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Divergent reactivity of α-oximino carbenoids: facile access to 2-isoxazolines and 2*H*-azirines†

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Mild catalytic reaction conditions for the synthesis of 2-isoxazolines and 2*H*-azirines have been developed *via* carbenoids derived from α-oximino diazo compounds. This has been utilized in the one-pot synthesis of pyrroles in the presence of 1,3-dicarbonyl compounds.

The reactivity of metallocarbenoids has been extensively utilized in the development of new synthetic methods including C–H insertion, addition and ylide formation.[1] The versatile reactivity of carbenoids allows for effecting various types of bond formation that are otherwise difficult to be realized. Functionalization of inert C–H bonds has recently drawn a great deal of attention which offers advantages such as increased synthetic efficiency and benign environmental impact.[2] Carbenoid-mediated C–H insertion has been extensively exploited in the formation of new C–C bonds.[3] While offering a powerful means for C–C bond formation, it has been largely limited to carbenoids derived from α-diazocarbonyl compounds.[4]

On the other hand, the potential of their nitrogen analogues, α-imino carbenoids remains to be explored. The introduction of nitrogen atoms adjacent to carbenoids would provide direct access to nitrogen-embedded products. While isomerization of α-imino diazo compounds to triazoles results in loss of reactivity in metal-catalyzed generation of carbenoids,[5] Fokin and co-workers recently reported a method to generate α-imino carbenoids from triazoles.[6] In this regard, we have also reported a method that allows for the preparation of α-oximino diazo compounds without isomerization to triazoles, and their utility as carbenoid precursors in the synthesis of *N*-alkoxypyrroles *via* [3 + 2] cycloaddition reaction.[7] In our continued efforts to explore their reactivity, Sintim and co-workers reported the development of C–H insertion reaction of α-diazo carbonyl compounds containing an N–O moiety.[8] Herein, we wish to describe the divergent reactivity of carbenoids derived from α-oximino diazo compounds leading to the formation of 2-isoxazolines and 2*H*-azirines (Fig. 1).

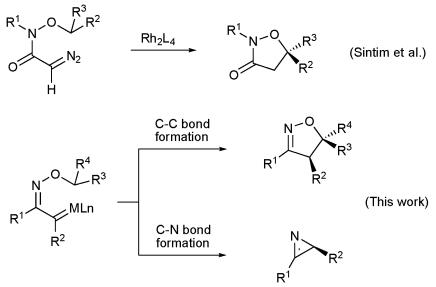

Fig. 1 Divergent reactivity of α-diazo oxime ethers.

Isoxazolines and azirines represent important classes of heterocycles that are widely found in drug molecules, natural products and synthetic intermediates. 2-Isoxazolines are, in general, synthesized by 1,3-dipolar cycloaddition of nitrile oxides,[9] and Michael addition of hydroxylamines.[10] The highly strained reactive heterocycle 2*H*-azirines have proven to be very useful intermediates in a number of synthetic transformations.[11] It has been shown that strain-driven ring opening of 1-azirine derivatives results in the generation of nitrenes which subsequently undergo C–H insertion to form indoles.[12] The electrophilic nature of 2*H*-azirines allows for facile nucleophilic additions and cycloadditions providing efficient routes for the synthesis of various heterocycles such as aziridines, indoles, isoxazoles, oxazolines and pyrazines. While considering the versatile utility of 2*H*-azirines, the availability of synthetic methods is rather limited, largely relying on the Neber reaction that employs strong bases.[13] Other approaches include thermal rearrangement of vinyl azides,[14] oxidation of aziridines[15] and addition of carbenes/nitrenes across nitriles/alkynes[16] albeit with moderate success.

During our investigation of the reactivity of α-oximino carbenoids, we observed facile intramolecular C–H insertion of oxime ether moieties resulting in the formation of 2-isoxazolines in good yields. Encouraged by these observations, we examined the catalytic activity of various catalysts employing compound **1a** as a substrate (Table 1). While the use of copper salts resulted in poor yields, screening of rhodium salts gave more promising results with the formation of 2-isoxazoline **2a** as the major product along with varying amounts of 2*H*-azirine **3a**.[17] Examination of the influence of steric and electronic properties of ligands revealed that rhodium complexes with electron deficient ligands

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. See DOI: 10.1039/c1cc11683e

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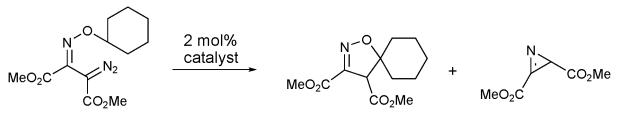
Table 1 Screening of catalysts and solvents



1a **2a** **3a**

Entry	Catalyst[a]	Solvent[b]	Temp./°C	Ratio[c] (**2a**/**3a**)	Yield[c] (%) **2a**
1	$Cu(OTf)_2$	DCE	80	—	0
2	$Cu(acac)_2$	DCE	80	—	0
3	$Rh_2(OAc)_4$	DCE	80	2.3 : 1	56
4	$Rh_2(TFA)_4$	DCE	80	—	0
5	$Rh_2(tfacam)_4$	DCE	80	1 : 2	10
6	$Rh_2(pfb)_4$	DCE	80	—	0
7	$Rh_2(Hex)_4$	DCE	80	3 : 1	49
8	$Rh_2(Oct)_4$	DCE	80	1.6 : 1	51
9	$Rh_2(esp)_4$	DCE	80	3.8 : 1	59
10	$Rh_2(Piv)_4$	DCE	80	15 : 1	59
11	$Rh_2(Piv)_4$	DCM	40	>20 : 1	47
12	$Rh_2(Piv)_4$	$CHCl_3$	60	>20 : 1	38
13	$Rh_2(Piv)_4$	PhH	80	>20 : 1	48
14	$Rh_2(Piv)_4$	$PhCF_3$	100	>20 : 1	53

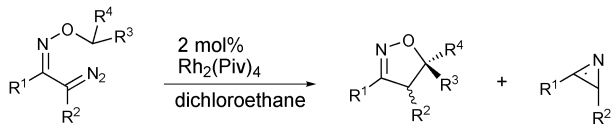
[a] acac = acetylacetonate, TFA = trifluoroacetate, tfacam = trifluoroacetamide, pfb = perfluorobutyrate, Hex = hexanoate, Oct = octanoate, esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, Piv = pivaloate. [b] DCE = dichloroethane, DCM = dichloromethane. [c] Determined by NMR *vs.* standard.

give poor results (Table 1, entries 4–6). Gratifyingly, the use of $Rh_2(OAc)_4$, $Rh_2(esp)_4$ or $Rh_2(Piv)_4$ afforded **2a** in good yields (Table 1, entries 3, 9, 10). Notably, an improvement of the selectivity for **2a** over **3** could be achieved with the use of $Rh_2(Piv)_4$ (Table 1, entry 10). Furthermore, screening of various solvents indicated dichloroethane as an optimal solvent.

With the optimized reaction conditions in hand, we investigated the substrate scope of the reaction (Table 2). It was noted that the electronic influence of substituents has a profound impact on determining the reaction pathway. Hence, substrates with electron withdrawing groups adjacent to oxime ethers strongly favor C–H insertion resulting in the formation of 2-isoxazolines as major products (Table 2, entries 1–7), whereas those substituted with alkyl groups favor formation of 2*H*-azirines as major products (Table 2, entries 8–14). Comparison of the reactivity of oxime ethers bearing a cycloalkane with an acyclic group showed a preference for a cycloalkane (Table 2, entries 1 *vs.* 2). The substrate bearing benzyl ether afforded a mixture of *cis*/*trans*-2-isoxazolines[18] in a ratio of 1.4 : 1 in 65% yield along with a minor amount of 2*H*-azirine (Table 2, entry 3). Alteration of the electronics of benzyl groups sheds light on the electronic impact of C–H bonds undergoing insertion (Table 2, entries 3–6). Contrary to the general preference of carbenoid-mediated insertion for electron-rich C–H bonds,[19] it is of note that a reversed trend was observed with substrates bearing electron-poor C–H bonds affording products in higher yields and selectivities. Meanwhile, C–H insertion on **1g** smoothly proceeded to give the product with a quaternary stereogenic center (Table 2, entry 7).[20]

With these results in hand, we turned our attention to the formation of 2*H*-azirines. A brief survey of substrates revealed that those bearing electron donating groups adjacent to oximes (R^1) provide 2*H*-azirines *via* displacement of alkoxy groups on oxime ethers. Thus, when **1h** bearing a methyl group was treated with 2 mol% $Rh_2(Piv)_4$ at RT, a rapid formation of 2*H*-azirine **3h** was observed in 60% yield along with 2-oxazoline **2h** in 20% yield (Table 2, entry 8). Subsequent examination of the substitution on the ether moieties revealed that an isopropyl group is optimal for the 2*H*-azirine formation, presumably due to its high propensity as a leaving group. On the other hand, examination of the substitution adjacent to oximes showed (R^1) that various alkyl groups are tolerated

Table 2 Synthesis of 2-isoxazolines and 2*H*-azirines



1 **2** β-R^2 **2′** α-R^2 **3**

Entry[a,b]	**1**	R^1	R^2	R^3	R^4	Yield[c] (%) **2** + **2′** (**2** : **2′**)[d]	Yield[c] (%) **3**
1	**1a**	CO_2Me	CO_2Me	$(CH_2)_5$		60	4
2	**1b**	CO_2Me	CO_2Me	CH_3	CH_3	46	6
3	**1c**	CO_2Me	CO_2Me	Ph	H	65 (1.4 : 1)	24
4	**1d**	CO_2Me	CO_2Me	4-ClC_6H_4	H	63 (1.7 : 1)	21
5	**1e**	CO_2Me	CO_2Me	4-$MeOC_6H_4$	H	50 (1 : 1.2)	30
6	**1f**	CO_2Me	CO_2Me	4-$NO_2C_6H_4$	H	73 (2.4 : 1)	16
7	**1g**	CO_2Me	CO_2Me	Ph	CH_3	50 (2.5 : 1)	27
8	**1h**	CH_3	CO_2Bn	CH_3	CH_3	20	60
9	**1i**	Bn	CO_2Me	CH_3	CH_3	16	63
10	**1j**	Bn	CO_2*tert*-Bu	CH_3	CH_3	16	56
11	**1k**	4-$MeOC_6H_4CH_2$	CO_2Me	CH_3	CH_3	23	61
12	**1l**	4-$ClC_6H_4CH_2$	CO_2Me	CH_3	CH_3	20	53
13	**1m**	3-$ClC_6H_4CH_2$	CO_2Me	CH_3	CH_3	21	51
14	**1n**	$PhCH_2CH_2$	CO_2Me	CH_3	CH_3	23	62

[a] Entries 1–7; reflux, 2 h. [b] Entries 8–14; RT, 3–12 h. [c] Yields of isolated products. [d] Ratios determined by NMR.

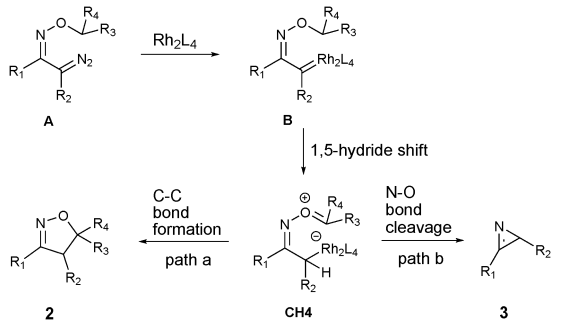
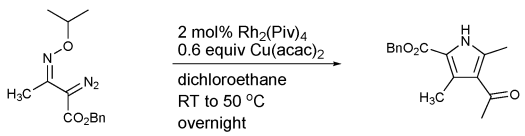


Fig. 2 Proposed reaction mechanism.

including substituted benzyl groups affording 2*H*-azirines in good yields along with minor amounts of oxzaolines arising from the C–H insertion pathway.

With the identification of the mild conditions for the formation of 2*H*-azirines, we next explored the feasibility of pyrrole synthesis *via* a one-pot tandem reaction of 2*H*-azirine formation followed by reaction with 1,3-dicarbonyl compounds.[21] Remarkably, gentle warming of the solution of **1h** in the presence of $Rh_2(Piv)_4$ and $Cu(acac)_2$ as the source of 1,3-dicarbonyl compound smoothly produced pyrrole **4** in 50% yield.



Based on the observations including the stereochemical outcome of the reactions and the competing reaction pathways, we propose the plausible mechanism shown in Fig. 2. Thus, the reaction is initiated by a 1,5-hydride shift to the electrophilic carbenoid center.[22] Depending on the electronic character of substituent R^1, the resulting zwitterionic intermediate **C** takes part in the competing pathways (path a/b). In the case where R^1 equals electron withdrawing groups, the propensity for the cleavage of N–O bond appears to be attenuated due to the build-up of a partial positive charge on the nitrogen, resulting in trapping of the oxocarbenium ion by the anion to form 2-isoxazolines **2**. Conversely, those with alkyl groups for R^1 undergo facile N–O bond cleavage with concomitant formation of a C–N bond to give 2*H*-azirines **3**.

In summary, we have described the development of the catalytic methods under mild reaction conditions for the synthesis of highly valuable heterocycles such as 2-isoxazolines and 2*H*-azirines. Furthermore, the development of a one-pot tandem reaction for pyrrole synthesis was achieved where the formation of 2*H*-azirine is promoted by the rhodium complex followed by reaction with 1,3-diketone.

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