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Boron Trifluoride-Assisted Ziegler-Zeiser Reaction of Perfluoroalkyllithiums. An Efficient Synthesis of Perfluoroalkylated Heterocycles

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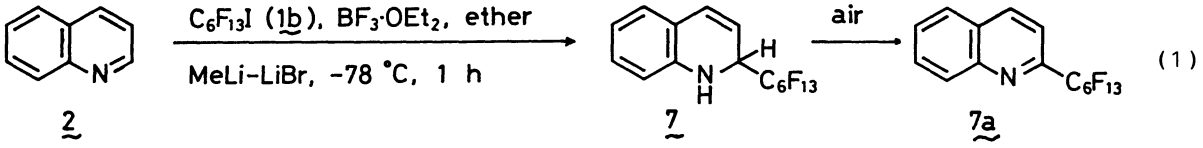
Quinoline, isoquinoline, quinaldine, phthalazine, and quinoxaline are all found to react smoothly with perfluoroalkyllithiums in the presence of $BF_3 \cdot OEt_2$, giving the corresponding perfluoroalkyl addition and/or substitution products in good yields. Perfluoroalkylation occurs at the carbon atom next to the nitrogen.

Polyfluoroalkyl-containing heterocycles have been attracting much attention as pharmaceutical drugs and pesticides[1] and many successful syntheses of such compounds have been reported so far. However, almost all of these syntheses require multi-stage processes which involve the construction of the heterocyclic ring systems simultaneous with incorporation of polyfluoroalkyl moieties.[2] Although a few methods based on organometallic reagents have been proposed for the direct introduction of polyfluoroalkyl group into heterocycles,[3] perfluoroalkyllithiums find no uses for such a purpose as yet probably because of the thermodynamic instability and low nucleophilicity of perfluoroalkyl carboanions. In a previous paper,[4] we have reported that imines are activated by $BF_3 \cdot OEt_2$ to react smoothly with perfluoroalkyllithiums to give the perfluoroalkylated amines in good yields. This methodology is now found to be satisfactorily applicable to aza-

arenes, providing an efficient one-pot preparation of perfluoroalkylated azacycles.

The following experimental procedure is representative: To an ethereal solution (20 ml) of quinoline (**2**) (0.258 g, 2 mmol) and perfluorohexyl iodide (**1b**) (1.784 g, 4 mmol) was added $BF_3 \cdot OEt_2$ (0.52 ml, 4 mmol) at -78 °C. To the resulting suspension was added an ethereal solution of MeLi-LiBr (4 mmol) over *15 min* at -78 °C. The mixture was stirred for 1 h at this temperature, then quenched with saturated aq-NH_4Cl. The organic phase was separated and the aqueous phase was extracted twice with ether. The combined extracts were washed with brine, dried, and evaporated to afford a pale yellow solid (1.051 g), which was recrystallized from hexane to give analytically pure 2-perfluorohexyl-1,2-dihydroquinoline (**7**) as colorless crystals. Yield, 0.561 g (61%). The mother liquor was evaporated and the residue was passed through a silica-gel column (hexane-CH_2Cl_2) to give a mixture (0.248 g, 28%) of **7** and 2-perfluorohexylquinoline (**7a**) (**7**:**7a**= ca. 9:1, estimated by NMR) (Eq. 1). When dissolved in $CHCl_3$ and left in open air at room temperature for two days, dihydroquinoline **7** was completely converted into **7a**.

Perfluoroalkylation reactions of other azomethine heterocycles were carried out under the similar conditions and the results are summarized in Table 1. Perfluoroalkylation occurred preferentially at the carbon atom next to the nitrogen, even in the case of quinaldine (**3**) (entries 4 and 5)[5] where the Ziegler-Zeiser reaction usually leads to metallation products.[6] A slow generation of perfluoroalkyllithiums (45-60 min) was necessary for the reaction of quinaldine (**3**); Perfluoroalkylation with **1b** gave **11** only in a 40% yield, when the addition of MeLi-LiBr was made within 10 min. In the reaction of isoquinoline (**4**), partial oxidation of the initial product occurred easily to give a mixture of 1-perfluoroalkylisoquinoline (**13**) (50%) and, rather surprisingly, a hydroxylic compound (23%). We tentatively assign the structure **14** to the latter compound on the basis of analytical and spectral data, although the mechanistic details of its unexpected formation remain to be clarified. Quinoxaline (**5**) underwent a facile double perfluoroalkylation when 2.4 equiv. of $C_6F_{13}Li$ was used, while monoperfluoroalkylation product **18** was mainly obtained from phthalazine (**6**) under the similar conditions (entries 7 and 9).

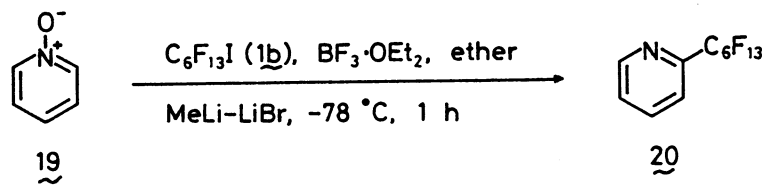


(1)

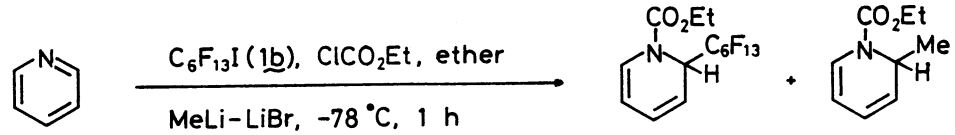
Table 1. Perfluoroalkylation of Condensed Azaarenes

Entry	Perfluoroalkyl iodide 1[a]	Azaarene	Products (Yield/%)[b]
1	n-$C_8F_{17}I$ 1a	2	8 (84)[c]
2	n-C_4F_9I 1c	2	9 (99)[c]
3	C_2F_5I 1d	2	10 (93)[c]
4	n-$C_6F_{13}I$ 1b	3	11 (72)
5	1d	3	12 (91)
6	1b	4	13 (50) + 14 (15)
7	1b	5	15 (88)
8	1b[d]	5	15 (11) + 16 (55)
9	1b	6	17 (16) + 18 (71)
10	1b[d]	6	18 (61)

a) Othewise noted, two equiv. of 1 to a heterocycle were used. b) Yields refer to the isolated compounds. All new compounds gave satisfactory spectral and analytical data (C, H, N, ±0.4%). c) Accompanied by small amounts of 2-perfluoroalkylquinoline. d) Reagent/substrate ratio was 1.0/1.1.



19 20 (2)



21 22 23 (3)

Unfortunately, this perfluoroalkylation method could not be successfully applied to pyridine. Thus, the similar reactions of pyridine (**21**) and pyridine N-oxide (**19**) with $C_6F_{13}Li$ gave 2-perfluorohexylpyridine (**20**) only in low yields (5-10%) (Eq. 2). Attempted perfluoroalkylation of pyridine (**21**) under the Reissert-like conditions led to the formation of 2-perfluoroalkylated compound **22** and 2-methylated compound **23** in 24% and 17% yields, respectively (Eq. 3).[7)]

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