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# An Unusual Reaction of Benzalaminoacetals in Trifluoroacetic Acid: Facile Synthesis of 2-Benzylpyrazines

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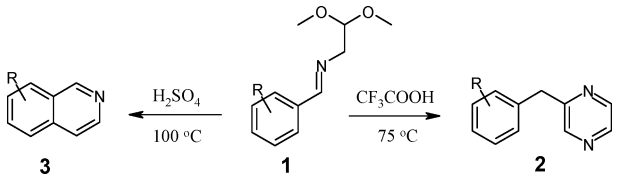
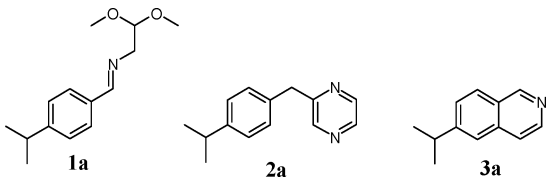



Benzalaminoacetals (**1**), upon refluxing with trifluoroacetic acid, lead to 2-benzylpyrazines, rather than the expected isoquinolines. This unusual reaction represents another useful way to prepare a variety of 2-benzylpyrazines from the corresponding benzaldehydes.

The structural diversity and biological importance of nitrogen-containing heterocycles have made them attractive targets for synthesis over many years. They are found in various natural products and have been identified as products of chemical and biological importance.[1] In the course of our studies directed toward the synthesis of nitrogen-containing heterocycles as pharmaceutical intermediates, we were in need of several isoquinoline analogues. To this end, we had occasion to explore the Pomeranz−Fritsch isoquinoline synthesis, wherein an aromatic aldehyde is condensed with aminoacetaldehyde dimethyl acetal to Schiff's base, which is further cyclized in the presence of sulfuric acid or polyphosphoric acid (PPA) to provide the isoquinoline.[2]

However, the Pomeranz−Fritsch reaction is substrate dependent. Electron-donating substituents on the substrate are found to accelerate the isoquinoline formation, while electron-withdrawing groups retard the reaction. The yields with methoxy as substituents are reported to be good, while with the nitro group, oxazoles are produced as byproduct.[3] In our hands, we found this reaction sequence to be problematic, particularly on a larger scale, due to inconsistent yields. As a measure to improve the yield, we decided to investigate the use of reagents alternative to concentrated sulfuric acid or PPA that could promote the cyclization of benzalaminoacetals using **1a** as a model compound. The reagents employed in the study included neat trifluoromethane sulfonic acid, propionic acid, acetic acid, and trifluoroacetic acid. While trifluoromethane sulfonic acid afforded unidentified tarry material, anhydrous acetic acid and propionic acid were found to be inefficient in promoting the cyclization, even at refluxing temperatures. To our surprise, when neat trifluoroacetic acid was employed as the cyclization medium, benzylpyrazine **2a** was isolated instead of the expected isoquinoline **3a**. This result drew our attention to the reaction mechanism and its application in the synthesis of substituted pyrazines.




In initial studies, we treated the Schiff's base **1a** with an excess (10 equiv) of neat trifluoroacetic acid at reflux for 25 min and obtained **2a** and 4-isopropyl benzaldehyde in equimolar quantities. Intrigued by this result, we examined the reaction under various conditions to optimize the reaction. The employment of solvent-free conditions proved to be particularly convenient; for instance, when the experiment of entry 1 (Table 1) was repeated in dichloromethane (25 mL) with an excess of $CF_3COOH$ (10 equiv) at reflux, 13 h were required for the complete conversion of **1a** as confirmed by $^1H$ NMR of the crude reaction mixture. Similarly, when toluene at reflux was employed as the reaction medium in place of dichloromethane, 11 h were required for the complete disappearance of **1a**. Under solvent-free conditions, we examined the reaction by decreasing the amount of $CF_3COOH$ in a step-by-step approach. This experimentation revealed that reducing the trifluoroacetic acid to a stoichiometric amount (4 equiv) was also effective in providing the pyrazine **2a** without any loss of yield.[4]

Next, we studied the outcome of this reaction in various acids under solvent-free conditions. A side-by-side comparison of trifluoroacetic acid, trichloroacetic acid, tribromoacetic acid, methanesulfonic acid, acetic acid, and formic acid was carried out with **1a** as a test compound. The results are depicted in Table 2. While the reaction of **1a** in anhydrous trichloroacetic acid afforded **2a** in 44% yield in 2 h, the reaction was too sluggish in anhydrous tribromoacetic acid, even at elevated temperatures. Formic acid and methane sulfonic acid failed to produce **2a**, rather providing 4-isopropylbezaldehyde due to the decomposition of **1a**. Anhydrous trifluoroacetic acid was found to be the most suitable reaction medium to yield 2-benzylpyrazines in good yields.

Apparently, the formation of pyrazine **2a** was mediated by $CF_3COOH$. With the optimal reaction conditions in hand,

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(1) Pozharskii, A. F.; Soldatenkov, A. T.; Katritzky, A. R. *Heterocycles in Life and Society;* John Wiley and Sons: Chichester, UK, 1997.

(2) (a) Pomeranz, C. *Monatsch. Chem.* **1894**, *15*, 299. (b) Fritsch, P. *Chem. Ber*. **1893**, *26*, 419. (c) Gensler, W. J. *Org. React.* **1951**, *6*, 191−206. (d) Bobbitt, J. M.; Roy, D. N.; Marchand, A.; Allen, C. W. *J. Org. Chem.* **1967**, *32*, 2225−2227.

(3) (a) Cass, W. E. *J. Am. Chem. Soc*. **1942**, *64*, 785. (b) Brown, E. V. *J. Org. Chem*. **1977**, *42*, 3208.

(4) The reaction did not proceed at room temperature even after 6 h with stirring.

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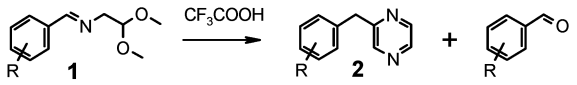
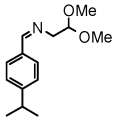
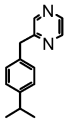
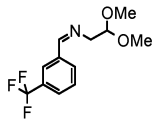
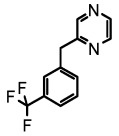
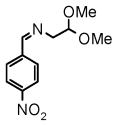
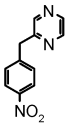
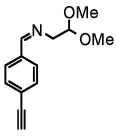
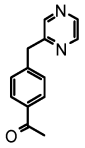
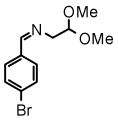
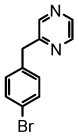
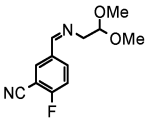
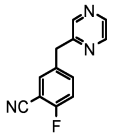
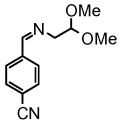
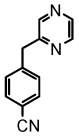
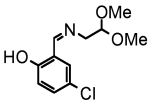
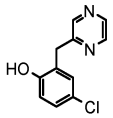
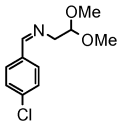
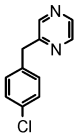
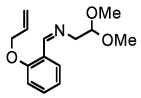
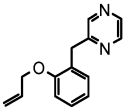
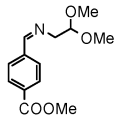
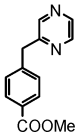
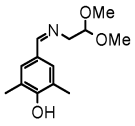
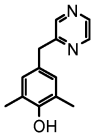
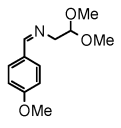
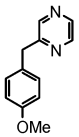
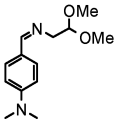
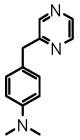
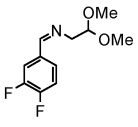
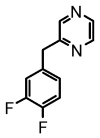
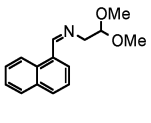
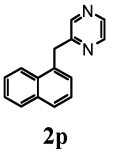
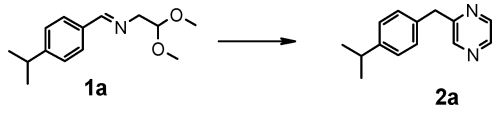
**TABLE 1. Synthesis of 2-Benzylpyrazines from Benzalaminoacetals**




| Entry | Substrate[a] | Time (min) | Product[b] | Yield (%)[c] | Entry | Substrate[a] | Time (min) | Product[b] | Yield (%)[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 |  **1a** | 25 |  **2a** | 90 | 9 |  **1i** | 30 |  **2i** | 87 |
| 2 |  **1b** | 30 |  **2b** | 87 | 10 |  **1j** | 30 |  **2j** | 81[d] |
| 3 |  **1c** | 20 |  **2c** | 85 | 11 |  **1k** | 40 |  **2k** | 86 |
| 4 |  **1d** | 25 |  **2d** | 89 | 12 |  **1l** | 25 |  **2l** | 83 |
| 5 |  **1e** | 20 |  **2e** | 86 | 13 |  **1m** | 35 |  **2m** | 88 |
| 6 |  **1f** | 35 |  **2f** | 83 | 14 |  **1n** | 30 |  **2n** | 91 |
| 7 |  **1g** | 35 |  **2g** | 91 | 15 |  **1o** | 40 |  **2o** | 86 |
| 8 |  **1h** | 40 |  **2h** | 92 | 16 |  **1p** | 25 |  **2p** | 89 |

[a] Substrates are prepared from the commercial aldehydes by refluxing with aminoacetaldehyde dimethyl acetal in toluene. [b] Isolated by column chromatography. [c] Yields are calculated relative to the theoretical yield of benzylpyrazines. [d] The acetylene group is hydrated under acidic conditions to the acetyl group.

**TABLE 2. Comparison of Efficiency of Various Acids in Promoting 1a into 2a**




| entry | solvent[a] | temp (°C) | time (h) | yield of **2a** (%) |
|---|---|---|---|---|
| 1 | $CF_3COOH$ | 75 | 0.5 | 90 |
| 2 | $CCl_3COOH$ | 75 | 2 | 44 |
| 3 | $CBr_3COOH$ | 125 | 2 | 17[b] |
| 4 | $MeSO_3H$ | 100 | 0.5 | 0[c] |
| 5 | HCOOH | 100 | 0.5 | 0[c] |
| 6 | AcOH | 100 | 3 | NR[d] |
| 7 | $H_2SO_4$ | 100 | 0.5 | 47[e] |

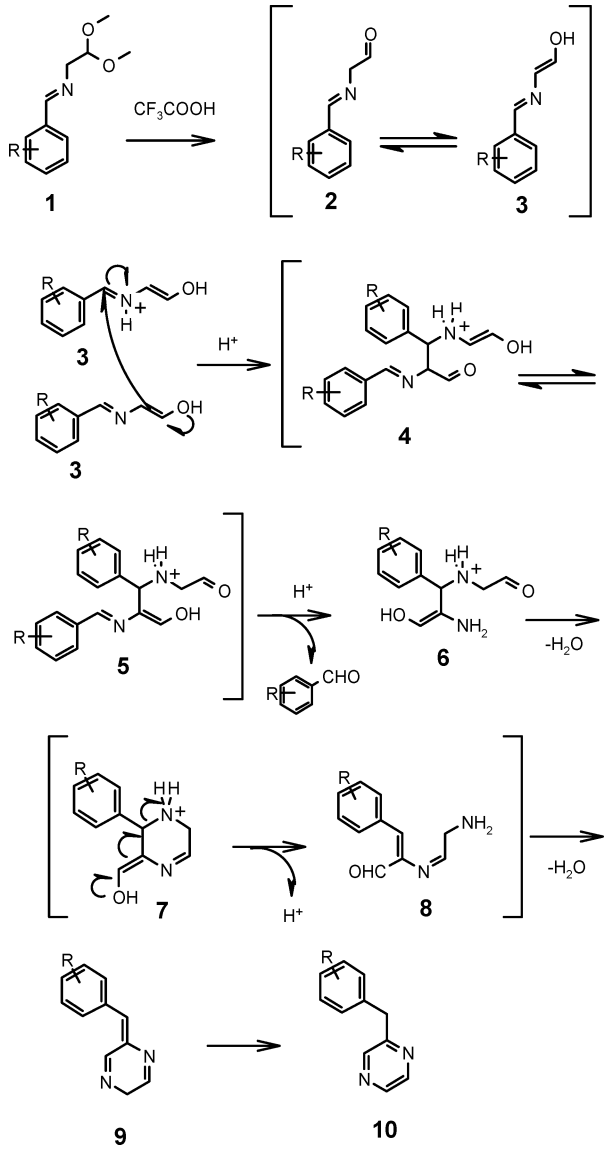
[a] Anhydrous acids (4−5 equiv) were used as solvent. [b] 4-Isopropylbenzaldehyde was the major byproduct. [c] 4-Isopropylbenzaldehyde was the only product isolated. [d] No reaction. [e] Isolated as isoquinoline **3a**.

subsequently, we investigated the scope of this reaction. Various benzalaminoacetals (**1b**−**p**) were subjected to the reaction under the standard conditions to obtain corresponding 2-benzyl pyrazines in good yields. We now wish to report that such a transformation is general in scope among the reactions we examined and the results are summarized in Table 1.

In general, the treatment of benzalaminoacetals **1** with neat trifluoroacetic acid (4−5 equiv) at reflux for 20−40 min affords 2-benzylpyrazines in good yields (Table 1), while sulfuric acid provides isoquinolines. The aldimines could be readily obtained on refluxing the corresponding aldehydes with aminoacetaldehyde dimethyl acetal in toluene under a Dean−Stark trap.[5] As illustrated in Table 1, pyrazines are formed mostly in good yields and electron-withdrawing or electron-donating groups on the substrate did not affect the yield of benzylpyrazine. From Table 1, we can discern that this reaction tolerated a wide scope of functional groups, such as alkyl, nitro, halo, cyano, carboxylate, methoxy, trifluoromethyl, hydroxy, allyloxy, and substituted amine (entry 15, Table 1), and provided the corresponding pyrazines in moderate to good yields. A substrate possessing an acetylene group on the ring (entry 10, Table 1) provided the corresponding acetophenone due to hydration of the acetylene group under acidic conditions.[6] Thus, compound **1j** afforded exclusively **2j**, along with the byproduct 4-formyl acetophenone.

As evidenced by us, the byproduct of this reaction was the corresponding aromatic aldehyde, which was found in equimolar quantities relative to the pyrazine as observed by the $^1$H NMR of the crude reaction mixture. This observation suggested that two molecules of Schiff's base were involved in the reaction to produce 1 mol of 2-benzylpyrazine and aldehyde. Consequently, a postulate for the formation of 2-benzylpyrazines is outlined in Scheme 1. The first step of the reaction is initiated by trifluoroacetic acid to produce enol **3**. Addition of the enol **3** to a second molecule of enol gives the self-condensation species **4**. The dimerization of **3** into **4** is probably acid catalyzed, where protonation of the nitrogen atom of the electrophile facilitates the nucleophilic attack. The sequential loss of a molecule of aldehyde and water provides **7**. The protonation of the NH-group in **7** will facilitate the breakdown

**SCHEME 1. Proposed Mechanism of the Reaction between Two Molecules of Schiff's Base in Trifluoroacetic Acid to Produce 2-Benzylpyrazine**




of the C−N bond with double bond rearrangement and expulsion of a proton from the OH-group to form **8**. Finally, **8** undergoes ring closure to provide 2-benzylpyrazine **10**. The formation of 2-benzylpyrazine is spontaneous and we did not find any of the postulated intermediates by LCMS or $^1$H NMR of the crude reaction mass during the progress of reaction. However, we found starting material, benzylpyrazine, and byproduct benzaldehyde by $^1$H NMR. This indicates that as soon as the acetal protection is lost, the intermediate undergoes self-dimerization to afford benzylpyrazine.

In conclusion, an unusual reaction for the synthesis of 2-benzylpyrazines from benzalaminoacetals is unveiled. This novel finding provides an interesting insight into the effect of trifluoroacetic acid on the reaction outcome and represents another useful way to prepare 2-substituted pyrazines, since the starting materials are readily available. Furthermore, substituted pyrazines are extremely useful intermediates in the pharmaceutical and food industry. Further application of this reaction for the construction of substituted pyrazines from ketones and

(5) For a general procedure, see: (a) Perchonock, C. D.; Lantos, I.; Finkelstein, J. A.; Holden, K. A. *J. Org. Chem.* **1980**, *45*, 10, 1950−1953. (b) Abramovitch, R. A.; Struble, D. L. *Tetrahedron* **1968**, *24*, 705−716.

(6) Modena, G.; Rivetti, F.; Scorrano, G.; Tonellato, U. *J. Am. Chem. Soc.* **1977**, *99*, 3392−3395.

heteroaromatic and aliphatic aldehydes is underway in our laboratory and will be reported in due course.

## Experimental Section

**General.** $^1$H NMR and $^{13}$C NMR spectra were recorded on 400-MHz and 100-MHz Bruker spectrometers, respectively. Elemental analysis was performed on a Thermo Finnigan FLASH EA 1112 CHN analyzer. Melting points were recorded (uncorrected) on a Buchi Melting Point B-545 apparatus. All the substrates (**1a**−**p**) were synthesized in-house from the corresponding commercially available aldehydes by refluxing with aminoacetaldehyde dimethyl acetal on a Dean−Stark setup with toluene as the solvent. The crude benzalaminoacetals were immediately used in the next reaction without further purification. The products were characterized by $^1$H NMR, $^{13}$C NMR, LCMS, and elemental analysis. The structure of compound **2b** was further confirmed by single-crystal X-ray analysis (see the Supporting Information).

**Representative Procedure for the Synthesis of Benzalaminoacetals from Benzaldehydes.** A mixture of 4-isopropylbenzaldehyde (10 g, 0.067 mol) and aminoacetaldehyde dimethyl acetal (7.75 g, 0.073 mol) in toluene (100 mL) was refluxed under a Dean−Stark trap with azeotropic removal of water for 4 h. The reaction was monitored by TLC (10% EtOAc/hexane). The solvent was removed under vacuum to give *N*-[(4-isopropylphenyl)-methylene]-2,2-dimethoxyethanamine[7] **1a** (15.2 g, 96%) as a yellow oil. This compound was immediately used in the next step without any further purification.

**Representative Procedure for the synthesis of 2-Benzylpyrazines from Benzalaminoacetals.** A mixture of **1a** (15.2 g, 0.064 mol) and $CF_3COOH$ (29 g, 0.254 mol) was heated to 75 °C under nitrogen atmosphere for a given period of time (entry 1, Table 1). The completion of reaction was confirmed by TLC. Upon completion of reaction, we found only two products on TLC (10% EtOAc/hexane). The polar compound corresponds to benzylpyrazine. The brown reaction mixture was concentrated under vacuum and the residue was diluted with $CH_2Cl_2$ (100 mL) and washed with a saturated solution of sodium bicarbonate (2 × 20 mL) and water (2 × 25 mL) and dried over sodium sulfate. The organic phase was evaporated under vacuum and the residue was directly loaded onto a silica gel column. Eluting with 5% ethyl acetate in hexanes afforded 6.2 g (90%) of 2-(4-isopropylbenzyl)pyrazine **2a** as a yellow oil.

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**Supporting Information Available:** $^1$H NMR and $^{13}$C NMR and LCMS report for compounds **2a**−**p**, single-crystal X-ray report (CIF and ORTEP) for compound **2b**, and $^1$H NMR for new substrates **1d**, **1h**, and **1i**−**p**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Applied Research Systems, patent WO2007/48788, 2007; Appl. No. WO2006-EP67713.