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Synthesis of tetrasubstituted pyrazines and pyrazine *N*-oxides

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ABSTRACT

An efficient synthesis of tetrasubstituted unsymmetrical pyrazines and their related pyrazine *N*-oxides has been developed from commercially available 2-chloro-3-methylpyrazine. The procedure and scope of these synthesis routes are described.

Pyrazines are important pharmacophores present in an array of biologically active compounds such as the antimycobacterial agent pyrazinecarboxamide, the antibacterial agents Sulfaclozine and Sulfalene, the antidiabetic agent Glipizide, and the hypnotic/sedative agent Zopiclone.[1] The most commonly utilized method for the synthesis of pyrazines is the condensation of α-diketones with 1,2-diamines or α-aminoketones followed by oxidation.[1,2] This synthetic methodology has broad applicability for the preparation of symmetrical pyrazines ($R_1 = R_3$ and $R_2 = R_4$, Fig. 1). However, this method has not found widespread applicability for the preparation of unsymmetrical pyrazines due to issues associated with regioselectivity. Recently several methods have been reported for the synthesis of unsymmetrical pyrazines[3] from various starting materials such as epoxides,[3b] azirines,[3c] and chloropyrazines.[3d] To the best of our knowledge, no efficient synthetic methods have been disclosed for the synthesis of unsymmetrical pyrazines with four different substituents ($R_1 \neq R_2 \neq R_3 \neq R_4$, alkyl, or aryl, Fig. 1). During the course of our investigations to identify small molecule antagonists of the calcium receptor, we became interested in preparing and evaluating the biological effects of a series of unsymmetrical pyrazines and pyrazine *N*-oxides such as **I** and **II** as isosteric analogs of a previously identified class of pyrimidinone antagonists generically represented in structure **III**.[4] Herein we report our work on the regioselective preparation of tetrasubstituted, unsymmetrical pyrazines **I** as well as pyrazine *N*-oxides **II** ($R_1 = R_3$ = aryls and $R_2 = R_4$ = alkyls) as mimetics of the pyrimidonone scaffold **III** (Fig. 1).

As outlined in Scheme 1, commercially available 2-chloro-3-methylpyrazine **1**[5a] was used as the starting material for our synthesis to prepare the key intermediates disubstituted pyrazine 1-oxides **4a** and **4b**. Palladium-catalyzed cross-coupling of 2-chloro-3-methylpyrazine **1** with arylboronic acids such as (5-methyl-2-thienyl)boronic acid and phenylboronic acid in the presence of Pd(P-*t*-Bu_3)$_4$ (5 mol %) provided the disubstituted pyrazines **2a** and **2b** in moderate yield (53% and 54%, respectively). Oxidation of **2a** and **2b** using *m*-CPBA in CH_2Cl_2 at room temperature provided the disubstituted pyrazine 1-oxides **4a** and **4b** (73% and 78% yield, respectively). Interestingly, the formation of either the regioisomeric *N*-oxide or the *N,N′*-dioxide (not shown) was not observed in these transformations. The regioselectivity of oxidation to **4a** and **4b** was also confirmed by the oxidation[5b] of **1** to **3** (95% yield) directly followed by a subsequent palladium-catalyzed

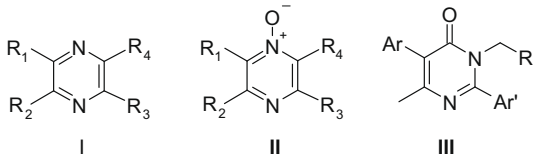
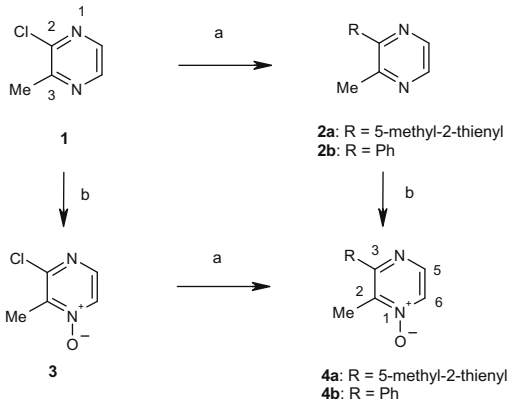


Figure 1. Tetrasubstituted pyrazines and pyrazine *N*-oxides, and pyrimidinones.



Scheme 1. Reagents and conditions: (a) $RB(OH)_2$, Pd(P-*t*-Bu_3)$_4$, Na_2CO_3, toluene–EtOH–H_2O (100:1:1), reflux, 5 h; (b) *m*-CPBA, CH_2Cl_2, rt.

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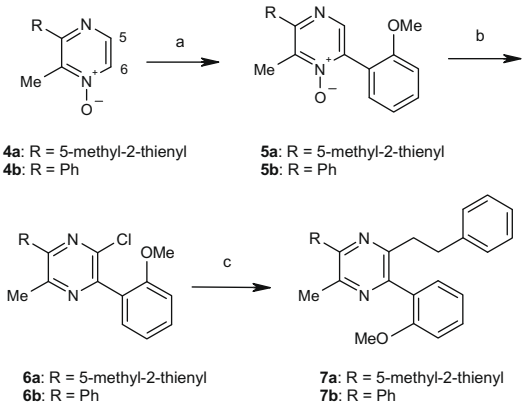


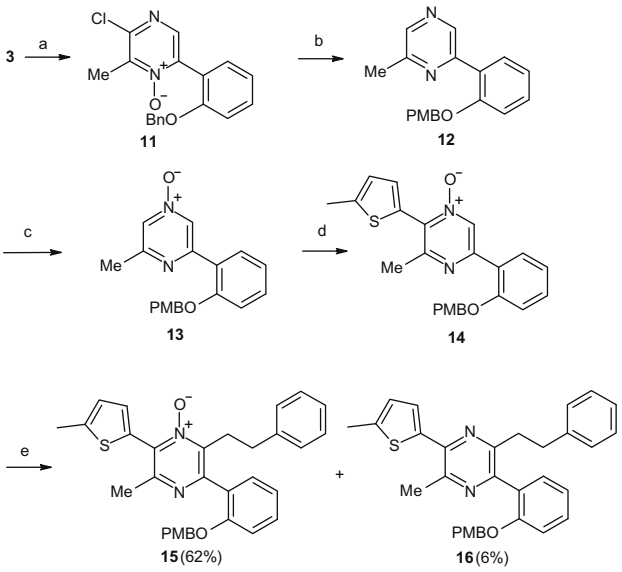
Scheme 2. Reagents and conditions: (a) 1-bromo-2-(methyloxy)benzene, $Pd(OAc)_2$, K_2CO_3, P-*t*-Bu_2Me–HBF_4, toluene, 110 °C, 16 h; (b) $POCl_3$, 110 °C, 30 min; (c) $PhCH_2CH_2ZnBr$, PEPPSI-IPr, THF/DMI, LiBr, microwave, 100 °C, 10 min.

cross-coupling reaction to provide analogs **4a** (an unoptimized yield of 49%) and **4b**.

The regioselective introduction of the *N*-oxide of **4a** and **4b** was instrumental for the subsequent incorporation of the C6 aryl as well as the C5 phenethyl substituents (Scheme 2). Utilizing the procedure originally described by Fagnou and co-workers for the direct arylation of pyridine *N*-oxides,[6] the *N*-oxide moiety of the pyrazine 1-oxide **4a** facilitated regioselective arylation with 1-bromo-2-(methyloxy)benzene to provide the trisubstituted pyrazine 1-oxide **5a** in 64% yield[7,8] followed by a conversion to 5-chloropyrazine **6a** using $POCl_3$ at 110 °C in 88% yield. Cross-coupling of 5-chloropyrazine **6a** with phenethylzinc bromide in the presence of PEPPSI-IPr[9] under microwave conditions with heating provided the tetrasubstituted pyrazine **7a** in 68% yield.[10]

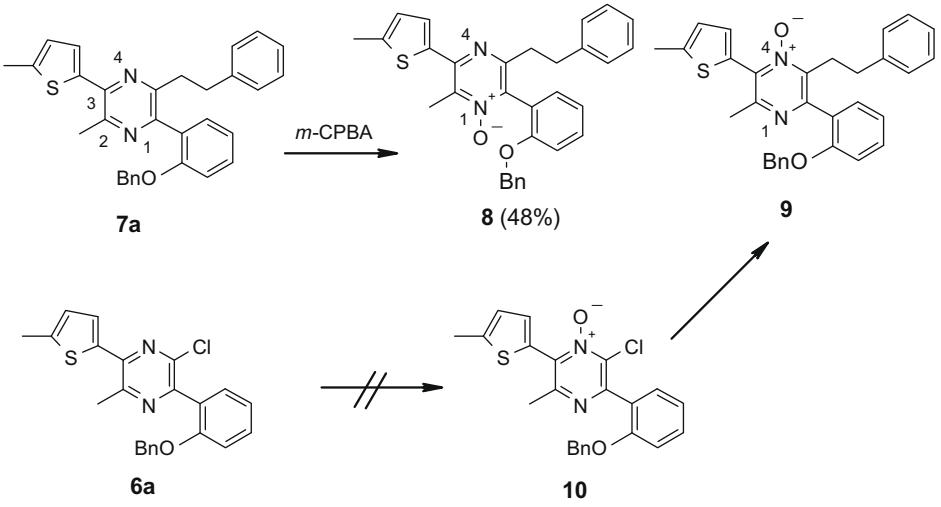
This cross-coupling reaction could be utilized with a variety of substrates to introduce various alkyl groups (sp^2–sp^3 cross-coupling reactions) as well as aryl groups (sp^2–sp^2 cross-coupling reactions). The 2-phenylpyrazine **7b** was obtained from **4b** using the reaction conditions described above in similar yields (33% for 3 steps). In addition, Pd-catalyzed cross-coupling conditions such as those detailed by Suzuki, Stille, and Negishi could also be incorporated into this synthesis sequence.

To obtain the desired tetrasubstituted pyrazine 4-oxide **9**, a direct oxidation of the tetrasubstituted pyrazine analog **7a** was attempted as outlined in Scheme 3. Unfortunately, oxidation of **7a** with 1.7 equiv of *m*-CPBA in CH_2Cl_2 at room temperature gave the undesired tetrasubstituted pyrazine 1-oxide **8** as a major product (48%, isolated yield).[11] Other oxidation conditions such as urea/hydrogen peroxide and hydrogen peroxide with $MeReO_3$ did not provide the desired product **9** in any substantial quantity. Alternatively, the oxidation of 5-chloropyrazine **6a** with $K_2S_2O_8$ and H_2SO_4 to give the 4-oxide **10** also met with limited success.[12]



Scheme 4. Reagents, conditions, and yields: (a) 1-bromo-2-[(phenylmethyl)oxy]benzene, $Pd(OAc)_2$, K_2CO_3, P-*t*-Bu_2Me–HBF_4, toluene, 110 °C, 16 h, 63%; (b) (i) Pd/C, HCO_2NH_4, MeOH, 50 °C, 16 h, 82%; (ii) PMBCl, *n*-Bu_4NI, K_2CO_3, DMF, rt, 16 h, 81%; (c) *m*-CPBA, CH_2Cl_2, rt, 2 h, 77%; (d) 2-bromo-5-methylthiophene, $Pd(OAc)_2$, K_2CO_3, P-*t*-Bu_2Me–HBF_4, toluene, 110 °C, 16 h, 70%; (e) $PhCH_2CH_2MgBr$, −30 °C, THF, 2 h, then O_2, 1 h.

In order to address the vexing undesired regioselective oxidation of pyrazine **7a,** we developed an efficient synthetic route to obtain the tetrasubstituted pyrazine 4-oxide **15** as shown in Scheme 4. Palladium-catalyzed cross coupling of 3-chloropyrazine 1-oxide **3** with *o*-benzyloxy-phenyl bromide provided intermediate **11** in 63% yield. Reduction of **11** with ammonium acetate and Pd/C followed by reprotection of phenol using *p*-methoxybenzyl chloride provided the 1,5-disubstituted pyrazine **12**. Oxidation of



Scheme 3. Oxidation of tetrasubstituted pyrazines.

12 using *m*-CPBA provided 1,5-disubstituted pyrazine 4-oxide **13** (77%) as the major *N*-oxide along with the trace amount of the undesired regioisomeric *N*′-oxide (not shown, <5%). Palladium-catalyzed cross-coupling of **13** with 5-methylthienyl bromide provided the desired trisubstituted pyrazine 4-oxide **14** in 70% yield. The regioselectivity of this transformation is likely a result of the greater steric bulk of the C6 aryl moiety over that of the smaller C2 methyl group. Installation of the C5 phenethyl moiety from **14** was accomplished utilizing a direct alkylation method[13] with an excess (3 equiv) phenethyl magnesium bromide in THF at −30 °C followed by stirring with air-bubbling to provide the desired tetrasubstituted pyrazine 4-oxide **15** in 62% yield.[14] The tetrasubstituted pyrazine **16** was also obtained as a side product (6%) resulting from the elimination of magnesium hydroxide from the reaction intermediate, which was originally described in the reaction of quinoline *N*-oxides by Goto and co-workers.[13] The trisubstituted pyrazine 4-oxide **14** is also a versatile intermediate which may be utilized in sp^2–sp^2 cross-coupling reactions to further explore the preparation of additional tetrasubstituted pyrazine analogs within this template.[9,15]

In this Letter we have detailed the development of efficient synthesis routes to tetrasubstituted unsymmetrical pyrazines and pyrazine *N*-oxides which are important pharmacophores present in a variety of biologically active compounds. The methods described here could also have broader application in the synthesis of other disubstituted and trisubstituted pyrazines as outlined in Schemes 2 and 4.

Acknowledgments

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7. The preparation of **5a**: K_2CO_3 (0.87 g, 6.30 mmol), P-*t*-Bu_2Me–HBF_4 (0.16 g, 0.63 mmol), $Pd(OAc)_2$ (0.14 g, 0.63 mmol), and 2-methyl-3-(5-methyl-2-thienyl)pyrazine 1-oxide (0.65 g, 3.15 mmol) were weighed to air and placed in a 10 mL round-bottomed flask. 1-Bromo-2-(methyloxy)benzene (0.59 g, 3.15 mmol) was added under N_2 followed by the addition of toluene (2 mL). The reaction mixture was then heated to 110 °C overnight. The solution was cooled to room temperature and filtered. The filtrate was evaporated under reduced pressure and the residue was purified by flash column chromatograph to provide 0.63 g of the title product (64%); LC–MS: $[MH]^+ = 313.2$; ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.58 (s, 3H), 2.81 (s, 3H), 3.85 (s, 3H), 6.86 (d, $J = 2.4$ Hz, 1H), 7.10 (m, 2H), 7.32 (d, $J = 2.4$ Hz, 2H), 7.49 (m, 2H), 8.41 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 14.70, 15.46, 55.80, 111.34, 119.34, 120.62, 126.26, 129.04, 131.06, 131.42, 138.66, 140.01, 141.32, 144.14, 144.92, 149.54, 157.73; TLC $R_f = 0.20$ (eluent: 20% EtOAc in hexane).
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10. The preparation of **7a**: LiBr (38 mg, 0.45 mmol) and PEPPSI-IPR (10 mg, 0.015 mmol) were added to a solution of 0.5 mL of DMI (1,3-dimethyl-2-imidazolidinone) and 0.5 mL of THF. The solution was allowed to stir under N_2 until the solid was dissolved. 0.48 mL of phenethylzinc bromide (0.5 M in THF) and 2-chloro-5-methyl-3-[2-(methyloxy)phenyl]-6-(5-methyl-2-thienyl) pyrazine **6a** (50 mg, 0.15 mmol) were then added. The reaction mixture was heated under microwave at 100 °C for 10 min. The solution was diluted with CH_2Cl_2, washed with water and brine, and dried over Na_2SO_4. After filtration, the solvent was evaporated and the residue was purified by flash column chromatograph to provide 41 mg of the title product (68%); LC–MS: $[MH]^+ = 401.2$; ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.60 (s, 3H), 2.85 (s, 3H), 2.88 (br, 2H), 3.09 (br s, 2H), 3.78 (s, 3H), 6.86 (d, $J = 2.4$ Hz, 1H), 6.97 (d, $J = 7.8$ Hz, 1H), 6.99–7.22 (m, 7H), 7.44 (m, 2H). $_{13}C$ NMR ($CDCl_3$, 151 MHz), δ (ppm): 15.51, 23.99, 34.25, 35.63, 55.33, 110.72, 120.93, 125.67, 126.35, 127.49, 127.63, 128.19 (2C), 128.42 (2C), 130.02, 130.79, 141.32, 142.04, 143.18, 144.89, 145.24, 147.87, 151.76, 156.61; TLC $R_f = 0.27$ (eluent: 10% EtOAc in hexane).
11. The starting material **7a** (19%) and other further oxidized product such as dioxide (14%) and trioxide (19%) were detected by LC–MS. Yields are based on LC–MS. Dioxide and trioxide were not isolated for full characterization.
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14. The preparation of **15**: To a solution of 3-methyl-5-[2-({[4-(methyloxy)phenyl]methyl}oxy)phenyl]-2-(5-methyl-2-thienyl)pyrazine 1-oxide **14** (42 mg, 0.1 mmol) in 1.5 mL of THF at −30 °C was slowly added 0.3 mL of phenethyl magnesium bromide (0.3 mmol, 1M in THF). The reaction mixture was stirred at −30 °C for 2 h and stirred with air-bubbling for 1 h. The reaction was quenched with saturated aqueous NH_4Cl at 0 °C. The aqueous layer was extracted with EtOAc and the combined organic solution was dried over Na_2SO_4. After filtration, the solvent was evaporated and the residue was purified by flash column chromatograph to provide 36 mg of the title product (62%); LC–MS: $[MH]^+ = 523.2$; ^1H NMR ($CDCl_3$, 400 MHz), δ (ppm): 2.59 (s, 3H), 2.61 (s, 3H), 2.88 (m, 4H), 3.78 (s, 3H), 5.02 (d, $J = 2.4$ Hz, 2H), 6.80 (d, 1H), 6.82–7.22 (m, 12H), 7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 15.10, 25.17, 30.61, 31.12, 55.22, 70.35, 113.05, 113.92, 121.22, 124.40, 125.85, 125.89, 127.29, 127.78, 128.18, 128.29, 128.41, 128.43, 128.57, 128.78, 130.10, 130.49, 131.27, 137.37, 141.36, 142.04, 143.23, 144.12, 151.13, 151.69, 155.56, 159.31; TLC $R_f = 0.23$ (eluent: 30% EtOAc in hexane).
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