Expedient Synthesis of Highly Substituted Pyrroles via Tandem Rearrangement of α-Diazo Oxime Ethers

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S *Supporting Information*

ABSTRACT: An efficient rhodium-catalyzed synthesis of 2*H*-azirines and pyrroles has been developed. Novel rearrangement of α-oximino ketenes derived from α-diazo oxime ethers provides 2*H*-azirines bearing quaternary centers and allows for subsequent rearrangement to highly substituted pyrroles in excellent yields.

Pyrroles[1] are among the most important heterocycles that are frequently found in natural products,[2] pharmaceuticals,[3] and functional materials.[4] These utilities continue to drive the interest in the development of new synthetic methods for pyrroles which include cycloaddition reactions,[5] multicomponent coupling reactions,[6] and transition metal-mediated reactions.[7] Padwa and co-workers reported synthesis of pyrroles via rearrangement of 2-vinyl-2*H*-azirines.[8] Inspired by the report, we aimed to develop a synthetic method for 2*H*-azirines and pyrroles based on novel rearrangement of α-dizao oxime ethers (eq 1).

(1)

2*H*-Azirines represent a highly valuable class of compounds found in natural products and synthetic intermediates.[9] Derived from the high ring strain present in these smallest heterocycles, their unique reactivity allows for 2*H*-azirines to serve as a versatile source of nitrenes, electrophiles, dienophiles, and dipolarophiles in various reactions.[10] These reactions lead to the development of efficient synthetic platforms for various nitrogen containing heterocycles including pyrroles, indoles, pyrazolo[1,5-a]pyridines, isoxazoles, and piperidines.[11] Despite their broad utility, the availability of synthetic methods for 2*H*-azirines is rather limited, primarily relying on the Neber reaction[12] and thermal/photochemical rearrangement of vinyl azides.[13] The efficiency of these reactions is, however, highly variable and dependent on substrates due to the sensitive nature of 2*H*-azirines that promotes further activation and subsequent decomposition. Also, these reactions typically require stoichiometric reagents and harsh reaction conditions. With the tandem synthesis of pyrroles in mind, we first set out to develop catalytic and neutral conditions for 2*H*-azirines

bearing *quaternary centers* required for the subsequent rearrangement.

Wolff rearrangement, among the fundamental reactions of diazo compounds, has found broad applications in organic synthesis.[14] Ketenes generated by metal-catalyzed or thermal/photochemical activation of diazo compounds have proven as versatile intermediates in various transformations including nucleophilic addition, cycloaddition, ring contraction, and homologation.[15] However, to the best of our knowledge, no examples of 2*H*-azirine synthesis via Wolff rearrangement have been reported. In conjunction with our recent studies on the chemistry of α-diazo oxime ethers,[16] we investigated the feasibility of metal-mediated cascade rearrangement leading to formation of 2*H*-azirine-2-carboxylic esters (eq 2) and subsequent rearrangement to pyrroles by introduction of vinyl groups on α-diazo oxime ethers (eq 1).

(2)
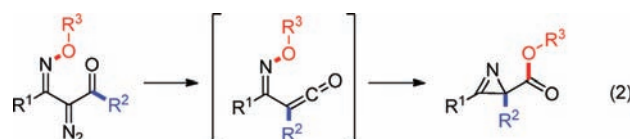
Our attempts began with a reaction on α-diazo-β-keto oxime ether **1a** employing Cu(OTf)$_2$ as catalyst (Scheme 1).[17]

Scheme 1. Selectivities of Catalysts between Wolff Rearrangement and 2-Alkoxy-2*H*-azirine[a]

	2a	**2a′**
Cu(OTf)$_2$	12%	19%
Ag(OBz)	46%	54%
Rh$_2$(OAc)$_4$	99%	-
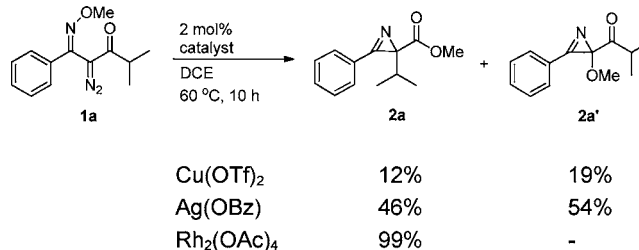
[a]OTf = trifluoromethanesulfonate, OBz = benzoate. Yields determined by NMR vs standard.

Thus, exposure of **1a** to Cu(OTf)$_2$ in 1,2-dichloroethane (DCE) at 60 °C resulted in formation of two products in low yields that were identified as **2a** and **2a′**. Compound **2a** appears to arise from the desired cascade rearrangement,
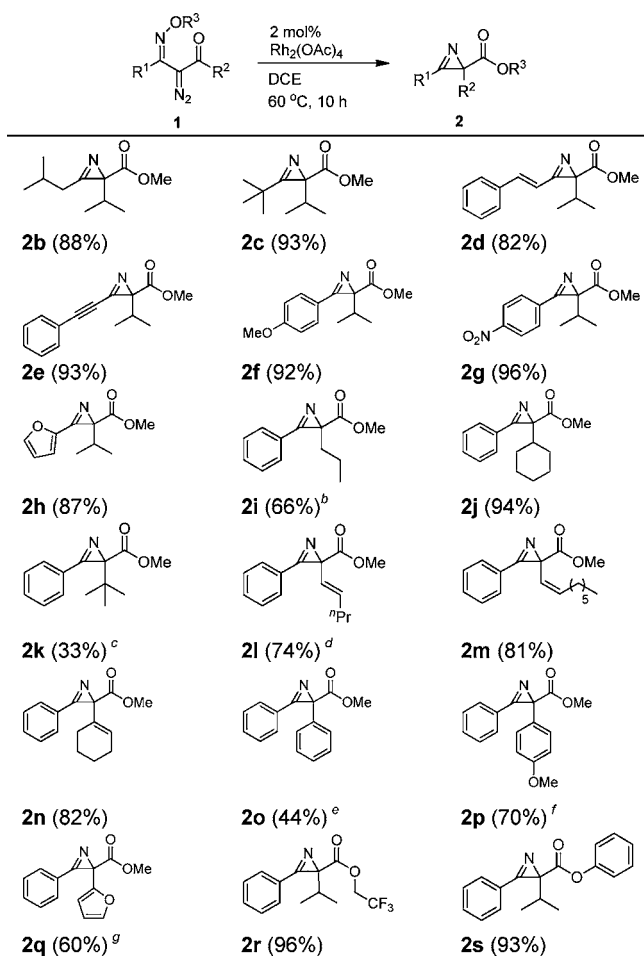
while **2a′** results from N−O insertion.[18] With the result in hand, we proceeded with screening of various metal salts (see the Supporting Information). Use of Ag(OBz) which is frequently employed in the Wolff rearrangement gave improvement in yield, while the selectivity between the cascade rearrangement and N−O insertion remained unsatisfactory. To our delight, exposure of **1a** to 2 mol % of $Rh_2(OAc)_4$ led to exclusive formation of **2a** in nearly quantitative yield.[19] Examination of solvent effects on the rearrangement revealed that the reaction is well tolerated in various solvents (see the Supporting Information).

With the optimal conditions in hand, we next examined the substrate scope of 2H-azirine formation (Table 1). Consistent

Table 1. Substrate Scope[a]

2b (88%) 2c (93%) 2d (82%)
2e (93%) 2f (92%) 2g (96%)
2h (87%) 2i (66%)[b] 2j (94%)
2k (33%)[c] 2l (74%)[d] 2m (81%)
2n (82%) 2o (44%)[e] 2p (70%)[f]
2q (60%)[g] 2r (96%) 2s (93%)

[a]The reported yields in parentheses are of the isolated products. [b]Byproduct: 1-(2-methoxy-3-phenyl-2H-azirin-2-yl)butan-1-one **2i′** (29%). [c]Byproducts: 1-(2-methoxy-3-phenyl-2H-azirin-2-yl)-2,2-dimethylpropan-1-one **2k′** (46%); 2,2-dimethyl-1-(3-phenyl-2H-azirin-2-yl)propan-1-one **2k″** (18%). [d]Byproduct: (E)-1-(2-methoxy-3-phenyl-2H-azirin-2-yl)hex-2-en-1-one **2l′** (18%). [e]Byproduct: (2-methoxy-3-phenyl-2H-azirin-2-yl)(phenyl)methanone **2o′** (44%) obtained as an inseparable mixture with **2o** (yields were determined by NMR). [f]Byproduct: (4-methoxyphenyl)(3-phenyl-2H-azirin-2-yl)methanone **2p″** (21%). [g]Byproduct: furan-2-yl(2-methoxy-3-phenyl-2H-azirin-2-yl)-methanone **2q′** (31%).

with the results in the optimization studies, reactions smoothly proceeded to afford 2H-azirine-2-carboxylic esters in good to excellent yields. To probe electronic and steric influences on

the rearrangement, various types of substituents for each of the three sites (R^1, R^2, and R^3) were examined. For R^1 adjacent to the oxime ethers, alkyl groups were well tolerated (**2b** and **2c**). Also, substrates with alkenyl, alkynyl, and aryl substituents smoothly reacted to give the corresponding 2H-azirine-2-carboxylic esters in excellent yields (**2d−g**). Examination of the electronic effect of R^1 by varying substituents on phenyl groups revealed little impact on the reaction efficiency; 92% and 96% for 4-methoxyphenyl (**2f**) and 4-nitrophenyl (**2g**) compounds, respectively. Furthermore, the substrate with heteroaryl group such as 2-furyl group afforded **2h** in 87% yield.
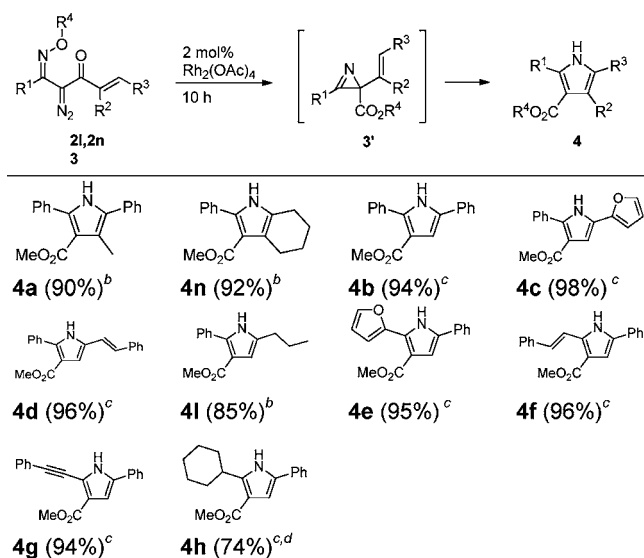
Next, we turned our attention to the influence of R^2 undergoing migration (Table 1, **2i−q**). Examination of various R^2 revealed the efficiency of the reaction in the order of secondary, vinyl ≈ primary followed by tertiary alkyl groups: **2j**, 94%; **2l**, 74%; **2i**, 66%; **2k**, 33%. For those with low yields, the major byproducts were the corresponding N−O insertion products (Table 1, footnote). For **1k**, additional byproduct **2k″** was isolated in 18% yield that results from 1,5-hydride shift from the methyl ether.[20,21] To examine the potential isomerization of (E)- and (Z)-alkenes during migration, **1l** and **1m** were subjected to the reaction conditions. Gratifyingly, both substrates gave the corresponding isomers with complete retention of geometry (Table 1, **2l** and **2m**). Moreover, **1n** with a cyclohexene moiety also produced **2n** in 82% yield. Next, we examined the influence of migrating groups when R^2 = aryl/heteroaryl groups. While the substrates with phenyl (**1o**) and 2-furyl (**1q**) groups afforded the expected products **2o** and **2q** (44% and 60%, respectively) along with N−O insertion products **2o′** and **2q′** (44% and 31%, respectively), **1p** bearing more electron-rich 4-methoxyphenyl group gave **2p** in higher yield (70%) along with byproduct **2p″** (21%) formed via 1,5-hydride shift[20] (Table 1, footnote). A brief examination of the alkoxy group (OR^3) of oxime ethers showed that both electron-deficient (**1r**) and phenyl (**1s**) groups are also well tolerated to afford the corresponding esters in excellent yields.

With the efficient synthetic protocol for 2H-azirines in hand, we explored the viability of tandem rearrangement to pyrroles (Table 2). The study by Padwa and co-workers demonstrated that 2-vinyl-2H-azirines undergo rearrangement to furnish pyrroles via nitrenes.[8] We reasoned that the rhodium catalysis in the formation of 2-vinyl-2H-azirines may be further exploited in the synthesis of pyrroles in tandem fashion. We were delighted to find that exposure of α-diazo oxime ether **3a** to 2 mol % $Rh_2(OAc)_4$ in refluxing toluene provided tetrasubstituted pyrrole **4a** in 90% yield. Encouraged by this result, we examined the substrate scope of the reaction. As shown in Table 2, this protocol offers highly flexible synthesis of pyrroles with various substituents. While substrates with alky groups on vinyl substituents required refluxing toluene (**4a**, **4n**, and **4l**), those with aryl groups for R^3 gave the corresponding pyrroles at 60 °C in excellent yields (**4b−h**).

Mechanistically, we propose that the rearrangement proceeds through ketene intermediate **C**. Thus, rhodium-catalyzed formation of carbenoid **B** promotes migration of the vinyl substitutent to the carbenoid center resulting in formation of ketene **C**. Attack of the oxygen atom of the oxime ether moiety on the ketene leads to formation of ylides **D/E** that further undergo rearrangement to afford 2H-azirine-2-carboxylic ester **F**. Rhodium−nitrene complex **G** formed via ring-opening of **F** undergoes C−H insertion to afford pyrrole **H**.

To probe the presence of ketenes as intermediates in the reaction pathway as shown in Scheme 2, we demonstrated that

**Table 2. Synthesis of Pyrroles via Tandem Reaction of α-Diazo Oxime Ethers**[a]

4a (90%)[b] **4n (92%)**[b] **4b (94%)**[c] **4c (98%)**[c]

4d (96%)[c] **4l (85%)**[b] **4e (95%)**[c] **4f (96%)**[c]

4g (94%)[c] **4h (74%)**[c,d]

[a]The reported yields in parentheses are of the isolated products. [b]Toluene, 110 °C. [c]DCE, 60 °C. [d](E)-3-(3-Cyclohexyl-2-methoxy-2H-azirin-2-yl)-1-phenylprop-2-en-1-one **4 h′** (19%) obtained as byproduct.

Scheme 2. Proposed Reaction Mechanism of the Rearrangement
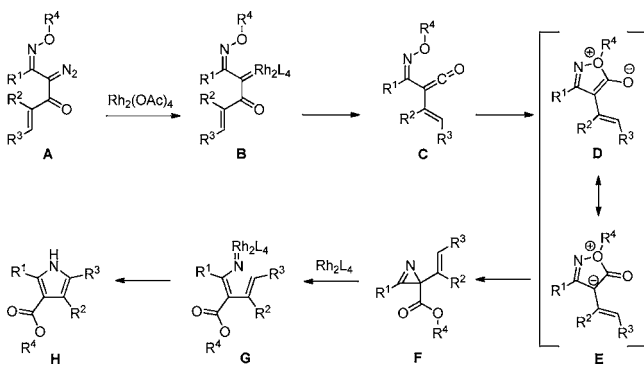
the ketene independently prepared from carboxylic acid **5** spontaneously undergoes rearrangement to afford **2t** in 85% (eq 3).
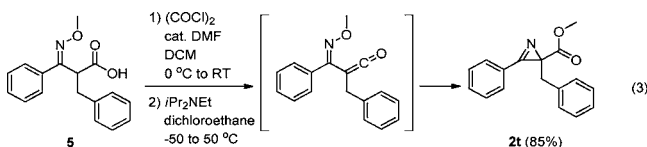
In summary, we have described development of highly efficient synthesis of 2H-azirine-2-carboxylic esters with quaternary centers and tandem synthesis of pyrroles. Novel rearrangement of α-oximino ketenes generated from α-diazo oxime ethers via the Wolff rearrangement results in formation of 2H-azirine-2-carboxylic esters in excellent yields. This reaction allowed us to further develop a tandem reaction for highly substituted pyrroles via cascade rearrangement of α-diazo oxime ethers.

ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(17) Preparation of α-diazo β-keto oxime ethers. For details, see ref 16 and the Supporting Information.
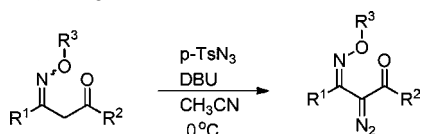
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