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Synthesis of substituted pyrazines from *N*-allyl malonamides†

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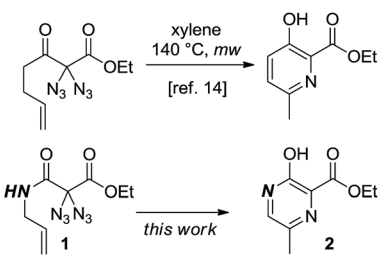
The synthesis of pyrazines is described using a sequence that begins with the diazidation of *N*-allyl malonamides followed by thermal or copper-mediated cyclization. The pyrazine products possess an ester and a hydroxy group at 2- and 3-positions of the heterocyclic core, while alkyl- and aryl groups may be introduced at the other positions. We also show how to modify the pyrazines obtained with our method; examples regarding alkylations, side-chain brominations, hydrogenations and cross-couplings are presented.

Amongst the countless classes of nitrogen-containing heterocycles, pyrazines[1] are distinguished from their kin by the ease of how to access the symmetrical members. For example, the self-condensation of α-amino ketones easily provides symmetrical pyrazines in an efficient way.[2] However, this approach provides mixtures of pyrazines when two different α-amino ketones are used.[3] The condensation of 1,2-diamines with 1,2-diketones (followed by dehydrogenation) is another typical method for the preparation of the pyrazine core that has severe limitations with respect to the regiospecifity.[4] In addition to these classical methods, a broad range of alternative methods were developed with the goal of addressing as many substituents as possible.[5] Pyrazines were synthesized starting from α-hydroxy ketones,[6] α-halo ketones,[7] nitro epoxides,[8] and 2*H*-azirines.[9] The pyrazine core was modified through lithiation;[10] halogenated pyrazines were submitted to palladium-catalyzed cross-coupling reactions.[11] A surprisingly small number of reports describe the synthesis of the pyrazine core through cyclization strategies, including electrocyclizations and cyclocondensations.[12]

As part of our ongoing studies to unveil the reactivity of geminal diazido compounds,[13] we recently showed that 2,2-diazido-3-oxohept-6-enoates gave 3-hydroxypyridines upon thermolysis (Scheme 1).[14] We then questioned whether, starting with diazido compounds **1** derived from *N*-allyl malonamides, pyrazines **2** may become accessible in a fully analogous way. The challenging and densely substituted pyrazine core of **2** shows potential to produce several variants through further heterocycle modifying endeavors.

Earlier studies demonstrated how nitrogen-containing heterocycles can be synthesized from precursor compounds possessing the geminal diazido moiety.[15] To our knowledge, this is the first study to successfully convert diazidated *N*-allyl malonamides into pyrazines through simple thermolysis. We began this study with the synthesis of the diazides **1** as summarized in Scheme 2. To this end, the malonic acid monoethylester **3** was submitted to standard amide-forming conditions using the respective allylic amine **4**, HOBT and EDC at room temperature in dichloromethane. The subsequent diazidation of the *N*-allyl malonamides **5** was achieved with iodine and sodium azide in aqueous DMSO at room temperature, a method we recently developed as a general entry toward diazides derived from 1,3-dicarbonyl compounds.[16] This two-step sequence provided an easy and rapid access to a range of diazidated *N*-allyl malonamides **(1a–1e)**. **Caution!** *Diazidated compounds are potentially hazardous and should be handled with care. Although we never encountered any problems, we advise the use of protective gear, in particular for scales > 1 mmol.*

To our delight, conventional heating of geminal diazide **1a** (R = H, R′ = H) in xylene gave the desired pyrazine core. Moderate yields were obtained when the reaction was carried out in xylene at 140 °C with a concentration of 0.05 mol L^{-1} affording the product **2a** in 43%. Unfortunately, our search for better reaction conditions was mainly fruitless: other solvents and temperatures led to markedly reduced yields. A range of



Scheme 1 Formation of heterocycles through the thermolysis of geminal diazides.

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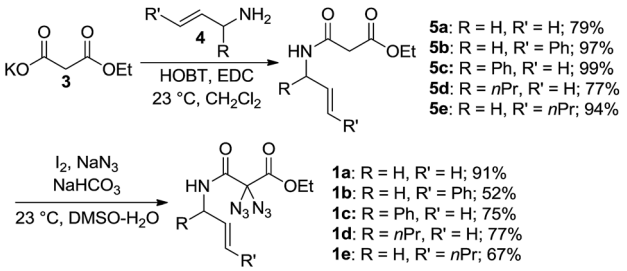


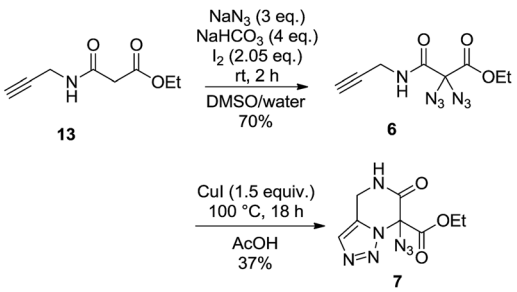
Scheme 2 Synthesis of gem-diazido *N*-allyl malonamides.

transition metal complex additives had simply no effect on the pyrazine formation; in a few cases (*e.g.*, with iron and palladium salts) pyrazine products were not even detected, despite complete consumption of the diazides. The use of stoichiometric amounts of copper(I)iodide in acetic acid at 120 °C, on the other hand, led to a substantial increase in yield, and the pyrazine **2a** was obtained in 68% yield in a fully reproducible manner. Although these conditions appeared somewhat unusual in terms of stochiometry and solvent, they typically gave better yields for pyrazine formation, in direct comparison to the simple heating in xylene, while the number of unidentified by-products was reduced.

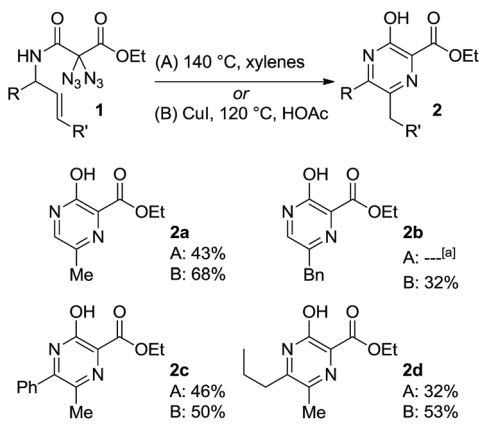
As summarized in Scheme 3, several diazidated amides **1** were successfully converted into the pyrazines **2** by relying on either the pure heating in xylene (A) or the copper-mediated version in acetic acid (B). Besides the parent structure **2a** with a methyl group at 6-position (R = H, R′ = H), the method also allowed for the construction of pyrazines having other substituents at 6-position (*e.g.*, **2b** with R′ = Ph). It was also possible to introduce additional substituents at 5-position as exemplified through the formation of **2c** (R = Ph) and **2d** (R = *n*Pr).

We point out that 3-hydroxy-2-pyrazinecarboxylic acid derivatives 2 are, in priciple, capable of prototropic tautomerism. The IR spectra of the neat compounds measured with ATR probes actually suggest the existence of the tautomeric 3-oxo-3,4-dihydropyrazine form since the spectra typically show IR signals for two independent carbonyl groups. On the other hand, NMR data in $CDCl_3$-solution appear to provide evidence for the aromatic pyrazine system: as exemplified with compound **2a**, the chemical shifts of −42.0 ppm for N-1 and −85.4 ppm for N-4 (approximated from 1H-15N-HMBC correlations) indicate the pyrazine core. This view is further supported by the downfield shift for H-5 (8.29 ppm, ^{1}H NMR spectrum). Although NMR data on derivatives of pyrazinecarboxylic acid are rare,[17] a recent study by Holzer, Eller and co-workers[18] on 3-amino-2-pyrazinecarboxylic acid and 3,4-dihydro-3-oxo-2-pyrazinecarboxylic acid confirms our structural assignment and suggests that we have an unusual case where the 3-hydroxy-2-pyrazinecarboxylic acid core is existent in solution, rather than its more common 3-oxo-3,4-dihydropyrazine tautomer.

Our rationale for the reaction is analogous to what we proposed for the formation of 3-hydroxypyridines through the thermolysis of diazides:[14] the reaction starts with an intramolecular 1,3-dipolar cycloaddition between one azide moiety and the olefin to provide a triazoline intermediate. After loss of elemental nitrogen and a 1,2-hydride shift, elimination of hydrazoic acid may lead to the heterocyclic product (Scheme 4). As shown in eqn (1), the reaction of diazide **6** having an alkyne moiety led to the bicyclic compound **7** where the triazole substructure remained stable, and the hydrazoic acid was still attached. This structural assignment was supported by NMR, HRMS and IR data, including the characteristic IR band at 2133 cm^{-1}.

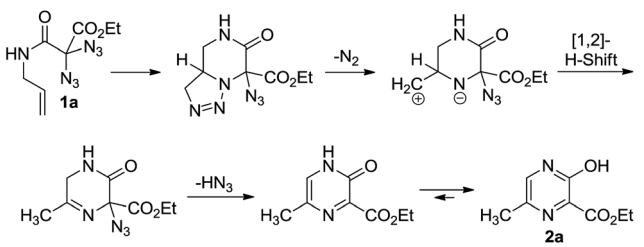


(1)

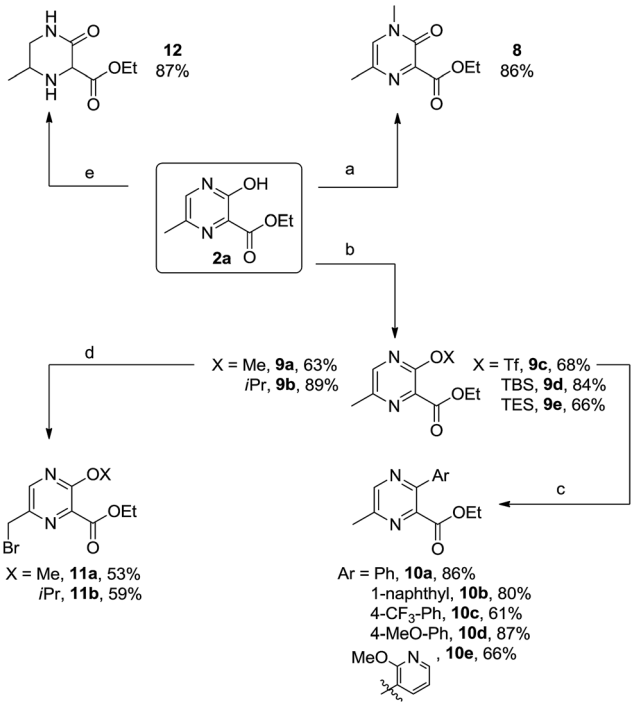


Scheme 3 Synthesis of pyrazines **2**. [a] = mixture of inseperable compounds.

Due to the great importance of flexibility and diversity in the application of this method, the direct modification of the 3-hydroxypyrazine **2a** was then investigated as summarized in Scheme 5. We showed that it is easily possible to modify the parent structure **2a** in various ways: for example, the nitrogen was selectively methylated with methyl iodide and cesium carbonate in acetonitrile at room temperature, leading to the



Scheme 4 Possible mechanism for the formation of pyrazine **2a**.



Scheme 5 Derivatization of the pyrazine **2a**. Reaction conditions: (a) MeI (1.2 eq.), Cs_2CO_3 (1.2 eq.), MeCN, 25 °C; (b) **9a**, **9b**: MeI (2 eq.) or iPrI (2 eq.), Ag_2CO_3 (1.2 eq.), *n*-hexane/benzene, 90 °C; **9c**: Tf_2O (1.3 eq.), NEt_3 (3 eq.), DCM; −20 °C to 0 °C, 100 min; **9d**: TBSCl (3 eq.), imidazole (3 eq.), pyridine, 25 °C; **9e**: TESOTf (3 eq.), 2,6-lutidine (3 eq.), DCM, 25 °C; (c) Ar–$B(OH)_2$ (1.5 eq.), Cs_2CO_3 (3 eq.), $Pd(PPh_3)_4$ (5 mol%), dioxane/water, 85 °C; (d) AIBN (10 mol%), NBS (1 eq.), CCl_4, 75 °C; (e) H_2 (30 bar), Rh/Al_2O_3 (10 mol%), EtOH, 25 °C.

N-methylated dihydro pyrazinone **8** (path a). On the other hand, the alkylation of the hydroxy oxygen was achieved through the use of silver carbonate giving the ethers **9a** (with X = Me) and **9b** (with X = iPr) (path b). High yields were also obtained for the silylation (*e.g.*, formation of **9d** and **9e**), and the triflate **9c** was formed with triflic anhydride under standard conditions (path b). The latter compound became an ideal starting point for further diversifications with classical palladium-catalyzed cross coupling methodologies. For example, Suzuki coupling of **9c** with various boronic acids provided a range of interesting structures **10a–e** featuring the densely functionalized pyrazine core (path c). With pyrazines not possessing a free hydroxyl, a further functionalization of the methyl group at 6-position was possible through radical bromination under Wohl–Ziegler conditions; for example, the brominated pyrazines **11a** and **11b** were formed in moderate yields. The hydrogenation of the aromatic core was achieved using rhodium on alumina in ethanol at 30 bar of hydrogen. The oxo-piperazine **12** was isolated as a mixture of diastereomers in 87% yield. Unfortunately, we were not able to install halogen atoms at the 5-position of the existing pyrazine core **9a**; all attempts using metalation or electrophilic substitution protocols failed, at least in our hands.

Conclusions

In summary, we have introduced a new and simple method for the synthesis of densely substituted pyrazines **2**. Starting from *N*-allyl malonamides, the title compounds are accessible through a two-step sequence consisting of diazidation and subsequent thermolysis. We have also shown how the parent pyrazine structure **2** can be further modified at almost every position, in a simple and straightforward manner, thus rendering the pyrazines **2** highly valuable as building blocks for the synthesis of naturally occurring and pharmaceutically active compounds.

Experimental

General procedure for the synthesis of gem-diazido *N*-allyl malonamides 1

N-Allyl malonamides **5** (1 eq.) were dissolved in DMSO/water (2/1) (0.1 M), and NaN_3 (4 eq.) and $NaHCO_3$ (3 eq.) were added under heavy stirring. The suspension was cooled to 0 °C, and iodine (2.05 eq.) was slowly added. The reaction maintained at this temperature for 10 min before warming to room temperature. The mixture was stirred at room temperature until complete consumption of the starting material (monitored *via* TLC) (~2 h). The reaction mixture was quenched with aqueous saturated solution of $Na_2S_2O_3$ until complete discoloration appeared. The mixture was extracted with EtOAc, and the combined organic phases were washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding gem-diazido *N*-allyl malonamides **1**.

Caution! Diazidated compounds are potentially hazardous. We advise the use of protective gear, in particular for scales > 1 mmol.

General procedure for the synthesis of pyrazines 2

A: The reaction was carried out under argon atmosphere. Gem-diazido *N*-allyl malonamide **1** (1 eq.) was dissolved in xylenes (0.05 M) and stirred at 140 °C for 24 h. The reaction mixture was cooled to room temperature and the solvent was evaporated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding pyrazines **2**.

B: The reaction was carried out under argon atmosphere. Gem-diazido *N*-allyl malonamide **1** (1 eq.) was dissolved in glacial acetic acid (0.05 M). Copper(I)iodide (1.5 eq.) was added, and the reaction was stirred at 120 °C for 24 h. The reaction mixture was cooled to room temperature and filtered through a short pad of celite. The filtrate was evaporated under reduced pressure. Purification by flash-chromatography on silica gel furnished the corresponding pyrazines **2**.

Conflicts of interest

There are no conflicts to declare.

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