A NOVEL SYNTHESIS OF 4-PERFLUOROALKYLQUINOLINES AND RELATED SUBSTITUTED QUINOLINES

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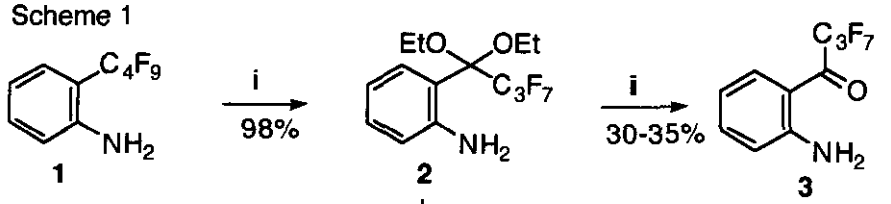
Abstract - In spite of inefficient hydrolysis of 1-(2-aminophenyl)-2,2,3,3,4,4,4-heptafluorobutan-1-one diethyl acetal (**2**), this compound undergoes readily the acid-catalyzed Friedländer reaction with enolizable ketones to give the corresponding quinolines (**4-6**). The reaction of **2** with pentanal yields quinoline (**12**) as the major product.

The Friedländer synthesis of quinolines involves condensation of 2-acyl-substituted anilines with enolizable aldehydes or ketones.[1] In this paper we report a related, albeit unconventional synthesis of 4-perfluoroalkylquinolines exemplified by **4-6** (Scheme 1). The key starting materials are readily available 2-perfluoroalkylanilines[2-5] such as **1**. The two-step chemistry involves the benzylic difluoromethylene portion of the C_nF_{2n+1} group of **1** or homologs, and this group becomes a C4-$C_{n-1}F_{2n-1}$ moiety of the quinoline. Few compounds of this class are known.[6] The presented methodology has been successfully

Scheme 1



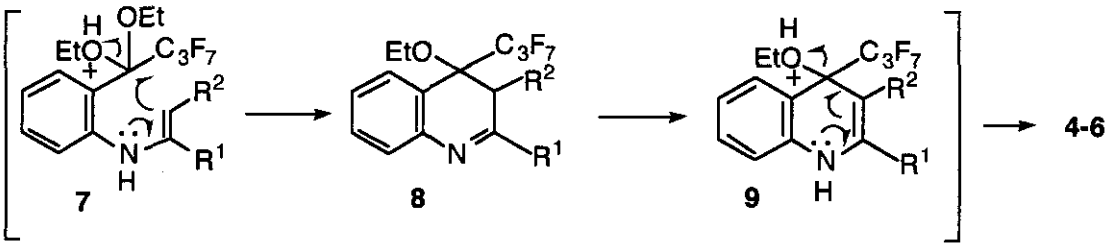
(i): **1** (2 mmol), EtONa (10 mmol), EtOH (10 mL), reflux (14 h); concentration, extraction (Et_2O), distillation (170 °C/10 mmHg).
(ii): see text
(iii): **2** (1 mmol), ketone (1.2 mmol, 3-pentanone, cyclohexanone, acetophenone for **4-6**, respectively), AcOH (5 mL), H_2SO_4 (3 drops), reflux (6-8 h); neutralization (30% NH_4OH), extraction (Et_2O), silica gel chromatography (CH_2Cl_2/pentanes, 3:2).
(iv): see (iii), reflux for 2 h.

4: R^1 = Et, R^2 = Me
5: R^1R^2 = -$(CH_2)_4$-
6: R^1 = Ph, R^2 = H

tested for several 2-(C_nF_{2n+1})-substituted anilines (n = 2-4), and the results with 2-nonafluorobutylaniline (**1**) are discussed for illustration.

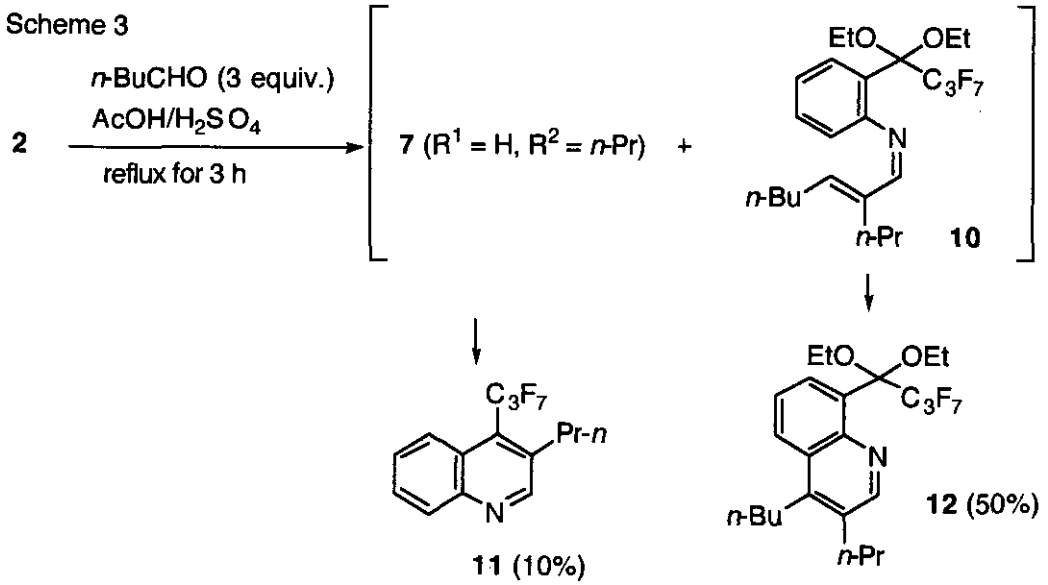
The treatment of **1** with sodium ethoxide furnishes diethyl acetal (**2**) in a virtually quantitative yield.[6] Our initial attempts focused on hydrolysis of **2** to ketone (**3**) which could serve as a classical substrate for the Friedländer reaction. Acetal (**2**) could not be hydrolyzed by heating a solution of **2** (1 mmol) and *p*-TsOH (20 mmol) in THF/H_2O (1:1, 25 mL) under reflux for several days.[7] Compound (**2**) was consumed and the desired ketone[8] (**3**) was isolated in a 30% yield following several consecutive additions of THF/benzene (1:1) to the mixture and continuous, slow removal of the solvent (presumably containing EtOH) by distillation.[9] In another experiment a mixture of **2** and aqueous H_2SO_4 (25%) was heated under reflux. The substrate (**2**) was consumed after 2 days and ketone (**3**) was isolated in a 35% yield.[10] The reactions of **3** with 3-pentanone, cyclohexanone, and acetophenone furnished the respective quinolines[11] (**4-6**) in poor overall efficiencies based on the acetal (**2**).

Scheme 2



A vastly superior synthesis of **4-6** is by direct condensation of ketones with acetal (**2**) (Scheme 1). As suggested in Scheme 2 the facility of this reaction is due to cyclization of the intermediate product (**7**) with

Scheme 3



the involvement of the enamine function (tautomer of the initially formed ketimine) and the protonated acetal. This enamine-assisted elimination of EtOH from the protonated acetal does not necessitate generation of a free carbonium ion that would be strongly destabilized by the perfluoroalkyl group. The resultant intermediate product (**8**) may undergo tautomerization to **9** followed by aromatization to **4-6** that is similar to the low-energy pathway suggested above.[12]

A similar condensation of **2** with pentanal (Scheme 3) furnished 4-heptafluoropropyl-3-propylquinoline (**11**, the expected product) in a 10% yield. The major product (50%) was quinoline (**12**) formed by electrophilic cyclization of Schiff base (**10**) derived from **2** and a dimeric self-condensation product of pentanal followed by oxidation of the resultant dihydroquinoline.[13] In concert with the high hydrolytic stability of acetal (**2**), the acetal function of the quinoline (**12**) is extremely stable under acidic conditions of the reaction.[14]

The novel quinolines described in this paper are representative examples selected from the many successful reactions of **1** and its perfluoroalkyl homologs with a variety of enolizable ketones and aldehydes. These reactions have a broad scope, and a full account will be published in due course.

ACKNOWLEDGMENT

We thank the Educational Aid Program of DuPont Co. and the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

REFERENCES AND NOTES

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7. For other examples of the high hydrolytic stability of fluoroacetals, see: H.E. Simmons and D.W. Wiley, *J. Am. Chem. Soc.*, 1960, **82**, 2288. The inertness of **2** is in sharp contrast to the high hydrolytic instability of 2-triethoxymethylaniline obtained by the reaction of 2-trifluoromethylaniline with EtONa.
8. Ketone (**3**) is an oil; ^{13}C NMR (DMSO-d_6): δ 180.7; IR: ν 1725 and 1773 cm^{-1}; MS m/z 289 (100, M^+).
9. The low yield of **2** (30%) was due to partial removal of this highly volatile product during distillation of the solvent, as shown by GC-MS analysis.
10. The material balance consisted of intractable tar and several, low molecular weight products, none of them major (yield of each less than 3%, as shown by GC-MS analysis).

11. Quinolines (**4-6**) gave satisfactory elemental analyses and exhibited intense molecular ion peaks in the mass spectra; **4**, an oil; **5**, mp 63-64 °C; **6**, mp 64-65 °C. ^{19}F NMR for **4-6** ($CDCl_3$, C_6F_6 as an internal reference): δ 37.6 ± 0.5 (2 F), 58.9 ± 4.7 (2 F), 81.9 ± 0.1 (3 F). The ^1H NMR ($CDCl_3$) for **5** is illustrative: δ 1.86 (m, 2 H), 1.97 (m, 2 H), 3.12 (m, 2 H), 3.21 (m, 2 H), 7.52 (t, J = 8 Hz, 1 H), 7.67 (t, J = 8 Hz, 1 H), 8.05 (d, J = 8 Hz, 1 H), 8.10 (d, J = 8 Hz, 1 H).
12. The uniqueness of this chemistry is emphasized by negative results of our attempts to synthesize **6** by substituting **1** for 2-trifluoromethylaniline in our previously published approaches to the construction of a quinoline ring system: ref. 3 and references cited therein. Lithium hexamethyldisilazide-mediated cyclization of ketimine derived from **1** and acetophenone furnished **6** in an overall yield of 15%, and an attempted reaction of **1** with lithium enolate of acetophenone did not produce any quinoline product.
13. Quinolines (**11**) and (**12**) are oils. Compound (**11**); ^1H NMR ($CDCl_3$): δ 1.09 (m, 3 H), 1.75 (m, 2 H), 2.89 (m, 2 H), 7.62 (t, J = 8 Hz, 1 H), 7.73 (t, J = 8 Hz, 1 H), 8.16 (m, 2 H), 8.86 (s, 1 H); MS m/z 310 (100), 339 (80, M^+). Compound (**12**); ^1H NMR ($CDCl_3$): δ 0.98 (t, J = 7 Hz, 3 H), 1.06 (t, J = 7 Hz, 3 H), 1.30 (t, J = 7 Hz, 6 H), 1.45 (m, 2 H), 1.73 (m, 2 H), 1.89 (m, 2 H), 2.74 (t, J = 7 Hz, 2 H), 2.95 (t, J = 7 Hz, 2 H), 3.69 (m, 4 H), 7.44 (t, J = 8 Hz, 1 H), 7.76 (d, J = 8 Hz, 1 H), 7.77 (s, 1 H), 8.19 (d, J = 8 Hz, 1 H); MS m/z 424 (100), 497 (5, M^+). The fast self condensation of pentanal has been observed by GC-MS analysis. The dimeric condensation product (m/z 154, M^+) has been isolated from the mixture and characterized.
14. In spite of the fact that no precautions were taken to exclude moisture from the reaction mixture, only traces of the parent ketone of **12** were found by GC-MS analysis [m/z 353 (100), 423 (5, M^+)]. This parent ketone (yield 30%), in addition to **11** (yield 10%), was obtained by the reaction of **3** with pentanal (see Scheme 3 for conditions).

Received, 18th July, 1997