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Synthesis of Unsymmetrical Pyrazines Based on α-Diazo Oxime Ethers

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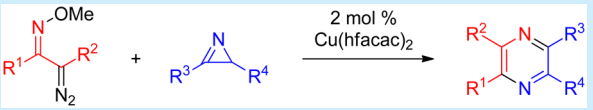
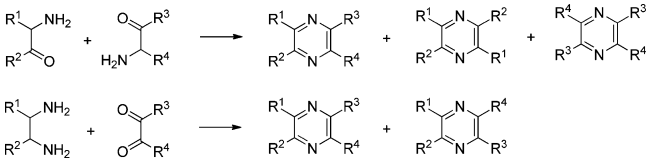
Supporting Information

ABSTRACT: Synthesis of unsymmetrically substituted pyrazines has been a challenge. The reactivity of α-imino carbenoids derived from α-diazo oxime ethers has been exploited for pyrazine synthesis, in which the reaction of α-diazo oxime ethers with 2*H*-azirines provides highly substituted pyrazines in good to excellent yields.



Pyrazines are an important class of N-heterocycles found in diverse bioactive natural products and therapeutic agents. Examples include the potassium-sparing diuretics amiloride and triamterene, which are used in the management of hypertension and congestive heart failure. Further, pyrazine derivatives pyrazinamide and morinamide are antibacterial drugs used to treat tuberculosis. The pyrazine moiety is also found in varenicline, which stimulates nicotine receptors more weakly than nicotine, and it is used to treat people addicted to smoking.

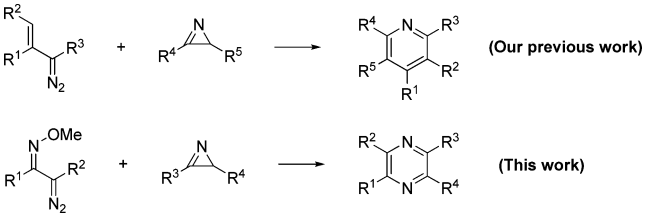
Despite their broad utility, efficient synthetic methods for pyrazines are primarily limited to symmetrical pyrazines. For example, the condensation of α-amino ketones allows an efficient synthesis for pyrazines; however, this approach gives rise to mixtures of regioisomeric pyrazines when two different α-amino ketones are employed. A similar problem is encountered when 1,2-diamines and 1,2-diketones are reacted.[1]



Likewise, dimerization of nitrile ylides derived from azirines and dehydrogenative dimerization of 1,2-amino alcohols provide symmetrical pyrazines.[2] Efforts have been made to develop a synthesis of unsymmetrical pyrazines. In the pioneering work, Buchi reported electrocyclization-based synthesis of pyrazines, although examples were limited by simple methyl- or ethyl-substituted pyrazines.[3] N−H insertion of α-amino acid-derived primary amides with α-keto carbenoids followed by cyclization to give pyrazines has been reported.[4]

An alternative approach involving substitution of pyrazine cores has also been developed.[5] Despite its harsh reaction conditions, direct lithiation allows introduction of various substitutions on pyrazine cores.[6] Halide-substituted pyrazines have been employed in palladium-catalyzed cross-coupling reactions to functionalize the cores.[7] Zirconium-mediated alkenylation of pyrazines has been reported, although substrates are limited to symmetrical disubstituted pyrazines due to regioselectivity.[8] Multistep synthesis of tetrasubstituted pyrazines has been reported by using nickel-catalyzed cross-coupling of chloropyrazines with alkyl zinc reagents followed by Friedel−Crafts acylation.[9]

Given the limitations of current methods, we were prompted to develop the synthesis of unsymmetrical pyrazines. α-Diazo oxime ethers have been demonstrated to serve as an excellent precursor for α-imino carbenoids, of which their synthetic utility has been explored in the synthesis of various N-heterocycles.[10] Among our earlier works, we have shown that activation of 2*H*-azirines by reacting with vinyl carbenoids leads to the formation of pyridines via electrocyclization of 3-azatrienes.[10d] We envisioned that this strategy could be extended to the synthesis of pyrazines by employing α-diazo oxime ethers.



Our initial efforts to realize the transformation commenced by screening different metal complexes with α-diazo oxime ether **1a** and 2*H*-azirine **2a** in 1,2-dichloroethane (DCE) at 90 °C and subsequently heating to 150 °C to ensure complete cyclization (Table 1).

Unlike the reaction of vinyl carbenoids and azirines, in which Rh-based catalysts showed superior activity while Cu catalysts were completely inactive,[10d] Rh catalysts failed to give pyrazine **4a** (Table 1, entries 1 and 2). Among the copper complexes screened, $Cu(OAc)_2$ and $Cu(acac)_2$ showed promising results

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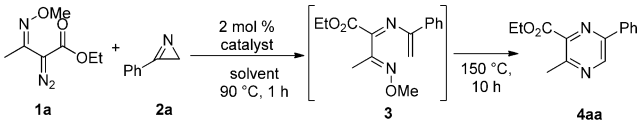
Table 1. Optimization of Pyrazine Synthesis[a]



entry	catalyst	solvent	yield[b] (%)
1	$Rh_2(OAc)_4$	DCE	
2	$Rh_2(esp)_2$	DCE	
3	$Cu(OAc)_2$	DCE	30
4	$Cu(acac)_2$	DCE	55
5	$Cu(OTf)_2$	DCE	64
6	$[Cu(OTf)]_2.PhH$	DCE	50
7	$Cu(tfacac)_2$	DCE	60
8	**$Cu(hfacac)_2$**	**DCE**	**87**
9	$Cu(hfacac)_2$	toluene	83
10	$Cu(hfacac)_2$	chlorobenzene	79

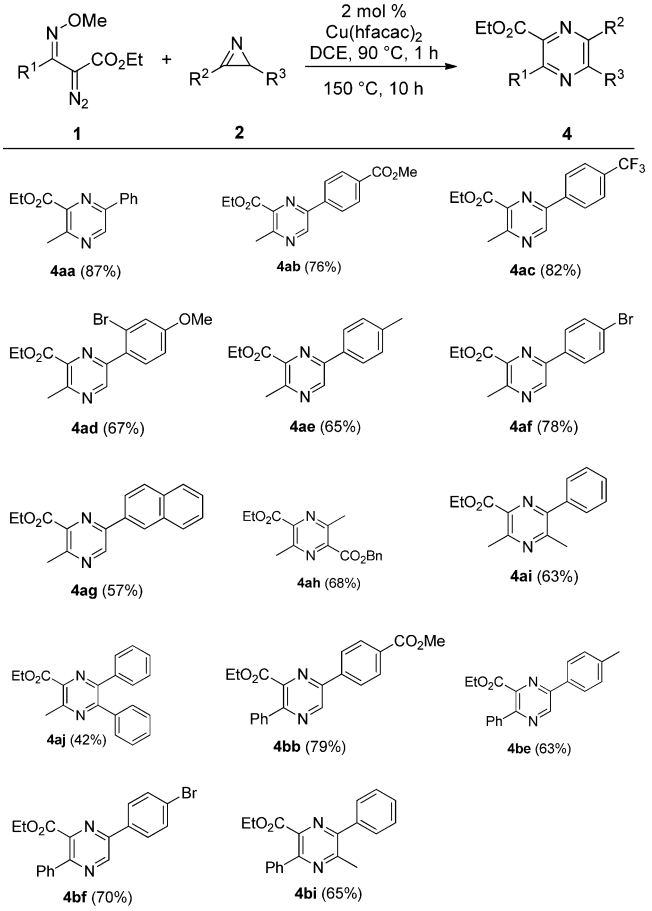
[a]Reaction conditions: **1a** (0.36 mmol), **2a** (0.3 mmol), solvent (0.15 M). [b]Isolated yields. esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate, tfacac = trifluoroacetylacetonate, hfacac = hexafluoroacetylacetonate.

providing the desired product *albeit* in low yields, 30% and 55%, respectively (Table 1, entries 3 and 4). A comparison was made between Cu(II) and Cu(I) for their efficiency, showing the superior activity of Cu(II) (Table 1, entries 5 and 6). The electronic effect of ligands was clearly observed from the series of reactions employing $Cu(OTf)_2$, $Cu(tfacac)_2$, and $Cu(hfacac)_2$; the most electron-deficient $Cu(hfacac)_2$ emerged as the catalyst of choice providing the pyrazine in 87% (Table 1, entries 5, 7, and 8). Reactions in different solvents including toluene and chlorobenzene gave comparable yields (83% and 79%, respectively, Table 1, entries 9 and 10).

With the optimized conditions in hand, we turned our attention to the substrate scope of the reaction. To assess electronic and steric influences in the formation of unsymmetrical pyrazines, we first surveyed various 2*H*-azirines by reacting with α-diazo oxime ethers **1a** and **1b** (Scheme 1). The transformation is generally well tolerated and provides the corresponding pyrazines in good yields. Electronic effect of 2*H*-azirines on the reaction was examined by substitution of the phenyl group of 2*H*-azirine **2a**, revealing broad tolerance for both electron-donating and -withdrawing groups (**4ab**–**ad**). The reaction with 2*H*-azirine **2d** bearing *ortho*-substitution also smoothly proceeded to give **4ad** indicating marginal steric influence. The feasibility of access to fully substituted pyrazines was examined by employing disubstituted 2*H*-azirine **2h**. Gratifyingly, pseudosymmetric tetrasubstituted pyrazine **4ah** was obtained in 68% yield, which may serve as a useful intermediate allowing for selective derivatization of the ester groups. Additional 2*H*-azirines were examined for the introduction of different types of substituents. While the reaction of 2-alkyl substituted 2*H*-azirine **2i** provided the corresponding pyrazine **4ai** in good yield, that of 2-phenyl-2*H*-azirine **2j** was sluggish to give **4aj** in 42% yield, presumably due to steric hindrance between the two phenyl groups. Consistent with the broad tolerability of the reaction with diazo compound **1a**, **1b** bearing phenyl substitution also efficiently participated in the reaction providing the corresponding pyrazines in good yields (**4bb**–**bi**).

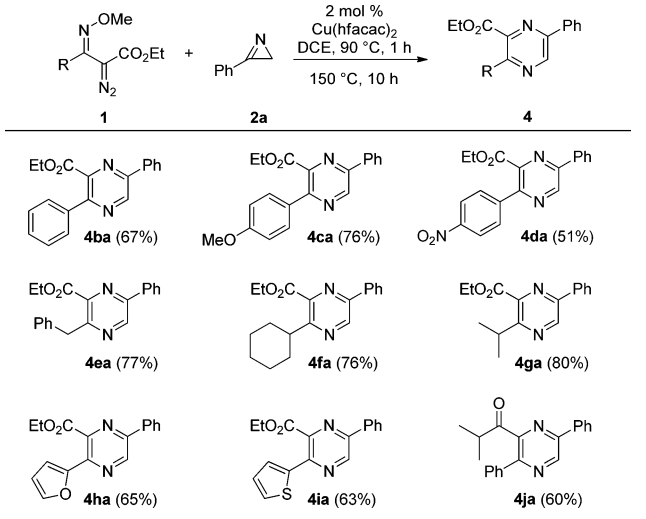
Encouraged by these results, we further explored the substrate scope by employing α-diazo oxime ethers with various substituents of electronic and steric characteristics (Scheme 2).

Scheme 1. Scope of 2*H*-Azirines for Pyrazine Synthesis[a]



[a]Reaction conditions: **1** (0.36 mmol), **2** (0.3 mmol), DCE (0.15 M). The reported yields in parentheses are of the isolated products.

Scheme 2. Scope of Diazo Compounds for Pyrazine Synthesis[a]



[a]Reaction conditions: **1** (0.36 mmol), **2a** (0.3 mmol), DCE (0.15 M). The reported yields in parentheses are of the isolated products.

The electronic effect examined by substituting the phenyl group of 2*H*-azirine with electron-donating and -withdrawing groups (**1b**, **1c**, and **1d**) clearly revealed the efficiency of the reaction in

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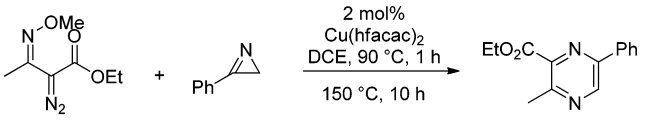
the order of 4-methoxyphenyl, phenyl, and 4-nitrophenyl (76%, 67%, and 51% for **4ca**, **4ba**, and **4da**, respectively). Both primary and secondary alkyl-substituted diazo compounds showed good conversion providing the corresponding pyrazines **4ea**, **4fa**, and **4ga** in yields of 77%, 76%, and 80%, respectively. 1,1′-Biheteroaryl derivatives are useful moieties that are frequently found in many bioactive molecules. As shown in Scheme 1, this type of pyrazines **4ha** and **4ia** could be readily synthesized in 65% and 63% yields. In addition to ester groups, keto-substituted pyrazines could be synthesized by employing the corresponding α-diazo oxime ethers (**4ja**, 60%).

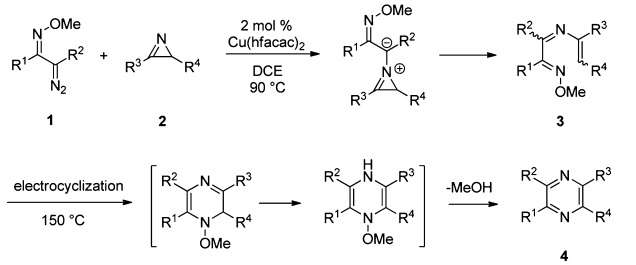
In order to check the feasibility of the pyrazine synthesis in a preparative scale, we performed the reaction in a gram scale. Gratifyingly, it proceeded smoothly to give the corresponding pyrazine in 72% yield under the optimized conditions.



1a 12 mmol 2.22g | **2a** 10 mmol 1.17g | **4aa** 72% 1.73g

Mechanistically, the reaction initiated by the metal carbene complex derived from diazo compound **1** reacting with azirine **2** leads to the formation of ylide, which isomerizes to 1,4-diazahexatriene **3** (Scheme 3). Subsequently, 1,2-dihydropyrazine formed via electrocyclization of **3** rapidly isomerizes to 1,4-dihydropyrazine, and spontaneous elimination of MeOH provides pyrazine **4**. This mechanistic pathway is consistent with the observed regiochemistry of pyrazines.

Scheme 3. Proposed Reaction Mechanism



In summary, we have developed a novel synthesis of unsymmetrical pyrazines via the reaction of α-diazo oxime ethers with 2*H*-azirines via electrocyclization of 1,4-diazahexatrienes. This method proves sufficiently general to provide various unsymmetrically substituted pyrazines.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and characterization data. 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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