Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8523-8526, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10304-5

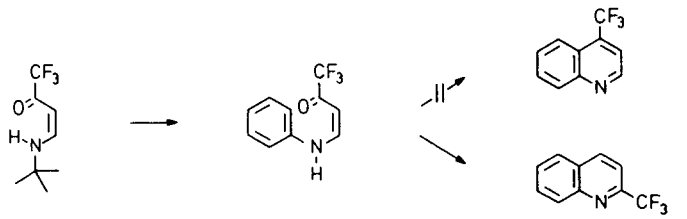
How 2-Anilinovinyl Perfluoroalkyl Ketones Can Be Mechanistically Correlated With Their Cyclization Products 2-(Perfluoroalkyl)quinolines

Manfred Schlosser *, Holger Keller, Shin-ichi Sumida and Jin Yang

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland
(Fax ++41 / 21 / 692 39 51)

Abstract: When heated in the presence of phosphoryl chloride, 2-anilinovinyl perfluoroalkyl ketones [*e.g.*, 4-anilino-1,1,1-trifluorobut-3-en-2-one] afford 2-(perfluoroalkyl)quinolines [*e.g.*, 2-(trifluoromethyl)quinoline]. As revealed by cross-over experiments, an efficient amine exchange process randomizes the structural component in the final products but not in their aminoenone precursors. 1,3-Diaminoallyl cations (vinologous formidinium salts) are postulated to act as the turntables.

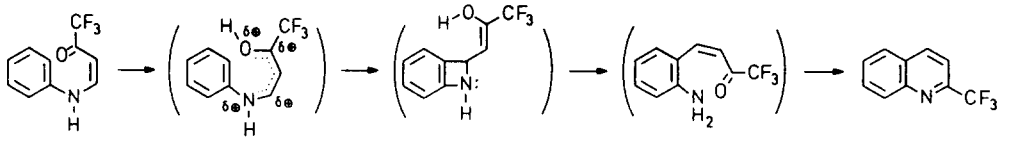
4-Anilino-1,1,1-trifluorobut-3-en-2-ones can be readily obtained from the ethyl trifluoroacetate derived 4-*tert*-butylamino-1,1,1-trifluorobut-3-en-2-one by simple amine/amine replacement [1]. Upon heating in the presence of phosphoryl chloride, they undergo ring closure to afford 2-(trifluoromethyl)quinolines rather than the expected 4-isomers in 50% average yield [1].



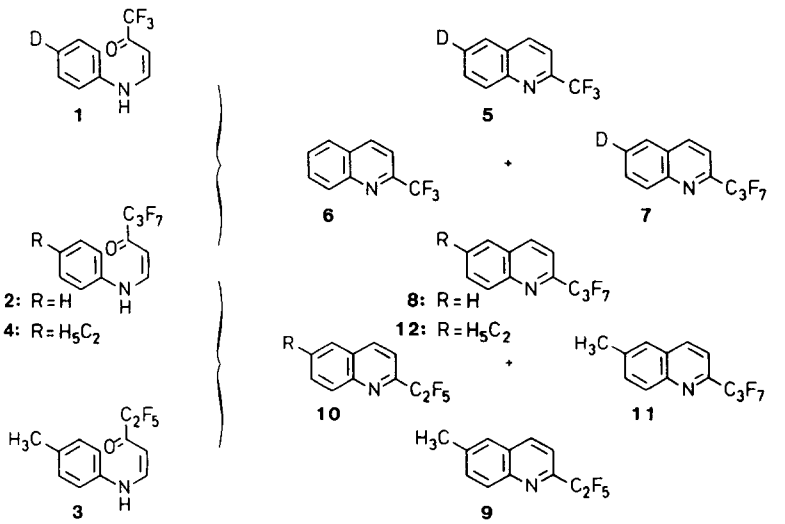
One precedent has been reported. While polyphosphoric acid at 165 °C was found to convert half a dozen of congeners into 4-(trifluoromethyl)quinolines, the parent compound 4-anilino-1,1,1-trifluorobut-3-en-2-one (prepared from 4-ethoxy-1,1,1-trifluorobut-3-en-2-one [2]) gave under the same conditions only trace amounts of the 4-isomer besides 21% of 2-(trifluoromethyl)quinoline [3]. The authors tentatively rationalized the regiochemical inversion by assuming a decomposition of the anilinoenone into aniline and 1,1,1-trifluorobut-3-yn-2-one. Recombination of these fragments in the sense of a 1,2- rather than 1,4-addition could generate *N*-phenyl-1-(trifluoromethyl)prop-2-ynylideneamine and eventually give rise to the final product. This explanation deems us not very plausible. Why should the imine cyclize more easily than its anilinoketone precursor ? Moreover, would the extremely volatile 1,1,1-trifluorobut-3-yn-2-one (bp 30 °C) not immediately escape from the hot reaction mixture ?

Before discussing other mechanistic options, we first wanted to find out whether the electrophilic aromatic substitution leading to the heterocyclic compound really involves elimination/addition or addition/elimination

sequences that could be monitored by exchange with external components. In other words, the attractive possibility of a strictly intramolecular vinologous Fries rearrangement, passing through a benzoazetidine as the crucial intermediate, had first to be ruled out on the basis of cross-over tests.

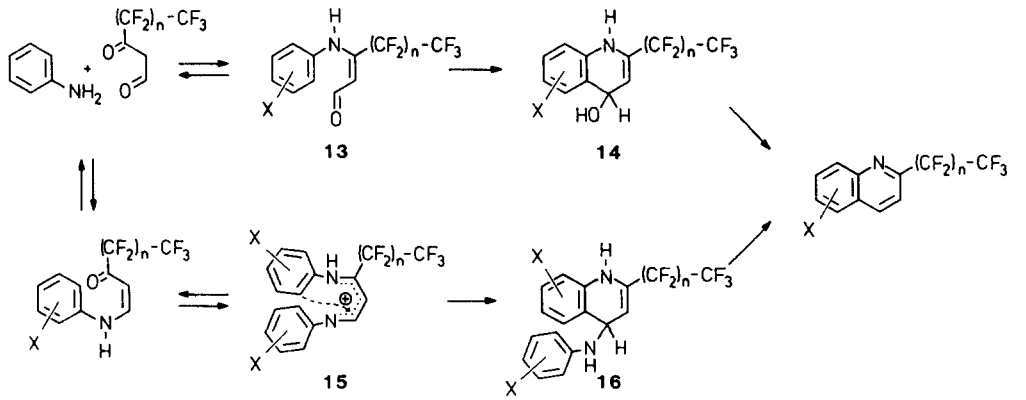


We have carried out three experiments which all demonstrate *amine randomization* on the way from the anilinoketone to the quinoline. First we have simply checked what happens when 4-anilino-1,1,1-trifluorobut-3-en-2-one is heated with phosphoryl chloride in the presence of a molar equivalent of *p*-toluidine. 2-(Trifluoromethyl)quinoline and 6-methyl-2-(trifluoromethyl)quinoline were formed in approximately equal amounts. Next, a 1 : 1 mixture of 4-(4-[^{1}H]anilino)-1,1,1-trifluorobut-3-en-2-one (**1**) and 1-anilino-4,4,5,5,6,6,6-heptafluorohex-1-en-3-one (**2**) was submitted to our standard cyclization conditions. The 2-(trifluoromethyl)quinoline (**5** + **6**; 56%) and 2-(heptafluoropropyl)quinoline (**7** + **8**; 49%) isolated contained deuterium to the extent of 65% and 35%, respectively. The unequal distribution of the isotopic label may be a consequence of differences in the reaction rates, the trifluoro substituted quinoline being formed 4.1 times more rapidly than its heptafluoro congener. Ultimately, an equimolar mixture of 4,4,5,5,5-pentafluoro-1-(4-toluidino)pent-1-en-3-one (**3**) and 4,4,5,5,6,6,6-heptafluoro-1-(4-ethylanilino)hex-1-en-3-one (**4**) was heated in the presence of phosphoryl chloride. The products were identified by their gas chromatographic retention times in comparison with those of authentic samples and their yields determined relative to a known quantity of tridecane as an internal reference ("standard"). Thus, 13% of 6-methyl-2-(pentafluoroethyl)quinoline (**9**), 12% of 6-ethyl-2-(pentafluoroethyl)-quinoline (**10**), 9% of 2-(heptafluoropropyl)-6-methylquinoline (**11**) and 9% of 6-ethyl-2-(heptafluoropropyl)-quinoline (**12**) were identified. This time, the two starting materials disappeared at virtually the same rate.



To explain the seeming "walk" of the perfluoroalkyl substituents and the observed cross-over of molecular subunits one may assume the 3-aminoenone to be cleaved hydrolytically, thus setting free an aniline and 4,4,4-

trifluoro-3-oxobutanal (if n = 0) or homologs thereof (if n = 1 or 2). Recombination of these components could simultaneously occur in two regioselectively contrasting ways : restoring the 3-aminoenone precursor or producing a 3-aminoenal isomer (**13**). The latter should undergo acid-catalyzed cyclization with particular ease to give, after dehydration of the transient 4-hydroxy-1,4-dihydroquinoline **14**, a 2-substituted quinoline. There is one objection, however. The principle of microscopic reversibility would require the aldehyde **13** also to revert to the isomeric ketone, the latter being thermodynamically at least as stable if not more stable. In other words, the amine part would have to be scrambled not only in the final heterocyclic products but already in the aminoenone precursors. This is in contradiction with the facts. For example, no trace of 4,4,5,5,5-pentafluoro-1-(4-ethylanilino)hex-1-en-3-one or 4,4,5,5,6,6,6-heptafluoro-1-(4-toluidino)pent-1-en-3-one was detected during the execution of the third cross-over experiment described above. Therefore, we postulate another course of the reaction featuring a vinylogous amidinium ion **15** (only one of four rapidly equilibrating coplanar conformers shown) as the key intermediate. Bond construction between an *ortho*-position of the newly entered anilino moiety and the sterically less hindered electrophilic carbon atom will result in a ring-closure which establishes the required connectivity. The resulting ephemeral dihydroquinoline **16** instantaneously loses the remaining anilino moiety thus leading to the 2-substituted quinoline.



Experimental

The new products specified below were prepared using the same methods as already described for analogous compounds [1]. The composition and isotope enrichment of the products obtained in the cross-over experiment carried out with the aminoenones **1** and **2** was determined by gas chromatography-coupled mass spectrometry. The crucial cross-over experiment involving the aminoenones **2** and **4** was evaluated by gas chromatographic analysis (30 m capillary column, DB-1701 silicone rubber, 10 min 50 °C, then → 225 °C [10 °C/min]). The nmr spectra were recorded at 400 MHz. For this purpose, quinolines were dissolved in perdeuterated acetone, other samples in deuterochloroform.

a) β-(*tert*-Butylamino)alk-α,β-enones

*1-(*tert*-Butylamino)-4,4,5,5,5-pentafluoropent-1-en-3-one* : mp 62 - 63 °C; 75%. - ^{1}H-NMR : δ 10.7 (1 H, m, very broad), 7.27 (2 H, dd, *J* 14.0, 7.1), 5.44 (1 H, dhex, *J* 7.1, 1.8), 1.37 (9 H, s). - Analysis : calc. for $C_9H_{12}F_5NO$ (245.19) C 44.09, H 4.93; found C 44.10, H 4.93%. - *1-(*tert*-Butylamino)-4,4,5,5,5-heptafluorohex-1-en-3-one* : mp 48 - 49 °C; 87%. - ^{1}H-NMR : δ 10.7 (1 H, m, very broad), 7.27 (2 H, dd, *J* 14.0, 7.1), 5.42 (1 H, dm, *J* 7.0), 1.37 (9 H, s). - Analysis : calc. for $C_{10}H_{12}F_7NO$ (295.20) C 40.69, H 4.10; found C 40.80, H 3.88%.

b) β-Anilinoalk-α,β-enones

2-(Trifluoromethyl)quinoline : mp 57.0 - 57.5 °C [1] (lit. : mp 61 - 62 °C [4]; mp 145 °C [5]; oil ? [no physical data] [3]). - *4-(4-[^{2}H]Anilino)-1,1,1-trifluorobut-3-en-2-one* (**1**) : mp 85 - 86 °C; 86%. - ^{1}H-NMR : δ 7.65 (1 H, dd, *J* 13.3, 7.5), 7.38 (2 H, d, *J* 8.2), 7.13 (2 H, *J* 8.1), 5.66 (1 H, d, *J* 7.5). - The starting material 4-[^{2}H]aniline was obtained by consecutive treatment of 4-bromo-*N,N*-[$^2H_2$]aniline with excess *tert*-butyllithium and heavy water. - *4,4,5,5,5-Pentafluoro-1-(4-tolyl)pent-1-en-3-one* (**3**) : mp 70 - 72 °C; 71%. - ^{1}H-NMR : δ 12.0 (1 H, m, very broad), 7.64 (1 H, dd, *J* 13.2, 7.4), 7.21 (2 H, d, *J* 8.2), 7.05 (2 H, d, *J* 8.4), 5.71 (1 H, dhex, *J* 7.4, 1.7), 2.35 (3 H, s). - Analysis : calc. for $C_{12}H_{10}F_5NO$ (279.21) C 51.62, H 3.61; found C 51.47, H 4.05%. - *1-(4-Ethylphenyl]amino)-4,4,5,5,5-pentafluoropent-1-en-3-one* (**4**) : mp 46 - 47 °C; 69%. - ^{1}H-NMR : δ 12.0 (1 H, m, very broad), 7.65 (1 H, dd, *J* 13.2, 7.4), 7.23 (2 H, d, *J* 8.6), 7.07 (2 H, d, *J* 8.4), 5.71 (1 H, dhex, *J* 7.4, 1.7), 2.66 (2 H, q, *J* 7.6), 1.24 (3 H, t, *J* 7.6). - Analysis : calc. for $C_{13}H_{15}F_5NO$ (239.24) C 53.25, H 4.12; found C 53.44, H 3.96%. - *1-Anilino-4,4,5,5,6,6,6-heptafluorohex-1-en-3-one* (**2**) : mp 48 - 49 ; 58%. - ^{1}H-NMR : δ 7.67 (1 H, dd, *J* 13.2, 7.5), 7.41 (2 H, ddt, *J* 8.5, 7.5, 2.0), 7.21 (1 H, tt, *J* 7.5, 1.0), 7.15 (2 H, d, *J* 8.0), 5.72 (1 H, dt, *J* 7.5, 1.2), 6.26 (1 H, s). - Analysis : calc. for $C_{12}H_8F_7NO$ (315.19) C 45.73, H 2.56; found C 45.48, H 3.04%. - *4,4,5,5,6,6,6-Heptafluoro-1-(4-tolylamino)hex-1-en-3-one* : mp 63 - 64 °C; 76%. - ^{1}H-NMR : δ 12.0 (1 H, m, broad), 7.64 (1 H, dd, *J* 13.2, 7.4), 7.21 (2 H, d, *J* 8.2), 7.05 (2 H, d, *J* 8.4), 5.69 (1 H, d, *J* 7.3), 2.35 (3 H, s). - Analysis : calc. for $C_{13}H_{10}F_7NO$ (329.22) C 47.43, H 3.06; found C 47.39, H 3.08%. - *1-([4-Ethylphenyl]amino-4,4,5,5,6,6,6-heptafluorohex-1-en-3-one* (**4**) : mp 55 - 57 °C; 75%. - ^{1}H-NMR : δ 12.0 (1 H, d-like m, *J* ~13, broad, 7.65 (1 H, dd, *J* 13.2, 7.4), 7.23 (2 H, d, *J* 8.5), 7.08 (3 H, t, *J* 7.6). - Analysis : calc. for $C_{14}H_{12}F_7NO$ (343.24) C 48.99, H 3.52; found C 48.85, H 3.60%.

c) 2-(Perfluoroalkyl)quinolines

6-Methyl-2-(pentafluoroethyl)quinoline (**9**) : mp 41 - 42 °C; 51%. - ^{1}H-NMR (D_3CCOCD_3) : δ 8.60 (1 H, d, *J* 8.6), 8.08 (1 H, d, *J* 8.7), 7.90 (1 H, s), 7.89 (1 H, d, *J* 8.3), 7.79 (1 H, dd, *J* 8.7, 1.9), 2.59 (3 H, s). - Analysis : calc. for $C_{12}H_8F_5N$ (261.19) C 55.18, H 3.09; found C 55.30, H 2.98%. - *6-Ethyl-2-(pentafluoroethyl)quinoline* (**10**) : mp 26 - 27 °C; 43%. - ^{1}H-NMR (D_3CCOCD_3) : δ 8.61 (1 H, d, *J* 8.6), 8.11 (1 H, d, *J* 8.8), 7.92 (1 H, s), 7.90 (1 H, d, *J* 8.6), 7.84 (1 H, dd, *J* 8.7, 2.0), 2.92 (2 H, q, *J* 7.6), 1.34 (3 H, t, *J* 7.6). - Analysis : calc. for $C_{13}H_{10}F_5N$ (275.28) C 56.72, H 3.66; found C 56.88, H 4.18%. - *2-(Heptafluoropropyl)quinoline* (**8**) : yellow needles (from hexane); mp 14 - 16 °C; 41%. - ^{1}H-NMR (D_3CCOCD_3) : δ 8.33 (1 H, d, *J* 8.6), 8.24 (1 H, d, *J* 8.5), 7.89 (1 H, d, *J* 8.3), 7.81 (1 H, ddd, *J* 8.2, 7.6, 1.3), 7.72 (1 H, d, *J* 8.6), 7.67 (1 H, t, *J* 7.5). - Analysis : calc. for $C_{12}H_6F_7N$ (297.17) C 48.50, H 2.04; found C 48.35, H 2.09%. - *2-Heptafluoropropyl-6-methylquinoline* (**11**) : mp 73 - 75 °C; 41%. - ^{1}H-NMR (D_3CCOCD_3) : δ 8.58 (1 H, d, *J* 8.7), 8.09 (1 H, d, *J* 8.6), 7.90 (1 H, s), 7.88 (1 H, d, *J* 8.7), 7.80 (1 H, dd, *J* 8.6), 7.90 (1 H, s), 7.88 (1 H, d, *J* 8.7), 7.80 (1 H, dd, *J* 8.6, 1.9), 2.60 (3 H, s). - Analysis : calc. for $C_{13}H_8F_7N$ (311.20) C 50.17, H 2.59; found C 49.79, H 2.89%. - *6-Ethyl-2-(heptafluoropropyl)quinoline* (**12**) : mp 45 - 46 °C; 68%.- ^{1}H-NMR (D_3CCOCD_3) : δ 8.61 (1 H, d, *J* 8.6), 8.11 (1 H, d, *J* 8.7), 7.93 (1 H, s), 7.88 (1 H, d, *J* 8.6), 7.84 (1 H, dd, *J* 8.7, 2.0), 2.92 (2 H, q, *J* 7.6), 1.35 (3 H, t, *J* 7.6). - Analysis : calc. for $C_{14}H_{10}F_7N$ (325.23) C 51.70, H 3.10; found C 51.47, H 2.99%.

Acknowledgment : The authors are indebted to the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung (grant 20-41'887-94) and to the Bundesamt für Bildung und Wissenschaft (COST-D2 project 874-12-02), both in Bern, for financial support.

References

1. Keller, H.; Schlosser, M.; *Tetrahedron* **1996**, *52*, 4637 - 4644.
2. Hojo, M.; Masuda, R.; Okada, E.; Sakaguchi, S.; Naraumiya, H.; Morimoto, K.; *Tetrahedron Lett.* **1989**, *30*, 6173 - 6176.
3. Linderman, R.J.; Kirollos, K.S.; *Tetrahedron Lett.* **1990**, *31*, 2689 - 2692.
4. Raasch, M.S.; *J. Org. Chem.* **1962**, 1406 - 1409.
5. Dey, A.S.; Joullié, M.M.; *J. Heterocycl. Chem.* **1965**, *2*, 113 - 119.

(*Received in France* 22 *September* 1997; *accepted* 2 *October* 1997)