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Alkylations and Hydroxymethylations of Pyrazines via Green Minisci-Type Reactions

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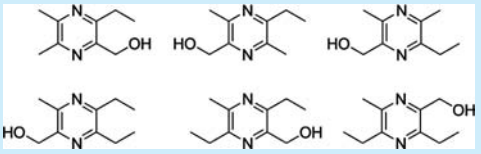
Supporting Information

ABSTRACT: A new general methodology utilizing Minisci-type chemistry has been developed that cleanly and efficiently prepares alkyl- and (hydroxymethyl)pyrazines. The new methods eliminate toxic catalysts and halogenated solvents, providing a greatly improved route to these natural products which are prevalent in many natural systems as bacterial volatiles, plant volatiles, and insect pheromones.



Pyrazine natural products are well-known for their involvement in chemical communication in several biological systems, most commonly in insects.[1−12] Furthermore, many pyrazine-derived compounds are used in the food industry as flavoring agents, and these compounds are formed naturally from amino acids in Maillard reactions as food is heated.[13−19] Pyrazines have also been found in bacterial odors,[20−22] and recently an increasing number of more complex derivatives have been discovered as products from microorganism reactions.[23−31]

We have recently identified several alkylated and hydroxymethylated pyrazines as semiochemicals involved in the pollination of sexually deceptive orchids and as wasp sexual pheromones.[32,33] Sexually deceptive orchids employ mimicry of the sex pheromones of female insects to lure sexually excited males as pollinators.[34,35] One of the most sophisticated of all sexually deceptive systems is that of the Western Australian hammer orchids *Drakaea* (Orchidaceae), which mimic both the chemistry of the sexual pheromone and morphology of the flightless female thynnine wasps.[36] *Drakaea* exploit a diversity of wasp genera,[37] thus providing the opportunity to explore a range of pheromone systems.

In addition to the compounds involved in the attraction of sexually deceived *Zaspilothynnus* and *Catocheilus* wasps (Thynnidae) to *Drakaea livida*,[32,33] we have further investigated seven more species of *Drakaea*. In all of these systems, tri- or tetrasubstituted pyrazinylmethanols were identified and confirmed to be biologically active. In *D. glyptodon*, pollinated by *Z. trilobatus*, we have very recently identified the wasp sexual pheromone blend and orchid semiochemicals, confirming a novel hydroxymethylpyrazine to be a key component of both.[38] Owing to the small quantity of sample available in the natural extracts (~1−10 ng/flower and wasp),[33] further identification of the physiologically active compounds relied solely on GC−MS analysis. Utilizing the softer ionization technique available through chemical ionization (CI−MS) allowed confident assignment of the quasimolecular ions. Careful analysis of lower m/z fragments clearly indicated a pyrazine skeleton, and further analyses of the mass spectra suggested which substituents were present. The fragmentation-based hypothesis was further supported by microderivatization experiments. However, without the benefit of techniques such as NMR and IR, the substitution pattern around the ring and exact distribution of the atoms were unclear. In practice, this resulted in the need to prepare a series of (hydroxymethyl)-diethylmethylpyrazines and (hydroxymethylethyl)dimethylpyrazines to allow unambiguous identification of the natural products.

Existing methods for synthesis of substituted pyrazines normally involve Negishi or Kumada chemistry, where palladium, zinc, magnesium, and nickel reagents and/or catalysts are required and chlorinated solvents are used.[39−42] These reactions are reliable for the preparation of most compounds; however, apart from the toxicity of reagents and solvents employed and/or the demanding reaction conditions, the strategy generally involves multiple steps generating the products in low overall yields. There are also cases where these methods are not applicable, for example where the required chloropyrazine intermediate is difficult to prepare.[43] Other methods involve condensation of amino acids or their derivatives, which are labor-intensive and low-yielding reactions[44] and alkylations under harsh reaction conditions.[45]

Of interest to us were examples in the literature where Minisci-type chemistry had been used for C−H functionalization of heteroaromatic bases. These reactions proceed via a postulated radical addition process under aqueous acidic conditions, without the need for toxic catalysts.[46−50] By utilizing Minisci alkylations and hydroxymethylations, all six products **7**−**9** and **20**−**22** could be readily prepared in two to four steps from the commercially available dimethylpyrazines **1**−**3** without the use of toxic reagents or catalysts (Scheme 1).

The three (hydroxymethyl)ethyldimethylpyrazines **7**−**9** were prepared in two steps in 15−27% total yields (29−48% based

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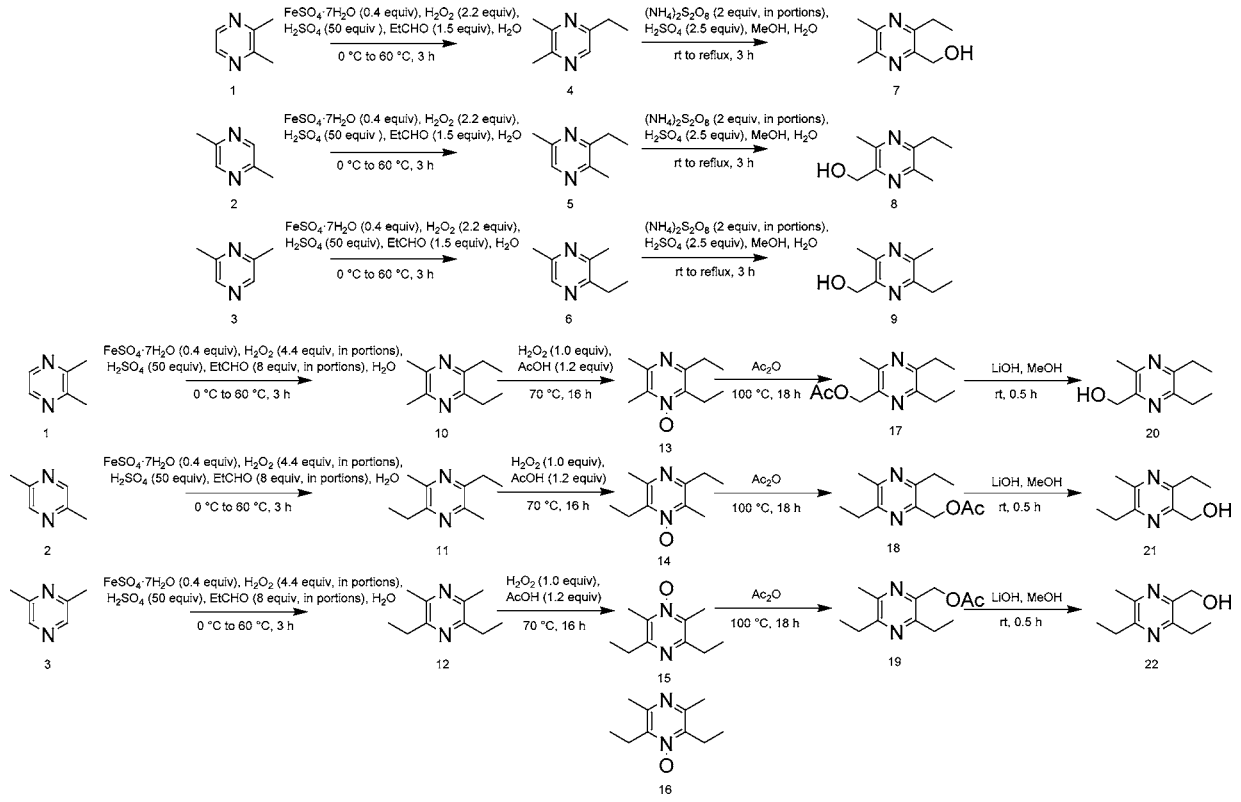
Scheme 1. Synthetic Route to New (Hydroxymethyl)trialkylpyrazines



on recovered starting materials) from the corresponding dimethylpyrazines **1**–**3**. Ethylation was achieved by an Fe-catalyzed Minisci reaction with propanal in water at rt. By adjusting the pyrazine/aldehyde ratio, temperature, and reaction time, the selectivity for the monoethylated product over the diethylated was over 80%. Compounds **4**–**6** were hydroxymethylated, utilizing modified Minisci conditions, to give the (hydroxymethyl)ethyldimethylpyrazines **7**–**9** in 38–59% yields.

In order to obtain the (hydroxymethyl)diethylmethylpyrazines **20**–**22**, a similar strategy was applied. The same starting material was used, but the reaction conditions for the Minisci alkylation were modified to optimize the yields of diethylated products. By using an 8-fold excess of propanal the reaction proceeded to complete alkylation affording the tetrasubstituted pyrazines. The diethyldimethylpyrazines **10**–**12** were *N*-oxidized to the intermediates **13**–**16**, which were hydroxymethylated using a Boekelheide rearrangement[39] via the intermediate acetate esters **17**–**19**, which were saponified to yield the desired products **20**–**22** in 26–43% total yields over four steps.

The optimization of the Minisci alkylations was simply to show that these reactions are general. For our purpose of preparing the target compounds, we used conditions for a less specific ethylation of **1**–**3**, yielding mixtures of **4**–**6** and **10**–**12**, which were easily separated by column chromatography (see the Supporting Information), streamlining the preparation.

On a side note, when the hydroxymethylation was attempted directly on dimethylpyrazines **1**–**3**, the desired products were obtained in decreased yields with *N*-oxidation occurring, indicating the preference of a trialkylated substrate for hydroxymethylation to take place in this system. We have successfully alkylated dimethylpyrazines using longer and branched chain aldehydes such as *n*-pentanal and isopentanal (unpublished data). In summary, we have developed a clean and reliable approach to prepare substituted pyrazines that avoids the use of toxic metals and chlorinated solvents. With the prevalence of pyrazines as flavoring agents in foods,[51] bacterial volatiles,[30,52] and their growing recognition as insect semiochemicals[2,3,9,32,33,53−55] we believe our methods constitute a significant improvement to the current methods used to prepare these increasingly important compounds.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, mass spectra, and ^{1}H and ^{13}C NMR spectra of final products. 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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