The Reaction of Enaminones with Pentafluorobenzaldehyde. A Novel Route to Substituted Quinolines

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Reaction of enaminone **1** and pentafluorobenzaldehyde (**2**) in glacial acetic acid afforded quinoline skeleton **3** in good yield.

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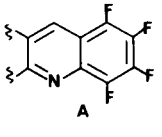
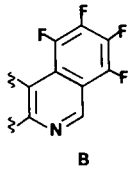
The chemistry of polyfluoroaromatic compounds has been extensively studied and well documented [2]. Many examples of ring formation arising from intramolecular fluorine displacement have been reported [3] usually in cases where the presence of other electronegative substituents on the aromatic ring contributes to the reactivity of the C-F bond in addition-elimination reactions. We now describe what we believe is the first example of such intramolecular fluorine displacement taking place between enaminones [4] and pentafluorobenzaldehyde to form a fused ring quinoline skeleton.

When an equimolar mixture of aminouracil **1a** and pentafluorobenzaldehyde (**2**) in glacial acetic acid was heated and stirred at reflux under nitrogen for 1 hour, a white crystalline solid was obtained (87%) upon cooling and was assigned the quinoline structure **3a** (Scheme). Similarly enaminone **1b** [5] was treated with **2** under the same conditions to afford **3b** (50%) after chromatography.

Two tricyclic regioisomeric structures (**A** and **B**) may be written for the product in accord with the spectroscopic data. The well known fact of C-C bond formation between



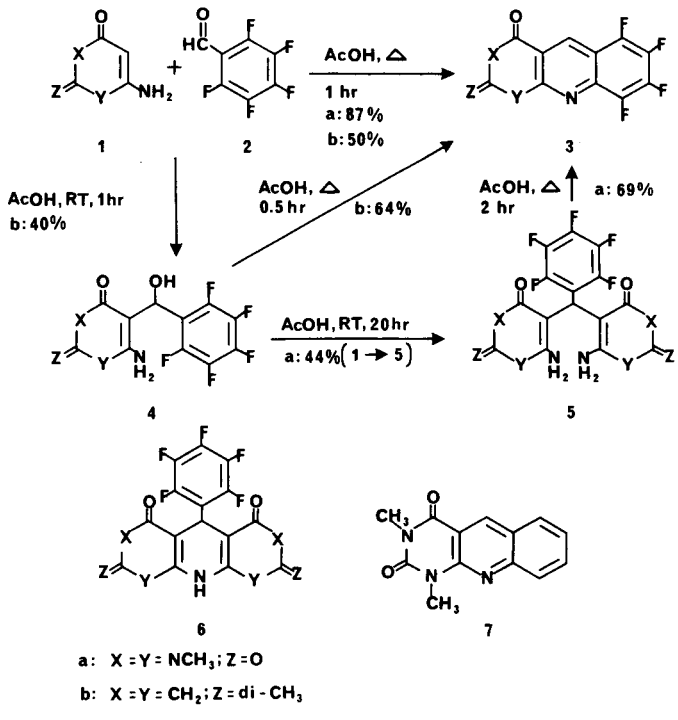
A



B

enaminones and aldehydes [6] would rule out the isoquinoline structure **B** as a possibility. Nevertheless, we have conducted the following experiments to further support our structural assignments. When **1b** and **2** reacted in glacial acetic acid at room temperature, **4b** was isolated as a white solid and was subsequently converted to **3b** on heating in acetic acid. In a similar manner, compounds **1a** and **2** reacted at room temperature to give **5a** [7] which upon heating for 2 hours gave rise to **3a**. Interestingly, instead of the possible deamination of **5a** to **6a**, elimination of **1a** occurred and **3a** was isolated, presumably due to the instability of the C-F bond in the highly fluorinated aromatic system along with the strong driving force for the formation of the stable quinoline system. However, a minute amount of **6b** was obtained during the synthesis of **3b** from **1b** and **2** in refluxing acetic acid. These results show that **1** and **2** undergo initial reaction with C-C bond formation. The subsequent fluorine displacement by the amino group generates the quinoline structure **3**. The presence of the polyfluorinated ring appears to be important for this type of displacement since the corresponding reaction of **1a** with *o*-fluorobenzaldehyde failed to give the tricyclic product **7**.

SCHEME



This facile cyclization reaction should provide a useful entry to novel heterocyclic systems of medicinal interest and in particular to polyfluorinated deazaflavins.

EXPERIMENTAL

Melting points were measured on a Thomas-Hoover apparatus without correction. The ir spectra were taken on a Beckman IR-8 infrared spec-

trophotometer. The nmr spectra were measured in the indicated solvent with TMS as an internal standard on a Varian T-60A spectrometer. The EI/CI mass spectra were obtained on a Finnigan 1015D quadrupole mass spectrometer.

5,6,7,8-Tetrafluoro-1,3-dimethylpyrimidino[6,5-*b*]quinoline-2,4-dione (**3a**).

A mixture of **1a** (5.0 g, 32 mmoles) and **2** (6.3 g, 32 mmoles) in glacial acetic acid (45 ml) was stirred and heated to reflux under nitrogen for 1 hour, cooled to room temperature, and filtered. The white crystalline solid was rinsed with methanol and dried *in vacuo* at 110° for 2 days to furnish **3a** (8.7 g, 87%), mp 227-228°; ir (potassium bromide): 3060, 1725, 1665, 1615 cm^{-1}; ^1H nmr (trifluoroacetic acid): δ 9.62 (d, J = 1 Hz, 1 H, C-9 H), 4.05 (s, 3 H, N-3 CH_3), 3.73 (s, 3 H, N-1 CH_3); ms: m/e 313, 201 (B.P.).

Anal. Calcd. for $C_{13}H_7F_4N_3O_2$: C, 49.85; H, 2.25; N, 13.42. Found: C, 50.03; H, 2.21; N, 13.19.

5,6,7,8-Tetrafluoro-2,2-dimethylbenzo[2,1-*b*]quinolin-4-one (**3b**).

A mixture of **1b** (4.2 g, 30 mmoles) and **2** (6.0 g, 30 mmoles) in glacial acetic acid (30 ml) was stirred under nitrogen, heated to reflux for 1 hour, cooled to room temperature, evaporated *in vacuo*, and flash column chromatographed (2% methanol in methylene chloride on silica gel 60, E. Merck) to give after recrystallization from methylene chloride/hexanes a white crystalline solid **3b** (4.4 g, 50%), mp 150-154°; ir (potassium bromide): 1690, 1670, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.05 (b, 1 H, C-10 H), 3.27 (s, 2 H, C-3 H), 2.70 (s, 2 H, C-1 H), 1.15 (s, 6 H, two C-2 CH_3); ms: m/e 297, 241 (B.P.).

Anal. Calcd. for $C_{15}H_{11}F_4NO$: C, 60.61; H, 3.73; N, 4.71. Found: C, 60.56; H, 3.76; N, 4.54.

Preparation of **3b** *via* **4b**.

An equimolar mixture (30 mmoles) of **1b** and **2** in glacial acetic acid (30 ml) was stirred under nitrogen at room temperature for 1 hour. The white suspension was filtered and rinsed with ether to give **4b** (4 g, 40%); ^1H nmr (deuteriodimethylsulfoxide): δ 7.05 (b 2 H, NH_2), 6.45 (d, J = 5 Hz, 1 H, CH-O), 6.10 (d, J = 5 Hz, 1 H, OH), 2.25 (s, 2 H, CH_2CO), 1.90 (s, 2 H, $CH_2C{=}C$); ms: m/e 335, 317, 298, 296 (B.P.). The white solid **4b** was then suspended in glacial acetic acid (10 ml) and heated to reflux with stirring under nitrogen for 30 minutes. The mixture was then cooled to room temperature, evaporated *in vacuo*, and flash column chromatographed (2% methanol in methylene chloride on silica gel 60, E. Merck) to afford **3b** (2.3 g, 64%).

Preparation of **3a** *via* **5a**.

An equimolar mixture (18 mmoles) of **1a** and **2** in glacial acetic acid (75 ml) was stirred under nitrogen at room temperature for 20 hours. The solvent was evaporated *in vacuo* to afford a yellow oil. Flash column chromatography (5% methanol in methylene chloride on silica gel 60, E. Merck) gave **5a** (3.6 g, 44%, based on **1a**; ^1H nmr (deuteriodimethylsulfoxide): δ 7.10 (b, 4 H, two NH_2), 6.0 (b, 1 H, CHAr), 3.37 and 3.15 (two s, 6 H each, four NCH_3); ms: m/e 488, 313, 201 (B.P.). The white solid **5a** was suspended in glacial acetic acid (75 ml) and heated to reflux with stirring for 2 hours to afford **3a** (1.7 g, 69%).

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[7] Presumably **4a** formed as an initial product, and was then transformed into **5a** by reacting with unreacted **1a**.