Pergamon

*Tetrahedron*, Vol. 52, No. 13, pp. 4637-4644, 1996

0040-4020/96 $15.00 + 0.00

S0040-4020(96)00168-8

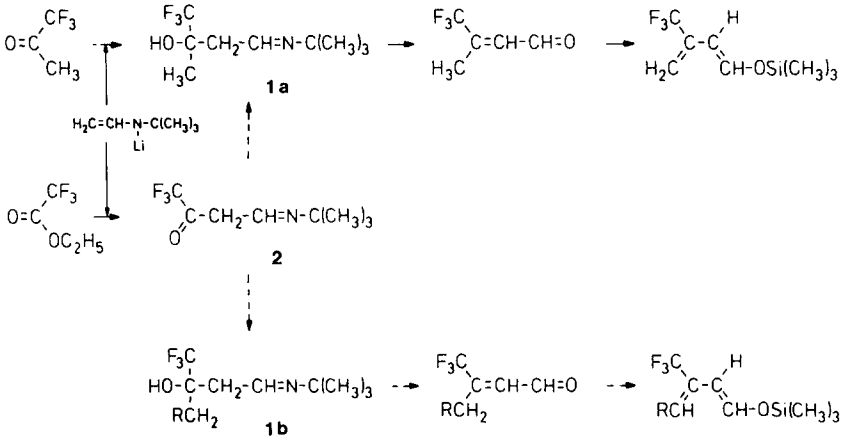
# 2-(Trifluoromethyl)quinolines from Anilines : A Novel Mode of Isomerization and Cyclization

**Holger Keller and Manfred Schlosser ***

Institut de Chimie organique de l'Université
Bâtiment de Chimie (BCh), CH-1015 Lausanne-Dorigny, Switzerland

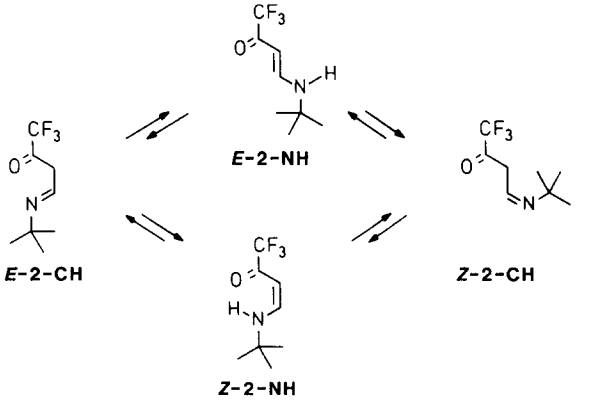
*Abstract*: Deprotonation of *N*-ethylidene-*tert*-butylamine with lithium diisopropylamide and subsequent condensation with ethyl trifluoroacetate gives 4-*tert*-butylamino-1,1,1-trifluorobut-3-en-2-one. An exchange of the amino substituent occurs when the latter compound is treated with anilines under mildly acidic conditions. When heated in the presence of phosphoryl trichloride, the resulting 4-anilino-1,1,1-trifluorobut-3-en-2-ones undergo an *N* → *ortho* shift of the side chain followed by cyclization and dehydration to afford 2-(trifluoromethyl)quinolines.

As described previously [1], α-deprotonation of *N*-ethylidene-*tert*-butylamine and its subsequent addition onto 1,1,1-trifluoroacetone afforded an azomethine **1a** which was hydrolyzed and dehydrated to give 4,4,4-trifluoro-3-methylbut-2-en-al. The aldehyde was eventually converted into 1-trimethylsilyloxy-3-(trifluoromethyl)buta-1,3-diene, a versatile component for Diels-Alder cycloaddition reactions. Trifluoroacetic acid being roughly 10 times less expensive than trifluoroacetone, we wondered whether we could not combine an ester thereof or its anhydride with lithiated *N*-ethylidene-*tert*-butylamine in order to obtain the iminoketone **2**. Nucleophilic transfer of a methyl group from a suitable organometallic reagent should then convert ketone **2** into the hydroxylated azomethine **1a**. This route would not only offer the advantage of economy, but also of flexibility. By using organometallics having alkyl moieties $RCH_2$ bigger than methyl, homologous azomethines **1b** could be made accessible.



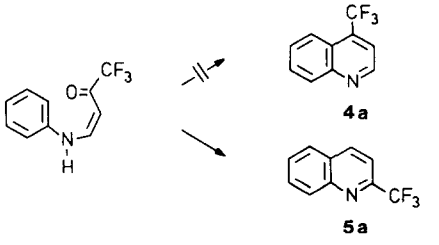
The expectation did not materialize. The reaction between ketone **2** and a variety of organolithium, -magnesium and -copper reagents, all employed in excess, was sluggish and only small amounts of the azomethines **1a** or **1b** were identified in the reaction mixtures. The relative inertness of ketone **2** can be easily

understood. As revealed by its nmr spectra and in agreement with the behavior of halogen-free model compounds [2], it does not exist in the imine forms **2-CH** but rather in the tautomeric enamine forms **2-NH**, the (*Z*) isomer strongly preponderating over the (*E*) isomer in solvents of low polarity. Therefore, any basic organometallic reagent will immediately abstract the nitrogen-bound hydrogen atom as a proton, leaving behind an enolate-like anion.




In the course of these investigations we have recognized a pronounced propensity of ketone **2** to undergo an acid catalyzed amine exchange. Thus, treatment with aniline causes the complete replacement of the *tert*-butylamino by the anilino moiety.

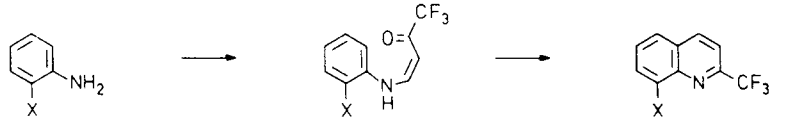

The new ketone **3a** [2, 3] is stable under ordinary conditions. However, in the presence of phosphoryl trichloride a smooth cyclization accompanied by dehydration takes place leading to a trifluoromethyl substituted quinoline in 59% yield. Initially we assumed this product to be 4-(trifluoromethyl)quinoline **4a**. This structure would have established an analogy with a literature report [4] according to which 3-(diethylamino)methylene-1,1,1,5,5,5-hexafluoropentan-2,4-dione [5] can be submitted to an iron trichloride catalyzed exchange of the dialkylamino against the anilino moiety followed by a titanium tetrachloride catalyzed cyclization to afford 4-trifluoromethyl-3-(trifluoroacetyl)quinoline. However, the preliminary assignment had to be revised on the basis of compelling spectroscopic evidence. Without doubt, the product is 2-(trifluoromethyl)-quinoline **5a**, the substituent occupying the nitrogen-adjacent position.



At present, any attempt to rationalize the observed shift of side chain attachment would be premature. Cross-over experiments will have to tell us whether the unprecedented positional exchange is brought about intramolecularly or intermolecularly.

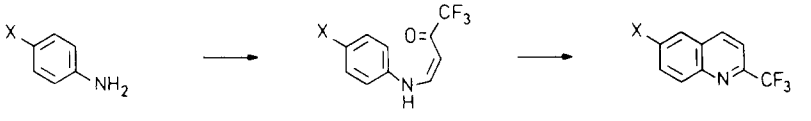
To evaluate the scope of the method we have probed the effect of substituents on the outcome of the reaction. Strongly electron-withdrawing functions such as nitro groups were found to impede the cyclization. In contrast, moderately electronegative substituents such as chlorine and bromine are well tolerated. Finally, electron-donating groups such as methyl, methoxy and fluorine accelerate the crucial ring-closure step. Actually, in a few cases it was not possible to isolate the 4-anilino-1,1,1-trifluorobut-3-en-2-one intermediate **3** due to rapid subsequent transformation to the quinoline **5**.

Obviously *ortho* substituents present in the aniline have to emerge at position 8 of the quinoline. Thus, 8-bromo- and 8-methyl-2-(trifluoromethyl)quinoline **5b** and **5c** can be obtained through ketones **3b** and **3c** in 38% and 31% overall yield, respectively.



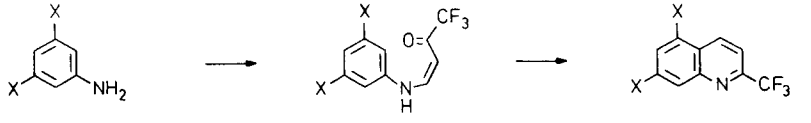
X = Br **3b** **5b**
X = $CH_3$ **3c** **5c**

In the same way, *para* substituted anilines give rise to 6-substituted quinolines. The cyclization of the ketones **3d** and **3e** afforded 6-bromo- and 6-methyl-2-(trifluoromethyl)quinoline **5d** and **5e** in 21% and 53% yield.



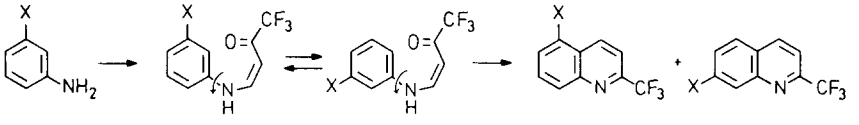
X = Br **3d** **5d**
X = $CH_3$ **3e** **5e**

Doubly *meta* substituted anilines are again converted into a single product. The readily occuring ring closure of the ketones **3f** and **3g**, derived from 3,5-dimethoxyaniline and 3,5-difluoroaniline produces 5,7-dimethoxy- and 5,7-difluoro-2-(trifluoromethyl)quinoline, both in 63% yield. Actually, intermediate **3f** cannot be isolated since, due to its electron-rich aromatic nucleus, it immediately cyclizes even under weakly acidic conditions.



X = $OCH_3$ **3f** **5f**
X = F **3g** **5g**

Positional uncertainty is encountered when the aniline carries only one *meta* substituent. As observed already previously [6], fluoro and methoxy substituents tend to discriminate against an attack of the electrophile at the position *ortho* with respect to the substituent X and to favor the attack at the *para* position. In agreement with this empirical rule, the aminoketones **3h** and **3i** gave the 5- and 7-isomers **5h** (54%) and **5i** (41%) with regioratios of 6 : 94 and 8 : 92, respectively. But also the aminoketones **3j**, **3k** and **3l** showed an exceptionally strong preference for the 7-isomers, producing the quinolines **5j** (63%), **5k** (68%) and **5l** (64%) in 5-/7-isomeric ratios ranging from 11 : 89 to 22 : 78.



| | | | |
|---|---|---|---|
| X = $OCH_3$ | **3h** | **5h-5** | **5h-7** |
| X = F | **3i** | **5i-5** | **5i-7** |
| X = Cl | **3j** | **5j-5** | **5j-7** |
| X = Br | **3k** | **5k-5** | **5k-7** |
| X = $CH_3$ | **3l** | **5l-5** | **5l-7** |

The method described above is related to the Combes synthesis [7 - 9] of 2,4-disubstituted anilines. There is, however, a fundamental difference between the two protocols : rather than to condense an aniline with a, generally symmetrical, 1,3-diketone, we employ the chemical equivalent of a 3-oxoaldehyde as the electrophilic component.

## EXPERIMENTAL

### 1. Generalities

*Starting materials* were purchased from Fluka AG (Buchs), Aldrich-Chemie (Steinheim), or Merck-Schuchardt (Hohenbrunn), unless literature references or details of the preparation are given. All commercial reagents were used without further purification.

*Ethereal extracts* were dried with sodium sulfate. Before distillation of compounds prone to radical polymerization or sensitive to acids a spatula tip of *hydroquinone* or, respectively, *potassium carbonate* was added.

The temperature of dry ice/methanol baths is consistently indicated -75 °C and "room temperature" (22 - 26 °C) as 25 °C. *Melting ranges* (m.p.) are reproducible after resolidification, unless stated otherwise ("dec."), and are corrected by using a calibration curve which was established with authentic standards.

Chromosorb G-AW of 80 - 100 and 60 - 80 mesh particle size was used as the support for packed analytical or preparative columns (2 - 3 m long, 2 mm inner diameter and 3 or 6 m long, 1 cm inner diameter, respectively). Packed columns were made of glass, while quartz served as the material for coated, Grob type capillary columns (≥ 10 m long). Mainly two types of stationary phases were employed : Carbowax 20 M (abbreviated C-20 M), a polyethylene glycol, and the silicone rubber DB-1701.

Silica gel (Merck Kieselgel 60) of 70 - 230 mesh (0.06 - 0.20 mm) particle size was used for *column chromatography*. The solid support was suspended in hexane and, when all air bubbles had escaped, was sluiced into the column. When the level of the liquid was still some 3 - 5 cm above the silica layer, the dry powder, obtained by adsorption of the crude product mixture on 15 - 20 g silica gel and subsequent evaporation of the solvent, was poured on top of the column.

$^1$H-NMR spectra were recorded, unless stated otherwise, in deuteriochloroform solution at 400 MHz and $^{13}$C-NMR spectra ($^1$H broad-band decoupled) in the same solvent at 100,6 MHz. Chemical shifts δ refer to the signal of tetramethylsilane. Coupling constants (*J*) are measured in Hz. Abbreviations of coupling patterns : s (singlet), d (doublet), t (triplet), q (quartet), td (triplet of doublets) and m (multiplet).

Mass spectra were obtained at 70 eV ionization potential maintaining a source temperature of 200 °C. They are not listed in the following text since all of them showed the expected fragmentation pattern.

Elementary analyses were made by the laboratory of I. Beetz, D-96301 Kronach, Germany. The new products described below contain between 19 and 41% of fluorine (by weight). Under these circumstances, the standard deviations of elementary analyses are larger (± 0.4 or 0.5%) than the ordinary average (± 0.3%), since special absorption techniques are required.

2. 4-Amino-1,1,1-trifluorobut-3-en-2-ones

Replacement of the *tert*-butylamine derivative **2** by an anilino moiety gave access to the required intermediates **3a**, **3b**, **3c**, **3d**, **3e**, **3g**, **3i**, **3j**, **3k** and **3l**. However, two aminoketones, **3f** and **3h**, proved to be too labile in acidic medium, being rapidly converted into the corresponding quinolines **5f-7** and **5h-7**.

**4-*tert*-Butylamino-1,1,1-trifluorobut-3-en-2-one (2)** : Precooled, anhydrous tetrahydrofuran (0.10 L), diisopropyl-amine (43 mL, 30 g, 0.30 mol) and *N*-ethylidene-*tert*-butylamine (*N*-ethylidene-1,1-dimethylethyl-amine; 42 mL, 31 g, 0.30 mol) were consecutively added to a solution of butyllithium (0.30 mol) in hexane (0.20 L) kept in a dry ice/methanol bath. After 30 min at -75 °C, ethyl trifluoroacetate (36 mL, 43 g, 0.30 mol) was added dropwise in the course of 30 min. The mixture was poured into water (0.20 L), neutralized with glacial acetic acid (35 mL) and extracted with diethyl ether (3 × 0.10 L). The combined organic layers were washed with brine (2 × 50 mL), dried and concentrated (to approximately 25 mL). Upon addition of pentane (0.10 L) the product **2** crystallized as colorless needles; mp 56 - 57 °C; 86%. - $^1$H-NMR : δ 10.8 (1 H, d, broad, *J* 14.0), 7.27 (1 H, dd, *J* 14.0, 7.2), 5.37 (1 H, d, *J* 7.1), 1.36 (9 H, s). - The signal at lowest field disappears, when the solution containing the sample is washed with heavy water. - Analysis : calc. for $C_8H_{12}F_3NO$ (195.18) C 49.23, H 6.20; found C 49.41, H 5.97%.

**4-Anilino-1,1,1-trifluorobut-3-en-2-one (3a)** : A mixture of the aminoketone **2** (9.8 g, 50 mmol), aniline 5.0 mL, 5.1 g, 55 mmol), glacial acetic acid (20 mL) and trifluoroacetic acid (20 mL) were heated 6 h to 75 °C. Upon addition of water (0.2 L), a precipitate was formed which was collected and dissolved in diethyl ether (0.10 L). The organic layer was washed with a saturated aqueous solution of sodium hydrogencarbonate (100 mL) and water before being dried and concentrated (to the approximate volume of 10 mL). Upon dilution with pentane (25 mL), pale yellow needles settled out; mp 84 - 85 °C; 92%. - $^1$H-NMR : δ 7.66 (1 H, dd, *J* 13.2, 7.5), 7.40 (2 H, dd, *J* 8.3, 7.7), 7.20 (1 H, tt, *J* 7.5, 1.1), 7.14 (2 H, d, *J* ~ 8), 5.66 (1 H, d, *J* 7.5). - When the solution of compound **3a** in chloroform is washed with heavy water (0.5 mL), the signal at lowest field is simplified : δ 7.65 (1 H, d, *J* 7.5). - Analysis : calc. for $C_{10}H_8F_3NO$ (215.17) C 55.82, H 3.75; found C 55.95, H 3.97%.

**4-(2-Bromoanilino)-1,1,1-trifluorobut-3-en-2-one (3b)** : Analogously obtained from 2-bromoaniline; mp 73 - 75 °C; 75%. - $^1$H-NMR ($CD_2Cl_2$) : δ 7.71 (1 H, dd, *J* 12.9, 7.7), 7.65 (1 H, dd, *J* 8.0, 1.5), 7.39 (1 H, td, *J* 7.8, 1.5), 7.33 (1 H, dd, *J* 8.2, 1.5), 7.08 (1 H, ddd, *J* 8.2, 6.7, 1.5), 5.75 (1 H, d, *J* 7.6). - Analysis : calc. for $C_{10}H_7BrF_3NO$ (294.07) C 40.84, H 2.40; found C 40.98, H 1.99%.

**1,1,1-Trifluoro-4-(2-methylanilino)but-3-en-2-one (3c)** : From *o*-toluidine; mp 45.0 - 45.5 °C; 84%. - $^1$H-NMR ($D_3CCOCD_3$) : δ 8.24 (1 H, dd, *J* 12.9, 7.3), 7.53 (1 H, d, *J* 8.0), 7.35 (2 H, t-like m, *J* 8.4), 7.16 (1 H, dt, *J* 7.9, 1.0), 5.76 (1 H, dd, *J* 7.3, 0.6), 2.41 (3 H, s). - Analysis : calc. for $C_{11}H_{10}F_3NO$ (229.20) C 57.64, H 4.40; found C 58.05, H 4.12%.

**4-(4-Bromoanilino)-1,1,1-trifluorobut-3-en-2-one (3d)** : From 4-bromoaniline; mp 74 - 75 °C; 73 %. - $^1$H-NMR : δ 7.60 (1 H, dd, *J* 13.1, 7.6), 7.51 (2 H, d, *J* 8.8), 7.02 (2 H, d, *J* 8.8), 5.68 (1 H, d, *J* 7.6). - Analysis : calc. for $C_{10}H_7BrF_3NO$ (294.07) C 40.84, H 2.40; found C 40.87, H 2.01%.

**1,1,1-Trifluoro-4-(4-methylanilino)but-3-ene-2-one (3e)** : From *p*-toluidine; mp 109.0 - 109.5 °C; 83%. - $^1$H-NMR : δ 7.62 (1 H, dd, *J* 13.4, 7.4), 7.19 (2 H, d, *J* 8.4), 7.03 (2 H, d, *J* 8.4), 5.62 (1 H, d, *J* 7.5), 2.35 (3 H, s). - Analysis : calc. for $C_{11}H_{10}F_3NO$ (229.20) C 57.64, H 4.40; found C 58.17, H 4.16%.

**4-(3,5-Dimethoxyanilino)-1,1,1-trifluorobut-3-en-2-one (3f)** : From 3,5-dimethoxyaniline; not isolated since immediate cyclization, to give **5f**, is occurring under the condensation conditions.

**4-(3,5-Difluoroanilino)-1,1,1-trifluorobut-3-ene-2-one (3g)** : From 3,5-difluoroaniline; mp 111 - 112 °C; 83%. - $^1$H-NMR : δ 7.55 (1 H, dd, *J* 12.8, 7.7), 6.7 (3 H, m), 5.72 (1 H, d, *J* 7.8). - Analysis : calc. for $C_{10}H_6F_5NO$ (246.12) C 47.82, H 2.41; found C 48.03, H 2.02%.

**1,1,1-Trifluoro-4-(3-methoxyanilino)but-3-ene-2-one (3h)** : From *m*-anisidine; not isolated since immediate cyclization, to give **5h**-7, is occurring under the condensation conditions.

**1,1,1-Trifluoro-4-(3-fluoroanilino)but-3-ene-2-one (3i)** : From 3-fluoroaniline; mp 80 - 81 °C; 73%. - $^1$H-NMR : δ 7.62 (1 H, dd, *J* 13.0, 7.5), 7.37 (1 H, td, *J* 8.2, 6.4), 6.9 (3 H, m), 5.70 (1 H, d, *J* 7.7). - Analysis: calc. for $C_{10}H_7F_4NO$ (233.16) C 51.51, H 3.03; found C 51.98, H 2.62%.

**4-(3-Chloroanilino)-1,1,1-trifluorobut-3-ene-2-one (3j)** : From 3-chloroaniline; mp 62 - 64 °C; 76%. - $^1$H-NMR : δ 7.61 (1 H, dd, *J* 13.0, 7.5), 7.32 (1 H, t, *J* 8.1), 7.17 (1 H, ddd, *J* 8.0, 1.8, 0.9), 7.15 (1 H, t, *J* 2.0), 7.01 (1 H, ddd, *J* 8.0, 2.0, 0.9), 5.69 (1 H, d, *J* 7.5). - Analysis : calc. for $C_{10}H_7ClF_3NO$ (249.62) C 48.12, H 2.83; found C 47.98, H 3.14%.

**4-(3-Bromoanilino)-1,1,1-trifluorobut-3-ene-2-one (3k)** : From 3-bromoaniline; mp 81.5 - 82 °C; 89%. - $^1$H-NMR ($D_3CCOCD_3$) : δ 7.66 (1 H, dd, *J* 13.0, 7.5), 7.37 (1 H, s), 7.35 (1 H, ddd, *J* 9.0, 1.2, 0.5), 7.29 (1 H, dt, *J* 8.0, 0.5), 7.12 (1 H, dq, *J* 8.0, 1.2), 5.70 (1 H, dd, *J* 7.5, 0.5). - Analysis : calc. for $C_{10}H_7BrF_3NO$ (294.07) C 40.84, H 2.40; found C 41.21, H 1.99%.

**1,1,1-Trifluoro-4-(3-methylanilino)but-3-ene-2-one (3l)** : From *m*-toluidine; mp 69 - 70 °C; 89%. - $^1$H-NMR : δ 7.65 (1 H, dd, *J* 13.2, 7.5), 7.27 (1 H, t, *J* 7.5), 7.01 (1 H, d, *J* 7.5), 6.94 (1 H, s), 6.92 (1 H, d, *J* 7.5), 5.64 (1 H, d, *J* 7.5), 2.37 (3 H, s). - Analysis : calc. for $C_{11}H_{10}F_3NO$ (229.20) C 57.64, H 4.40; found C 57.69, H 4.45%.

3. 2-(Trifluoromethyl)quinolines

Identical reaction conditions were applied in all cases. The work-up procedure used to isolate the products **5b**, **5c**, **5d**, **5e**, **5f** and **5g** was the same as the one described for 2-(trifluoromethyl)quinoline. The protocol was slightly modified when *meta* substituted aminoketones were cyclized to afford compounds **5h**, **5i**, **5j**, **5k** and **5l**. The ethereal extracts were dried and evaporated and the crude products were examined by nmr spectroscopy and capillary gas chromatography (30 m, DB-1701, 150 °C) in order to determine their regioisomeric composition prior to purification. All analytical samples were purified by sublimation if not by preparative gas chromatography.

**2-(Trifluoromethyl)quinoline (5a)** : A mixture of the aminoketone **3a** (5.4 g, 25 mmol) and phosphoryl trichloride (2.3 mL, 3.8 g, 25 mmol) and heptane (25 mL) was heated 6 h to 100 °C. The resulting suspension was poured into a saturated aqueous solution (0.20 L) of sodium carbonate. The product was extracted with diethyl ether (2 × 75 mL), absorbed on silica gel and eluted with a 1 : 6 (v/v) mixture of dichloromethane (or diethyl ether) and hexane to afford colorless needles; mp 57.0 - 57.5 °C; 59%. - $^1$H-NMR : δ 8.37 (1 H, d, *J* 8.5), 8.24 (1 H, d, *J* 8.5), 7.92 (1 H, d, *J* 8.3), 7.84 (1 H, dd, *J* 8.5, 7.2, 1.3), 7.75 (1 H, d, *J* 8.5), 7.69 (1 H, t, *J* 8.5). - $^{13}$C-NMR : δ 147.8 (q, *J* 34.4), 147.1 (s), 138.0 (s), 130.8 (s), 129.9 (s), 128.8 (s), 128.6 (s), 127.6 (s), 121.6 (q, *J* 275), 116.6 (s). - Analysis : calc. for $C_{10}H_6F_3N$ (197.16) C 60.92, H 3.07; found C 60.89, H 2.97%.

**8-Bromo-2-(trifluoromethyl)quinoline (5b)** : From aminoketone **3b**; mp 63.5 - 64.0 °C; 38%. - $^1$H-NMR : δ 8.37 (1 H, d, *J* 8.5), 8.17 (1 H, d, *J* 7.5), 7.89 (1 H, d, *J* 8.0), 7.80 ( 1 H, d, *J* 8.5), 7.53 (1 H, t, *J* 7.8). - $^{13}$C-NMR : δ 148.6 (q, *J* 34.5), 144.4 (s), 138.8 (s), 134.5 (s), 130.1 (s), 129.0 (s), 127.4 (s), 125.7 (s), 121.3 (q, *J* 275.5), 117.7 (s). - Analysis : calc. for $C_{10}H_5BrF_3N$ (276.05) C 43.51, H 1.83; found C 43.38, H 2.07%.

**8-Methyl-2-(trifluoromethyl)quinoline (5c)** : From aminoketone **3c**; colorless oil; $n_D^{20}$ 1.5236; 31%. - $^1$H-NMR : δ 8.29 (1 H, d, *J* 8.5), 7.72 (1 H, d, *J* 8.0), 7.71 (1 H, d, *J* 8.5), 7.65 (1 H, d, *J* 6.9), 7.54 (1 H, dd, *J* 8.0, 7.2), 2.83 (3 H, s). - $^{13}$C-NMR : δ 146.4 (q, *J* 34.5), 146.3 (s), 138.3 (s), 130.7 (s), 128.9 (s), 128.4 (s), 125.5 (s), 121.8 (q, *J* 274.8), 116.4 (s), 17.8 (s). - Analysis : calc. for $C_{11}H_8F_3N$ (211.19) C 62.56, H 3.82; found C 62.65, H 3.94%.

**6-Bromo-2-(trifluoromethyl)quinoline (5d)** : From aminoketone **3d**; mp 121 - 122 °C (prisms); 21%. - $^1$H-NMR : δ 8.28 (1 H, d, *J* 8.5), 8.11 (1 H, d, *J* 8.6), 8.09 (1 H, s), 7.90 ( 1 H, dd, *J* 8.8, 2.3), 7.77 ( 1 H, d, *J* 8.5). - Analysis : calc. for $C_{10}H_5BrF_3N$ (276.05) C 43.51, H 1.83; found C 43.38, H 2.00%.

**6-Methyl-2-(trifluoromethyl)quinoline (5e)** : From aminoketone **3e**; mp 88 - 89 °C; 53%. - $^1$H-NMR : δ 8.24 (1 H, d, *J* 8.5), 8.11 (1 H, d, *J* 9.2), 7.68 (1 H, d, *J* 8.5), 7.6 (2 H, m), 2.57 (3 H, s). - $^{13}$C-NMR : δ 147.0 (q, *J* 34.7), 145.8 (s), 138.9 (s), 137.3 (s), 133.2 (s), 129.7 (s), 128.9 (s), 126.5 (s), 121.8 (q, *J* 275), 116.7 (s), 21.7(s). - Analysis : calc. for $C_{11}H_8F_3N$ (211.19) C 62.56 H 3.82; found C 62.57, H 4.03%.

**5,7-Dimethoxy-2-(trifluoromethyl)quinoline (5f)** : From aminoketone **3f**; mp 112.5 - 113.5 °C (needles); 63%. - $^1$H-NMR : δ 8.59 (1 H, d, *J* 8.7), 7.55 ( 1 H, d, *J* 8.7), 7.10 (1 H, s), 6.57 (1 H, s), 3.99 (3 H, s), 3.82 (3 H, s). - $^{13}$C-NMR : δ 162.4 (s), 155.7 (s), 149.6 (s), 148.4 (q, *J* 34.5), 132.8 (s), 121.8 (q, *J* 275.5), 117.9 (s), 113.6 (s), 99.8 (s), 55.8 (s), 55.7 (s). - Analysis : calc. for $C_{12}H_{10}F_3NO_2$ (257.21) C 56.04, H 3.92; found C 55.97, H 4.12%.

**5,7-Difluoro-2-(trifluoromethyl)quinoline (5g)** : From aminoketone **3g**; mp 51 - 52 °C (prisms); 63%. - $^1$H-NMR : δ 8.60 (1 H, d, *J* 8.5), 7.77 (1 H, d, *J* 8.5), 7.71 (1 H, dd, *J* 9.5, 1.5), 7.19 (1 H, dddd, *J* 9.5, 8.5, 3.2, 1.0). - Analysis : calc. for $C_{10}H_4F_5N$ (233.14) C 51.52, H 1.73; found C 51.41, H 2.13%.

**7-Methoxy-2-(trifluoromethyl)quinoline (5h)** : From aminoketone **3h**; mp 65 - 66 °C (needles); 54%. - $^1$H-NMR : δ 8.25 (1 H, d, *J* 8.5), 7.77 (1 H, d, *J* 9.0), 7.60 (1 H, d, *J* 8.5), 7.52 (1 H, d, *J* 2.3), 7.31 (1 H, dd, *J* 9.0, 2.4), 3.97 (3 H, s). - $^{13}$C-NMR : δ 161.7 (s), 149.1 (s), 148.1 (q, *J* 34.7), 137.5 (s), 128.6 (s), 124.3 (s), 122.3 (s), 121.7 (s), 114.6 (s), 107.5 (s), 55.7 (s). - Analysis : calc. for $C_{11}H_8F_3NO$ (227.19) C 58.16, H 3.55; found C 58.02, H 3.89%.

**5-Fluoro-2-(trifluoromethyl)quinoline (5i-5)** and **7-fluoro-2-(trifluoromethyl)quinoline (5i-7)** : From aminoketone **3i**; 41%. - The 5- and 7-substituted isomers, formed in a 8 : 92 ratio, were separated by preparative gas chromatography (3 m, 5% C-20M, 160 °C). - **5i-5** : $^1$H-NMR : δ 8.68 (1 H, d, *J* 8.9), 8.06 (1 H, d, *J* 8.7), 7.81 (1 H, d, *J* 8.7), 7.78 (1 H, ddd, *J* 8.7, 8.0, 6.0), 7.36 (1 H, t, *J* 8.5). - **5i-7** : mp 52 - 53 °C (prisms; from pentane). - $^1$H-NMR : δ 8.36 (1 H, d, *J* 8.5), 7.92 (1 H, dd, *J* 9.0, 6.0), 7.86 (1 H, dd, *J* 9.9, 2.5),

7.72 (1 H, d, *J* 8.5), 7.48 (1 H, td, *J* 8.7, 2.5). - $^{13}$C-NMR : δ 163.7 (d, *J* 252.8), 148.6 ( q, *J* 34.8), 148.2 (d, *J* 13.2), 138.1 (s), 129.8 (d, *J* 7.8), 125.9 (s), 121.9 (q, *J* 275.4), 119.5 (d, *J* 25.9), 113.7 (s). - Analysis : calc. for $C_{10}H_5F_4N$ (215.15) C 55.83, H 2.34; found C 56.07, H 2.24%.

j) **5-Chloro-2-(trifluoromethyl)quinoline** (**5j-5**) and **7-chloro-2-(trifluoromethyl)quinoline** (**5j-7**) : From aminoketone **3j**; 63%. - The 5- and 7-substituted isomers, formed in a 21 : 79 ratio, were separated by preparative gas chromatography (3 m, 5% C-20M, 185 °C). - **5j-5** : $^1$H-NMR ($D_3CCOCD_3$) : δ 8.95 (1 H, d, 8.9), 8.20 (1 H, ddd, 6.1, 3.5, 0.8), 8.10 (1 H, d, *J* 8.9), 7.96 (1 H, d, *J* 6.2), 7.95 (1 H, d, *J* 3.5). - $^{13}$C-NMR : δ 148.4 (q, *J* 35.3), 147.8 (s), 135.3 (s), 131.5 (s), 130.5 (s), 129.3 (s), 128.5 (s), 127.1 (s), 121.3 (q, *J* 275.5), 117.6 (s). - **5j-7** : mp 107 - 109 °C (from pentane). - $^1$H-NMR ($CD_2Cl_2$) : δ 8.39 (1 H, d, *J* 8.5), 8.20 (1 H, d, *J* 2.9), 7.91 (1 H, d, *J* 8.8), 7.76 (1 H, d, *J* 8.5), 7.66 (1 H, dd, *J* 8.8, 2.0). - $^{13}$C-NMR : δ 148.8 (q, *J* 34.5), 147.3 (s), 138.0 (s), 136.9 (s), 129.7 (s), 128.9 (s), 127.1 (s), 121.7 (q, *J* 273.1), 116.9 (s). - Analysis : calc. for $C_{10}H_5ClF_3N$ (231.60) C 51.86, H 2.18; found C 51.24, H 2.21%.

k) **5-Bromo-2-(trifluoromethyl)quinoline** (**5k-5**) and **7-bromo-2-(trifluoromethyl)quinoline** (**5k-7**) : From aminoketone **3k**; 68%. - The 5- and 7-substituted isomers were separated by preparative gas chromatography (3 m, 5% C-20M, 200 °C). - **5k-5** : $^1$H-NMR : δ 8.76 (1 H, dd, *J* 8.8, 0.7), 8.21 (1 H, d, *J* 8.8), 7.97 (1 H, d, *J* 7.5), 7.84 (1 H, d, *J* 8.9), 7.69 (1 H, dd, *J* 8.7, 7.5). - **5k-7** : mp 70.0 - 70.5 °C (from pentane). - $^1$H-NMR ($D_3CCOCD_3$) : δ 8.74 (1 H, d, *J* 8.5), 8.40 (1 H, s), 8.13 (1 H, d, *J* 9.0), 7.99 (1 H, d, *J* 8.5), 7.93 (1 H, dd, *J* 8.9, 1.9) - $^{13}$C-NMR : δ 148.7 (q, *J* 34.8), 147.5 (s), 138.1 (s), 132.2 (s), 128.9 (s), 127.4 (s), 125.2 (s), 121.4 (q, *J* 275.4), 113.7 (s). - Analysis : calc. for $C_{10}H_5BrF_3N$ (276.06) C 43.51, H 1.83; found C C 43.45, H 1.85%.

**5-Methyl-2-(trifluoromethyl)quinoline** (**5l-5**) and **7-methyl-2-(trifluoromethyl)quinoline** (**5l-7**) : From aminoketone **3l**; 34% (crude, mixture (**5l-5**)/**5l-7**) 11 : 89). - The 7-isomer was obtained pure after column chromatography : mp 57.0 - 57.5 °C; 64%. - $^1$H-NMR : δ 8.29 (1 H, d, *J* 8.5), 8.01 (1 H, s), 7.79 (1 H, d, *J* 8.5), 7.66 (1 H, d, *J* 8.5), 7.50 (1 H, d, *J* 8.5), 2.59 (3 H, s). - $^{13}$C-NMR : δ 147.7 (q, *J* 34.5), 147.2 (s), 141.3 (s), 137.5 (s), 134.5 (s), 130.8 (s), 128.7 (s), 127.2 (s), 121.7 (q, *J* 275.1), 115.8 (s). - Analysis : calc. for $C_{11}H_8F_3N$ (211.19) C 62.56, H 3.82; found C 62.54, H 4.02%.

Acknowledgment : The authors are indebted to the Schweizerische Nationalfonds zur Förderung der wissenschaftlichen Forschung, Berne, (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 Schlosser, M.; Keller, H.; *Liebigs Ann.* **1995**, 1587 - 1589.
2 Fellieux-Blanchard, M.L.; Durand, H.; Bergeon, M.T.; Clesse, F.; Martini, G.J.; *J. Mol. Struct.* **1969**, *3*, 351 - 357; *Chem. Abstr.* **1969**, *71*, 60512u.
3 Nesmeyanov, A.N.; Rybinskaya, M.I.; *Izv. Akad. Nauk SSSR, Ser. Khim.* **1966**, 1764 - 1772; *Chem. Abstr.* **1967**, *66*, 94945z.
4 Soufyane, M.; Mirand, C.; Lévy, J.; *Tetrahedron Lett.* **1993**, *34*, 7737 - 7740.
5 Schreiber, S.L.; *Tetrahedron Lett.* **1980**, *21*, 1027 - 1030.
6 Mävers, U.; Berruex, F.; Schlosser, M.; *Tetrahedron*, in press.
7 Combes, A.; *Bull. Soc. Chim. Fr.* **1888**, *49*, 89 - 92.
8 Fischer, O.; Scheibe, G.; Merkel, P.; Müller, R.; *J. Prakt. Chem.* **1920**, *208[100]*, 91- 105.
9 Bonner, T.G.; Thorne, M.P.; Wilkins, J.M.; *J. Chem. Soc.* **1955**, 2351 - 2358; Bonner, T.G.; Wilkins, J.M.; *J. Chem. Soc.* **1955**, 2358 - 2360; Bonner, T.G.; Barnard, M.; *J. Chem. Soc.* **1958**, 4181 - 4186.

(*Received in Belgium* 11 *December* 1995; *accepted* 2 *February* 1996)