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2,3,4,4a,5,6-Hexahydro-1*H*-pyrazino[1,2-*a*]quinoline Synthesis Via a [3+2] Cycloaddition

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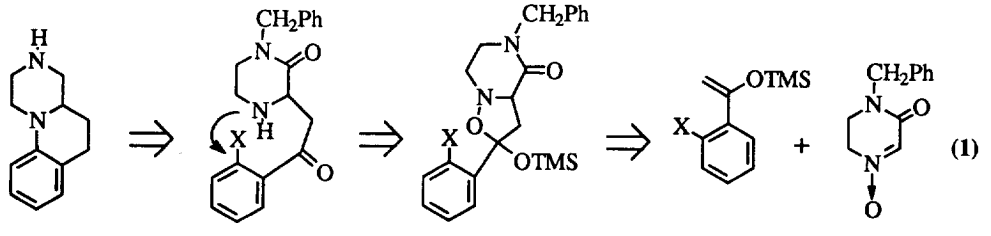
Abstract: A constrained aryl piperazine, 2,3,4,4a,5,6-hexahydro-1*H*-pyrazino[1,2-*a*]quinoline, has been synthesized using an intramolecular aromatic substitution as the key step.

As part of a program directed toward the discovery of serotonergic ligands, we were interested in novel synthetic approaches to constrained aryl piperazines, exemplified by **5**. In the preceeding communication, we described the [3+2] cycloaddition of nitrone **1** with 1-phenyl-1-(trimethylsilyloxy)ethylene (**2a**) to give cycloadduct **3a** which on reductive cleavage of the nitrogen-oxygen bond afforded phenone **4a**.[1] When we realized a phenone like **4a** but with a readily displaceable fluorine might undergo intramolecular aromatic substitution[2] to produce a close analog of **5**, the retrosynthetic approach below was suggested (Equation 1). The key step is an intramolecular cyclization of *ortho*-fluorophenone **4b** revealed upon reductive cleavage of the [3+2] cycloadduct **3b**. We report here the successful application of this strategy to the synthesis of **5**.



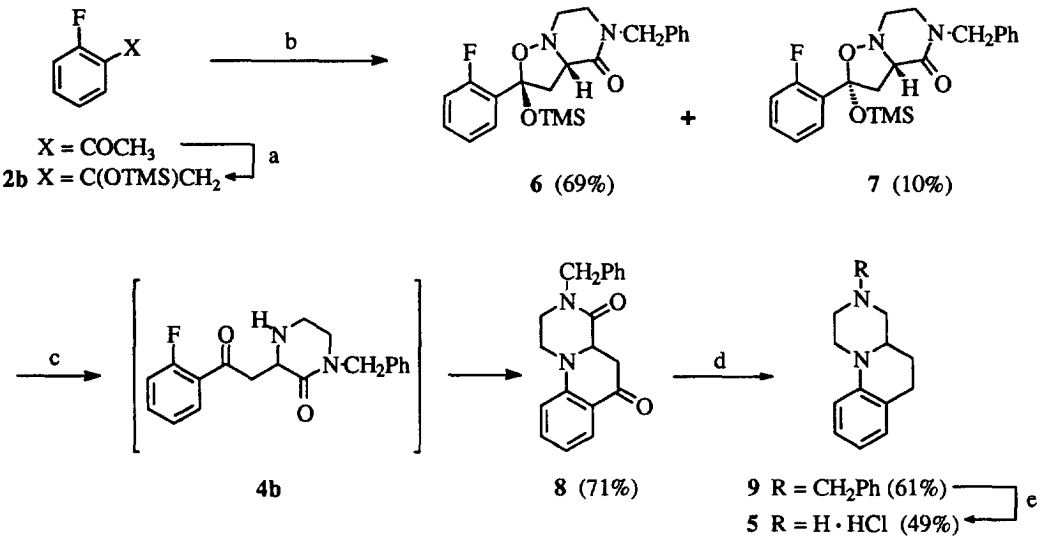
5 **4a** X = H, **4b** X = F **3a** X = H, **3b** X = F **2a** X = H, **2b** X = F **1**

The synthesis of **5** began with the preparation of silyl enol ether **2b** in a single step from commercially available 2'-fluoroacetophenone (see Scheme). Nitrone **1** was combined with three equivalents of **2b** in THF and heated at reflux for 24 hours affording a readily separable 7:1 mixture of cycloadducts **6** and **7**, respectively, in 79% combined yield.[3] No regioisomeric cycloadduct was isolated. The steric bulk of the trimethylsilyl ether and aryl ring on the disubstituted alkene may account for the high regioselectivity.

The next step was reductive cleavage of the N-O bond. Brandi has reported that $Mo(CO)_6$ in wet refluxing acetonitrile reductively cleaved isoxazolidines to give amino alcohols in good yields.[4] Submission of major diastereomer **6** to these conditions gave *ortho*-fluorophenone **4b**, accompanied by intramolecular aromatic substitution product **8**. While **4b** could be separated from **8** by flash chromatography, spontaneous cyclization of **4b** to **8** began upon concentration of the collected fractions. In practice, **8** was obtained directly by treating **6** under Brandi's conditions for 24 hours, bypassing the isolation of unstable **4b**. One-pot reduction

of the two carbonyl groups in **8** was accomplished using $LiAlH_4$ and $AlCl_3$ in refluxing ether to afford constrained aryl piperazine **9**, in moderate yield. Finally, hydrogenolysis of the hydrochloride salt of **9** with palladium on carbon removed the benzyl protecting group, completing the synthesis of **5**.[5] In a further improvement, enol ether **2b** and nitrone **1** were heated at reflux in THF, concentrated, and the crude product mixture heated with $Mo(CO)_6$ in aqueous acetonitrile to give **8** from **1** in one pot. The overall yield was 47% and the isolation of intermediates was eliminated. Thus, the utility of nitrone **1** for the synthesis of constrained neuroactive compounds has been demonstrated by a short synthesis of **5**.[6]

SCHEME



(a) LDA (1.2 equiv)/THF/-78°C, then TMSCl (1.2 equiv)/rt/3 h (b) **1** (3 equiv)/THF/reflux/24 h (c) $Mo(CO)_6$ (0.7 equiv)/H_2O/CH_3CN/reflux 24 h (d) $AlCl_3$ (4 equiv)/$LiAlH_4$ (4 equiv)/ ether/reflux 24 h (e) H_2 (55 psi)/10% Pd on C/ethanol/8 d

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REFERENCES AND NOTES

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2. Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1987**, 641-645.
3. Diasteromers were assigned based on NMR experiments on closely related compounds. Compounds **5**, **6**, **7**, **8**, and **9** gave satisfactory elemental analyses and ^1H NMR, ^{13}C NMR, CIMS, IR spectral data.
4. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F. *Tetrahedron Lett.* **1990**, *31*, 3351-3354.
5. Melting point of **5**-hydrochloride: 191-192° C; literature: 192-194° C (see reference 6d).
6. For other syntheses of this ring system: (a) Rupe, H.; Thommen, W. *Helv. Chim. Acta* **1947**, *30*, 920-931; (b) Baxter, C. A. R.; Richards, H. C. *J. Med. Chem.* **1972**, *15*, 351-356; (c) Huff, J. R.; King, S. W.; Saari, W. S.; Springer, J. P.; Martin, G. E.; Williams, M. *J. Med. Chem.* **1985**, *28*, 945-948; (d) Rossi, A; Sury, E., South African Patent 67 05 766, 1967; *Chem. Abstr.* **1969**, *70*, 47502a; and (e) ref. 2.

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