A Short, Novel Approach to 2,3,4a,5-Tetrahydro-1*H*-pyrazino[1,2-*a*] quinoline-4,6-diones

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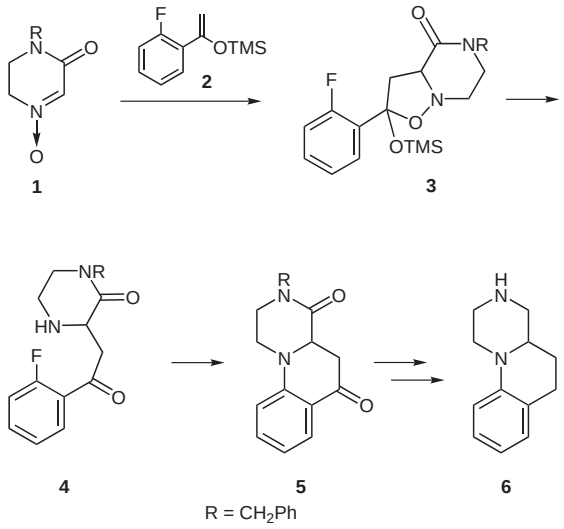
Abstract: An expeditious route to constrained arylpiperazinones has been developed. The key reaction formed the tricyclic system in one-pot via a 1,4-addition–lactamization–aromatic substitution sequence. Four examples were prepared.

Key words: 1,4-additions, nucleophilic aromatic substitutions, cyclizations, lactams, medicinal chemistry

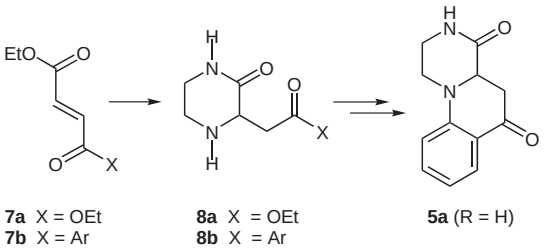
Arylpiperazines are a common motif found in G-protein-coupled receptor (GPCR) ligands.[2] As part of a program directed toward expanding libraries of such potential GPCR ligands, developing new approaches to constrained arylpiperazines **6** was of considerable interest.[3] Previously, a novel cycloaddition route to this class of compounds utilizing nitrone **1** was described.[4] Reaction of **1** with TMS-enol ether **2** afforded isoxazolidine **3** (Scheme 1). The nitrogen-oxygen bond in **3** was reductively cleaved to reveal *ortho*-fluorophenone **4**. This compound underwent a facile intramolecular S_NAr reaction to provide **5**, a 2,3,4a,5-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoline-4,6-dione. Ultimately, this compound was reduced to final target **6**.

A need for a shorter and potentially more versatile synthesis led to the investigation of other ways of constructing



Scheme 1

the ring system found in **5**. Some time ago, Phillips[5] reported that addition of ethylenediamine to diethylfumarate **7a** readily afforded piperazinone **8a** directly (Scheme 2). This suggested that replacing one of the ethoxy groups in **7a** with an ortho-fluoroaryl ring (**7b**) and reaction of **8a** with ethylenediamine should provide **8b** by a 1,4-addition to the more reactive enone (as opposed to the acrylate) followed by lactamization. Based on previous experience with the nitrone approach, it was anticipated that **8b** would then undergo a facile intramolecular S_NAr reaction providing **5a**. This paper describes the successful application of this route to the synthesis of tricyclic systems **5**.



Scheme 2

The requisite precursors to the cyclization reaction were readily made in two steps (Scheme 3). Addition of *ortho*-fluorobenzaldehyde **9a** to the lithium anion of ethyl propiolate, generated with LDA in THF at –78 °C, afforded propargylic alcohol **10a**.[6] This alcohol was rearranged to enone **11a** by treatment with 2 equivalents of triethylamine in dioxane at 55–60 °C for 6–8 hours. The presence of an *ortho*-fluoro substituent seemed to retard rearrangement since several hours of heating were required for the reaction to approach completion rather than the shorter time at ambient temperature reported for the unsubstituted phenyl ring.[7]

With the enone in hand, the cyclization strategy was examined. Compound **11a** in DMF was treated with 1.1 equivalents of ethylenediamine and heated at 60 °C for 6 hours. The reaction was then cooled resulting in precipitate formation. Addition of diethyl ether followed by suction filtration and ether trituration of the solid gave 2,3,4a,5-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoline-4,6-dione (**5a**) in good yield.[8]

After this initial success, three other analogs with additional substituents on the aromatic ring were investigated. Under conditions similar to those employed for **9a**, *ortho*-

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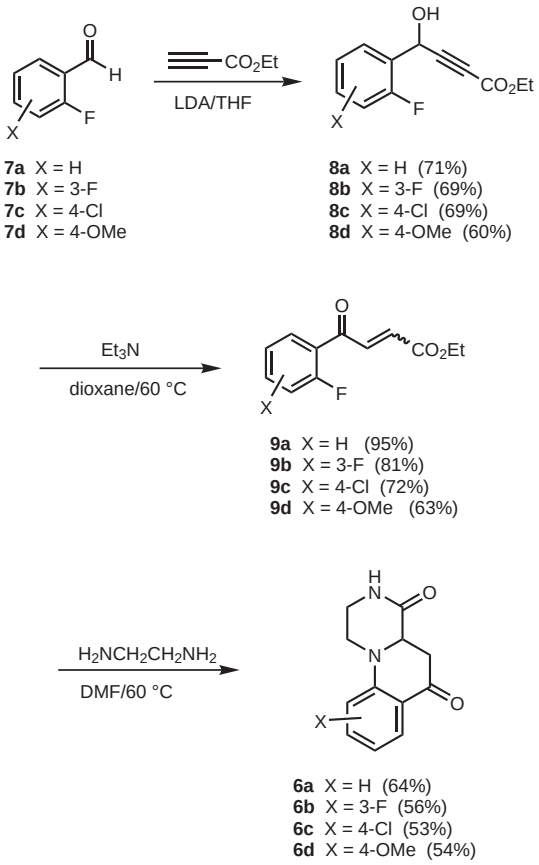
fluorobenzaldehydes **9b**–**d** were converted into alcohols **10b**–**d** and then rearranged to enones **11b**–**d**. The enones were reacted with ethylenediamine to provide **5b**–**d**, also in moderate yield.



Scheme 3

In conclusion, a new and expeditious route to 2,3,4a,5-tetrahydro-1*H*-pyrazino[1,2-*a*]quinoline-4,6-diones (**5**) has been developed. The key step in this approach to constrained arylpiperazinones was a cascade sequence of three reactions that constructed the tricyclic ring system: 1,4-addition, lactamization, and intramolecular S_NAr-type reaction. This work may be useful for synthesizing other related ring systems.

References

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(8) All compounds gave satisfactory spectral data (^{1}H NMR, ^{13}C NMR, and ^{19}F NMR, IR, and CI-MS). Spectral data for representative compounds: **10a** (gradually decomposes in $CDCl_3$): ^{1}H NMR ($CDCl_3$): δ = 7.59 (1 H, dt, *J* = 2.0, 7.9 Hz), 7.29 (1 H, m), 7.15 (1 H, t, *J* = 7.9 Hz), 7.04 (1 H, t, *J* = 8.9 Hz), 5.80 (1 H, s), 4.20 (2 H, q, *J* = 7.1 Hz), 1.31 (3 H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 159.8 (d, *J* = 249 Hz, F-coupled), 153.4, 130.6 (d, *J* = 9.0 Hz), 128.4 (d), 126.1 (d, *J* = 13.0 Hz, F-coupled), 124.5, 115.6 (d, *J* = 21.0 Hz, F-coupled), 85.4, 77.3, 62.3, 58.3, 13.91 ppm. ^{19}F NMR ($CDCl_3$): δ = –118.1 ppm. MS (CI/CH_4): *m/z* (%) = 223 (30) [M + H], 205 (100) [M + H – H_2O]. IR: 1712, 1613, 1589 cm^{-1}. Compound **11a**: ^{1}H NMR ($CDCl_3$): δ = 7.81 (1 H, dt, *J* = 2.0, 8.9 Hz), 7.74 (1 H, dd, *J* = 3.3, 15.6 Hz), 7.57 (1 H, m), 7.25 (1 H, t, *J* = 7.9 Hz), 7.15 (1 H, dd, *J* = 8.9, 10.9 Hz), 6.83 (1 H, dd, *J* = 2.0, 8.9 Hz), 4.30 (2 H, q, *J* = 7.1 Hz), 1.35 (3 H, t, *J* = 7.1 Hz) ppm. ^{13}C NMR ($CDCl_3$): δ = 188.1, 165.4, 163.4, 160.0, 139.1 (d), 135.2 (d), 131.6 (d, *J* = 48 Hz, F-coupled), 125.6 (d, *J* = 6.0 Hz, F-coupled), 124.7, 116.7 (d, *J* = 22.0 Hz, F-coupled), 61.3, 14.1 ppm. ^{19}F NMR ($CDCl_3$): δ = –109.2 ppm. MS (APCI): *m/z* (%) = 223 (100) [M + H]. IR: 1724, 1672, 1610 cm^{-1}. Compound **5a**: ^{1}H NMR (DMSO-d_6): δ = 8.18 (1 H, br s), 7.75 (1 H, d, *J* = 7.8 Hz), 7.50 (1 H, t, *J* = 7.8 Hz), 7.15 (1 H, d, *J* = 8.0 Hz), 6.85 (1 H, t, *J* = 7.8 Hz), 4.13 (1 H, br d), 4.06 (1 H, dd, *J* = 4.9, 12.8 Hz), 3.43 (1 H, app dt, *J* = 5.9, 11.8 Hz), 3.30 (1 H, br d), 3.10 (1 H, app dt, *J* = 4.0, 11.4 Hz), 2.91 (1 H, dd, *J* = 4.9, 16.8 Hz), 2.76 (1 H, dd, *J* = 12.8, 16.7 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ = 192.1, 167.8, 151.3, 135.6, 127.3, 120.3, 118.2, 114.3, 58.3, 42.1, 39.9, 39.2 (partly obscured by DMSO pattern) ppm. MS (APCI): 217 (100) [M + H]. IR: 1723, 1679, 1623 cm^{-1}.