-thiones (**B**)

Common strategies towards the target scaffolds include cyclization reactions of 1,2-diamines with either CO_2/CS_2 or (thio)phosgene under basic conditions in polar aprotic solvents (Scheme 1). Alternatively, reaction of iso(thio)cyanates with 2-amino alcohols, 2-bromoethylamines, or aziridines also provides access to imidazolidine-2-(thi)ones, although these routes might involve multiple steps. Imidazolidine-2-thiones can also be synthesized from the corresponding imidazolidine-2-ones using Lawesson's reagent.[10,11] Although a range of these scaffolds has already been synthesized by application of these methods, simple and efficient synthesis of structurally diverse libraries proved not straightforward due to the limited availability of substituted derivatives of these 1,2-difunctionalized compounds.



Scheme 1 Classical synthesis of imidazolidine-2-(thi)ones

Recently, we have reported some preliminary results on oxidation[10] and thionation[12] of 2-imidazolinium halides towards these scaffolds. The synthetic sequence was based on an initial complexity-generating multicompo-

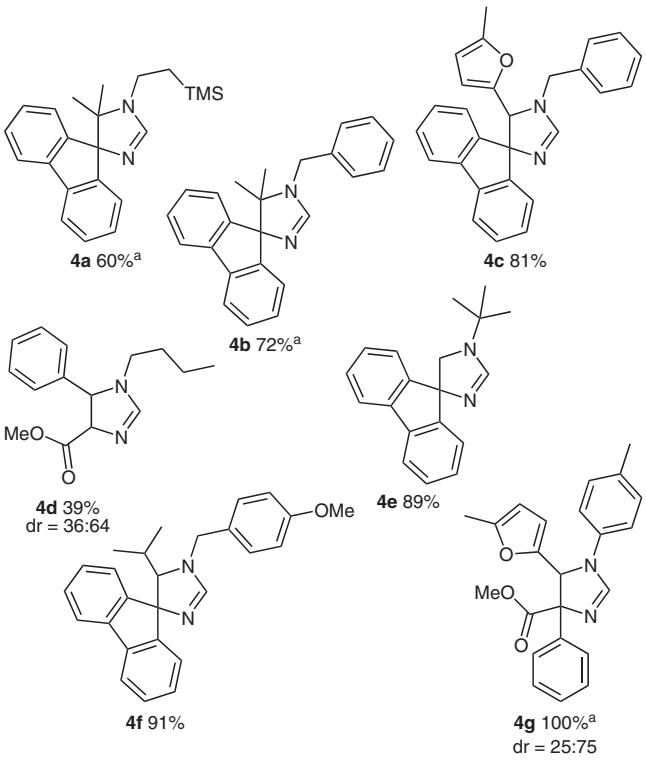
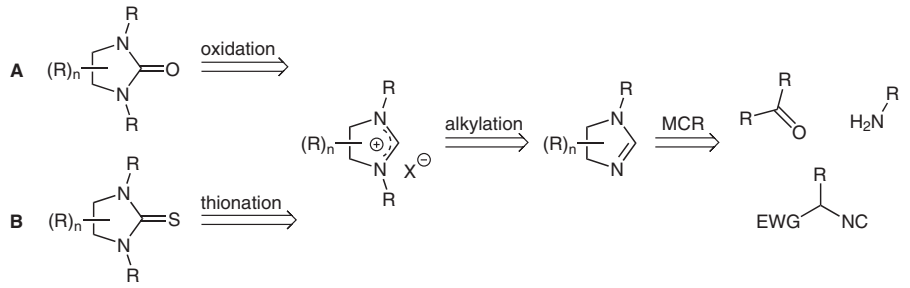


Figure 2 2-Imidazoline MCR products. [a] Catalyzed by addition of AgOAc (2 mol%).

SYNLETT 2012, 23, 80–84
Advanced online publication: 05.12.2011
DOI: 10.1055/s-0031-1290087; Art ID: B00311ST



Scheme 2 Retrosynthetic analysis for imidazolidine-2-(thi)ones

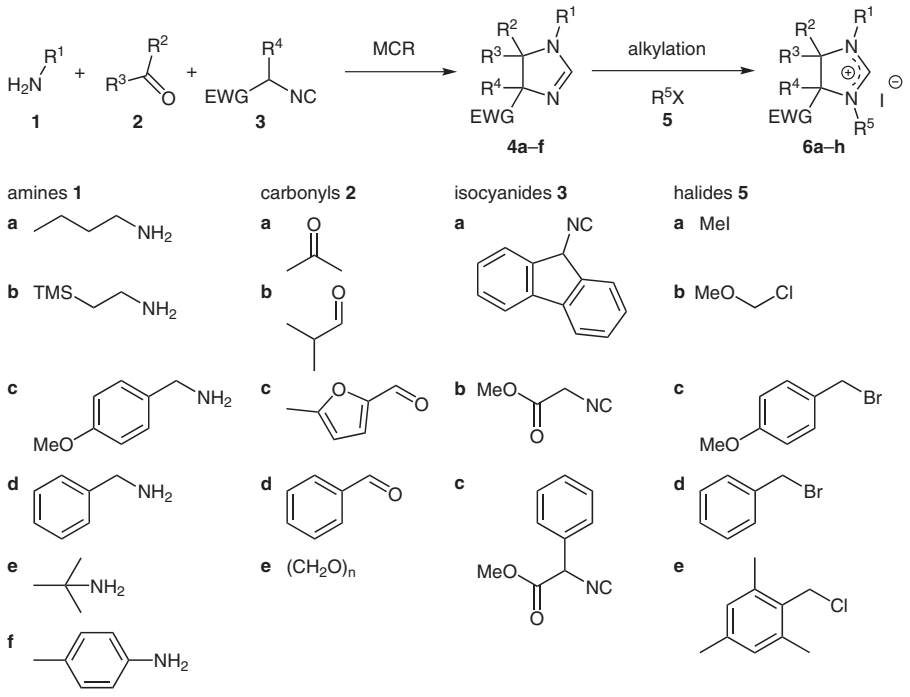
nent reaction (MCR) which allows introduction of diversity on five positions of the target scaffolds. However, no scope study was performed since these syntheses were focused on specific target compounds. Therefore, we now set out to determine the scope of these types of transformations.

A retrosynthetic analysis for this scope study is depicted in Scheme 2. Imidazolidine-2-ones (**A**) and imidazolidine-2-thiones (**B**) can be synthesized by C2-selective oxidation or thionation of 2-imidazolinium halides, which in turn can be synthesized by alkylation of an initial MCR product derived from amine, aldehyde or ketone, and α-acidic isocyanide components. This approach allows introduction of diversity on six positions of the target scaffold.

In the MCR, amines **1**, aldehydes or ketones **2**, and α-acidic isocyanides **3** are reacted to give 2-imidazolines. Product formation is assumed to proceed through a Mannich-type addition of the α-carbanion of an α-acidic isocyanide to the in situ formed (protonated) imine and subsequent cyclization.[13,14] From a collection of six amines, five aldehydes/ketones, and three isocyanides (Scheme 3), a diverse set of 2-imidazolines was synthesized in reasonable to excellent isolated yields (39–100%; compounds **4a–g**, Figure 2).

Given the reduced reactivity of ketones in this MCR, AgOAc (2 mol%) was added as catalyst for the reaction with acetone (**2a**) as the carbonyl component. Under these conditions, 2-imidazolines **4a** and **4b** were isolated in reasonable yield.[15] The moderate yield of **4d** can be explained by the relative low α-acidity of isonitrile **3b**.[15] AgOAc catalysis was also used in the synthesis of **4g**, affording the desired product in quantitative yield in this case.

Next, the 2-imidazolinium halides **6a–j** (Figure 3) were obtained in generally excellent isolated yields either by direct alkylation with the appropriate halide **5** in CH_2Cl_2 or by application of Finkelstein conditions. The somewhat lower yield of **6g** (84%) can be rationalized by the steric hindrance between the mesityl group and the spirofluorenyl moiety, hampering facile alkylation.



Scheme 3 Multicomponent and alkylation reactions

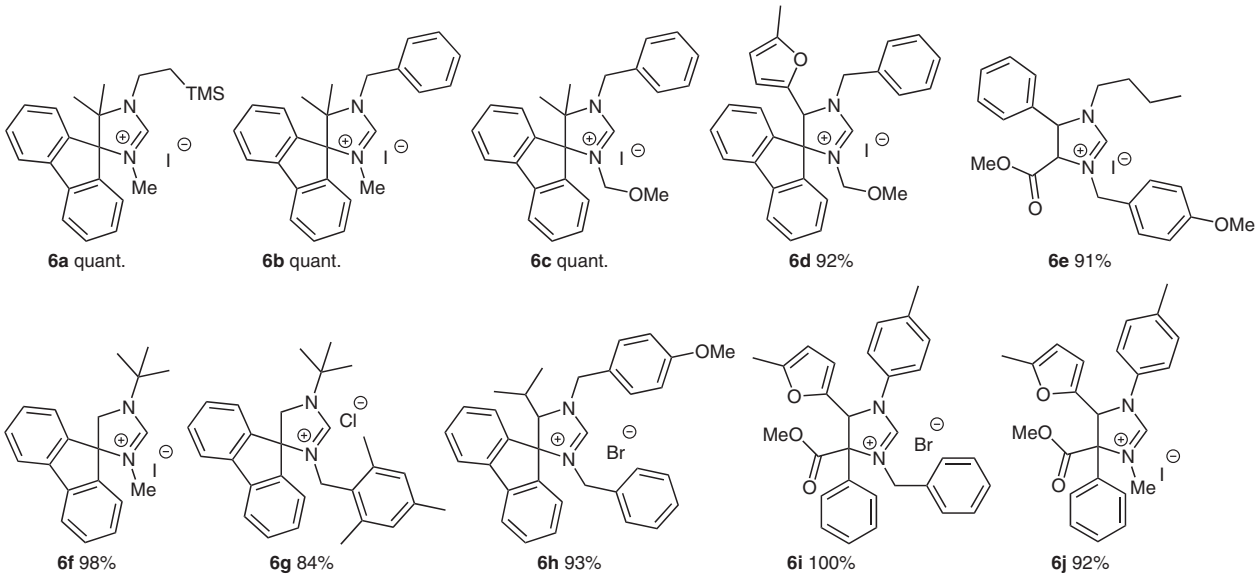


Figure 3 2-Imidazolinium halides by alkylation of 2-imidazolines

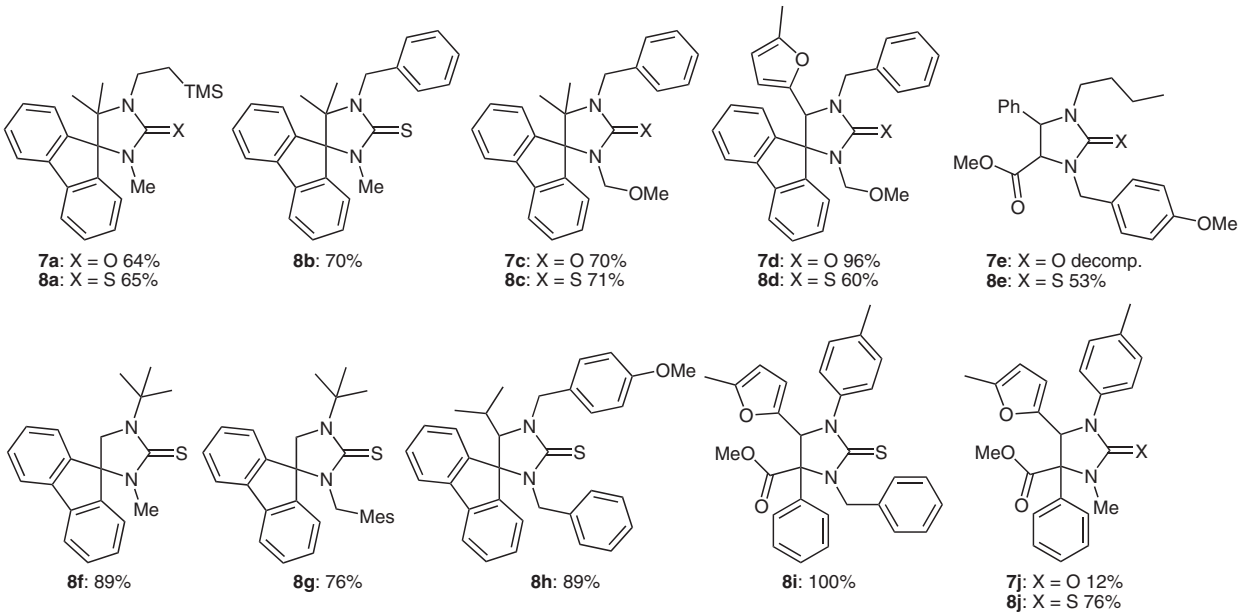
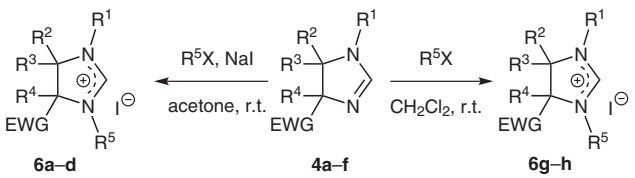


Figure 4 Imidazolidine-2-(thi)ones

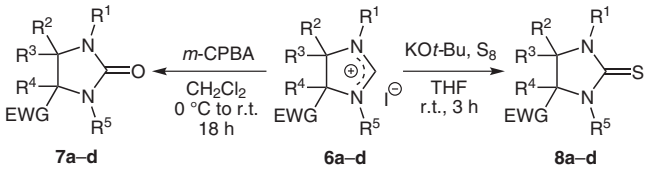
For the synthesis of the imidazolidine-2-ones a procedure was applied where oxidation is mediated by *m*-CPBA in CH_2Cl_2 at 0 °C.[10] For clean reactions it has proven essential to add the *m*-CPBA to a cooled (0 °C) solution of the 2-imidazolinium halides. To obtain the imidazolidine-2-thiones a modified procedure of Karkhanis et al. was applied.[16] In this modified procedure, 2-imidazolinium halides are reacted with S_8 and KO*t*-Bu at room temperature.

Imidazolidine-2-ones **7a**,**c**,**d** were obtained in good to excellent isolated yield (64–96%, Figure 4) by selective C2 oxidation, while no product was obtained from oxidation of substrate **6e**. This is probably due to oxidation to the corresponding imidazolium halide or oxidative cleavage of the *p*-methoxybenzyl group. The yield of **7j** was unexpectedly low (12%). In this case, we were not able to provide a plausible rationalization of this result.

Spirofluorene imidazolidine-2-thiones (**8a–d**,**f–h**) were obtained by selective C2-thionation in reasonable to excellent yield (60–89%, Figure 4). Imidazolidine-2-thione **8e**, however, was obtained in only 53% yield. This can be rationalized by taking into account the acidic nature of the



Scheme 4 Alkylation protocols of 2-imidazolines



Scheme 5 Oxidation and thionation of 2-imidazolinium halides

backbone protons, where, considering the basic conditions, deprotonation can lead to various competing side reactions, leading to scrambling of products. On the other hand, the other ester-functionalized imidazolidine-2-thiones **8j** and **8i** were obtained in good (76%) and quantitative yield, respectively. In the latter case, **8i** was synthesized in 94% yield over three steps starting from **3c**.

In summary, we have presented a short and resource-efficient three-step synthetic strategy towards imidazolidine-2-ones **7** and imidazolidine-2-thiones **8** by C2-selective oxidation and thionation of 2-imidazolinium halides. This methodology allows facile introduction of six points of diversity in the target scaffolds by a diversity-generating MCR and subsequent alkylation reaction. The target heterocycles were obtained in up to 70% and 94% overall yields, respectively, over three steps. With these results in hand, follow-up chemistry towards the synthesis of several of bioactive compounds is currently under investigation.

General Procedure for the Multicomponent Synthesis of 2-Imidazolines (4)

An aldehyde or ketone (**2**, 1.0 equiv) was added to a stirred solution of an amine (**1**, 1.0 equiv) in freshly distilled CH_2Cl_2 (or MeOH) containing anhyd Na_2SO_4, and the mixture was stirred at r.t. for 3 h. Then, an isocyanide (**3**, 1.0 equiv) [and in some cases, AgOAc (0.02 equiv)] were added, and the resulting reaction mixture was stirred for an additional 18 h, followed by filtration and concentration in vacuo. The crude product was purified by flash chromatography to furnish the 2-imidazolines.

General Procedure for the Synthesis of 2-Imidazolinium Salts 6 by N-Alkylation (Scheme 4)

For Iodides

Reactions were carried out at a concentration of 0.15–0.25 M of a 2-imidazoline **4** in dry CH_2Cl_2, unless noted otherwise. The alkyl iodide (1.0 equiv) was added to a stirred solution of the 2-imidazoline, and the reaction mixture was stirred at r.t. for 18 h. Then, the reaction mixture was concentrated in vacuo. The crude product was washed with pentane or Et_2O to afford the pure imidazolinium salt.

For Bromides and Chlorides

Reactions were carried out at a concentration of 1 M of a 2-imidazoline **4** in acetone. The alkyl halide (1.0 equiv) was added to a stirred solution of the 2-imidazoline and KI (1.0 equiv). The reaction mixture was stirred at r.t. for 18 h and concentrated in vacuo. Then the reaction mixture was taken up in CH_2Cl_2 and subsequently filtered over Celite and concentrated in vacuo to afford the pure imidazolinium salt.

General Procedure for the Synthesis of Imidazolidine-2-ones 7 by C2-Oxidation (Scheme 5)

To a solution of an imidazolinium salt **6** (0.05 M) in freshly distilled CH_2Cl_2, *m*-CPBA (3 equiv) was added at 0 °C. The reaction mixture was stirred at r.t. for 18 h and subsequently washed with Na_2CO_3 (2×), concentrated in vacuo, and purified by flash chromatography to afford the imidazolidin-2-one.

General Procedure for the Synthesis of Imidazolidine-2-thiones 8 by C2-Thionation (Scheme 5)

Reactions were carried out under an inert atmosphere of dry argon at a 0.04 M concentration of an imidazolinium salt **6** in freshly distilled THF. The reaction vessel was charged with imidazoline salt, KO*t*-Bu (1.0 equiv), and S_8 (1.0 equiv) and flushed twice with argon. THF was added, and the reaction mixture was stirred at r.t. for 2 h, after which H_2O was added. The mixture was subsequently extracted with Et_2O (2×), EtOAc (2×), and CH_2Cl_2 (2×). The combined organic layers were subsequently dried with Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography to afford the imidazolidin-2-thione.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

This work was performed with financial support from the Netherlands Organization for Scientific Research (NWO, VICI Grant). Dr. M. T. Smoluch (VU University Amsterdam) is kindly acknowledged for conducting HRMS measurements.

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