SYNTHESIS OF 2,3-BIS(TRIFLUOROMETHYL)INDOLE BY THE REACTION OF AROMATIC NITRONES WITH HEXAFLUOROBUT-2-YNE[1]

Yoshiro Kobayashi*, Itsumaro Kumadaki, and Tsutomu Yoshida
Tokyo College of Pharmacy, Horinouchi, Hachioji 192-03, Japan

Reaction of N-phenyl-α-aryl-nitrones with hexafluorobut-2-yne was examined. p-Anisyl-, phenyl-, and p-nitrophenyl-nitrones gave 2,3-bis(trifluoromethyl)indole through recyclization of the primary adducts to oxazoline compounds followed by hydrolysis and cyclization, while the isoxazoline compound underwent rearrangement to N,N-dimethyl-N'-phenyl-phenylenediamine compound, when the aryl was a p-dimethylaminophenyl group.

Interesting reactions of nitrones with acetylenic compounds have been reported by Winterfeldt et al.[2], where the primary dipolar cycloadducts underwent rearrangement through various paths. Now, we report 1,3-dipolar reaction of nitrones with hexafluorobut-2-yne, in which another type of rearrangement of the isoxazoline intermediate to oxazoline and further recyclization to 2,3-bis(trifluoromethyl)indole were observed.

The reaction is exemplified with N-phenyl-α-(p-anisyl)-nitrone (1). Solution of 1 in carbon tetrachloride was sealed with hexafluorobut-2-yne (2) in a stainless steel tube and kept

at room temperature overnight. Evaporation of the solvent gave a pale yellow oil (3). 3: mass spectrum m/e 389 (M^+); high mass spectrum calcd. for $C_{18}H_{13}F_6NO_2$ 389.0850, found 389.0825; ^{1}H-nmr ($CDCl_3$) δ 3.80 (3H, s, OCH_3), 6.37 (1H, s, CH), 6.8-7.5 (9H); ^{19}F-nmr δ[3] 1.6 (q, J=8.5 Hz), 6.2 (q, J=8.5 Hz). The low chemical shift and no coupling of the peak at 6.37 with fluorine in ^{1}H-nmr spectrum suggest that 3 is not an isoxazoline but an oxazoline compound. Possible mechanism is shown in Chart 1. Compound 3 was transformed to 2,3-bis(trifluoromethyl)indole (4) and anisaldehyde by repeated SiO_2 column chromatography in a benzene-hexane solution. 4: mp 49-52°C; mass spectrum m/e 253; high mass spectrum calcd. for $C_{10}H_5F_6N$ 253.0326, found 253.0352; ^{19}F-nmr δ -9.4 (q, J=7.5 Hz), -5.3 (q, J=7.5 Hz).

Three intermediates (5, 6, and 7 in Chart 1) were isolated by rapid separation with SiO_2 chromatography and their structures were estimated from elemental analysis and ^{1}H- and ^{19}F-nmr. All theses intermediates were converted to 4 by repeated chromatography or treatment with acid. Thus, the mechanism for formation of 4 might be one or more courses of a, b, and c in Chart 1.

α-phenyl- and α-(p-nitrophenyl)-N-phenyl-nitrone gave almost similar results. Therefore, not the primary adduct but the isomerized oxazoline compounds (3a and 3b) were isolated. 3a: pale yellow oil; mass spectrum m/e 359; ^{1}H-nmr (CCl_4) δ 6.40 (1H, s); ^{19}F-nmr (CCl_4) δ -7.0, +0.5 (both q, J=8.3 Hz). 3b: mp 84-85°C; mass spectrum m/e 404; ^{1}H-nmr ($CDCl_3$) δ 6.60 (1H, s); ^{19}F-nmr δ -6.3, -1.3 (both q, J=8.5 Hz). Both 3a and 3b were similarly converted to the indole compound 4.

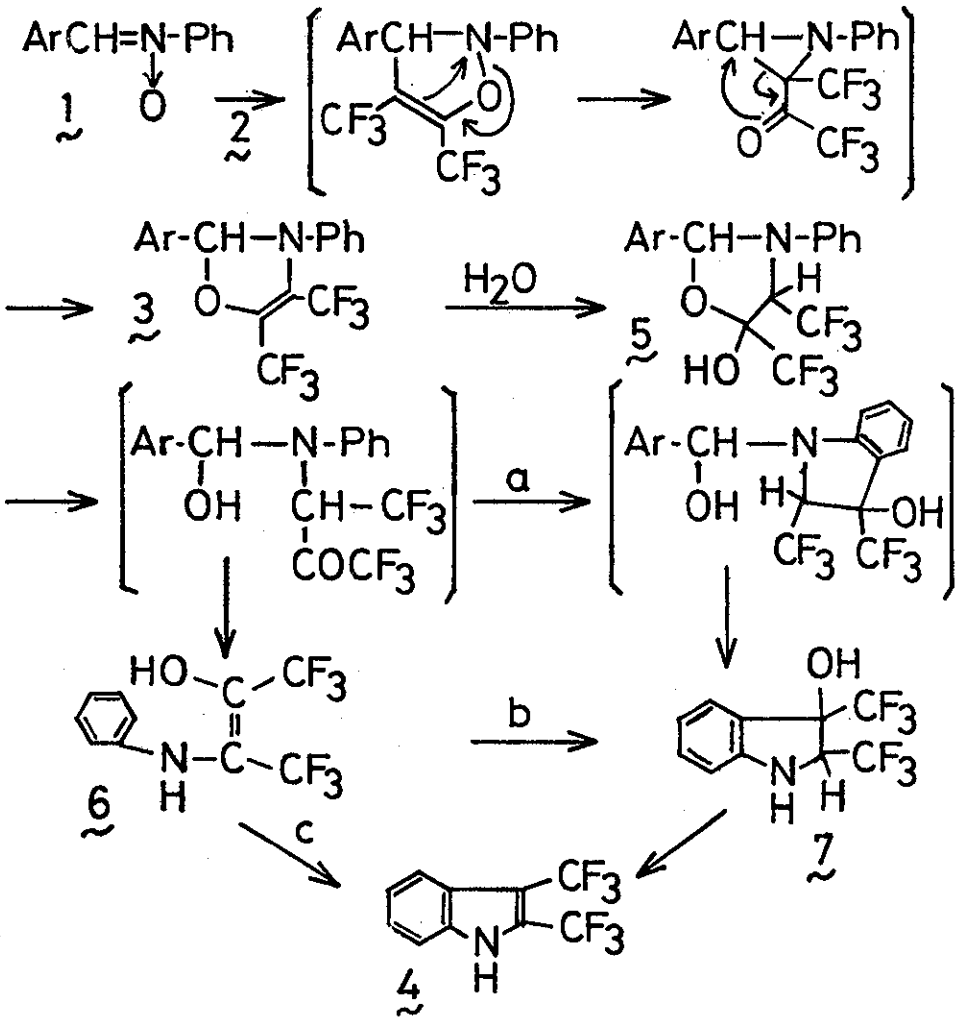

Chart 1

In contrast with the nitrones shown above, α-(p-dimethylaminophenyl)-N-phenylnitrone (8) showed rather a different mode of rearrangement, and N,N-dimethyl-N'-phenyl-N'-(2-trifluoromethyl 2-trifluoroacetylvinyl)-p-phenylenediamine (9) was isolated. 9: mp 148°C; mass spectrum m/e 402 (M^+). Compound 9 was easily

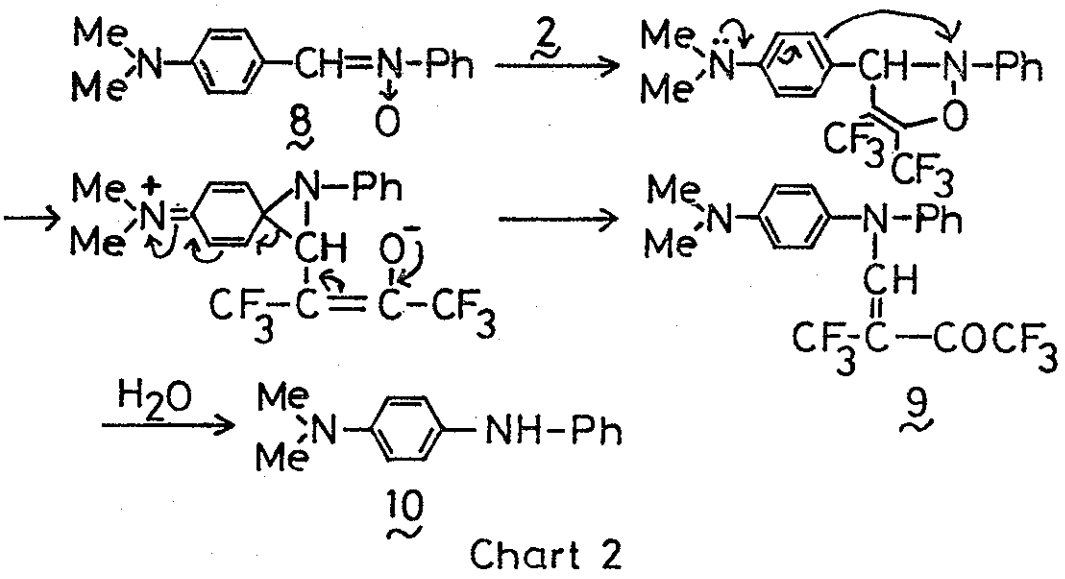

Chart 2

hydrolyzed to N,N-dimethyl-N'-phenylenediamine (10) on recrystallization from ethanol. In this case, a strong electron-donating effect of the dimethylamino group changed the course of the reaction, as shown in Chart 2.

Reference and Notes

1. Dedicated to Emeritus Professor S. Sugasawa on the occasion of his 80th birthday anniversary. Presented at the 97th Annual Meeting of the Pharmaceutical Society of Japan (1977).
2. E. Winterfeldt, W. Krohn, and H.U. Stracke, Chem. Ber., 1969, 102, 2346.
3. $C_6H_5CF_3$ δ 0.0; + value means a higher field.

Received, 9th August, 1977