Synthesis of 6-Trifluoromethyl-Phenanthridines from Diaryl Isonitriles

**Significance:** Reported is the synthesis of 6-trifluoromethyl phenanthridines (3–5) from the reaction of readily available isonitriles 1 with the Togni reagent (2, n = 1) involving a radical trifluoromethylation reaction. Initially, transition metals (salts of copper, iron, nickel, and cobalt) were used to carry out this transformation, but later it was realized that Bu4NI can be successfully used as a radical initiator. A range of 6-trifluoromethyl-phenanthridines were obtained in moderate to good yields.

For meta-substituted ring-C derivatives of 1, cyclization preferably occurred at the position distal to the meta substituents, but regiocontrol was low (1:1 to 7.4:1). The method was also applied to the synthesis of 6-perfluoroalkylated phenanthridines (CnF2n+1, n = 2, 3). The reaction did not proceed in the presence of TEMPO, suggesting a radical mechanism involving the addition of CF3 radical to the isonitrile group, followed by a cyclization event.


**Comment:** Trifluoromethylated (hetero)arenes are important structural motifs for drug discovery programs. Classic methods for the synthesis of CF3-substituted (hetero)arenes rely mostly on the commercial availability of CF3-bearing starting materials usually obtained by industrially unviable Swarts-type reactions (G. K. S. Prakash, J. Hu, J. Simon, D. R. Bellew, G. A. Olah J. Fluorine Chem. 2004, 125, 595). In more recent developments, the CF3 group has been introduced by transition-metal-mediated cross-coupling reactions or direct C–H trifluoromethylation (see Reviews below). Despite some modest improvement in this field, new routes for the high-yielding and site-selective introduction of CF3 groups on (hetero)arenes are required. The present method utilizes readily prepared isonitriles and provides 6-perfluoroalkylated phenanthridines without transition-metal-based catalysis. However, the Togni reagent is potentially explosive and should be handled with care (N. Fiederling, J. Haller, H. Schramm Org. Process Res. Dev. 2013, 17, 318). Conceptually, this method is similar to Zhou’s approach (Q. Wang, X. Dong, T. Xiao, L. Zhou Org. Lett. 2013, 15, 4846) in which, instead of the Togni reagent, a combination of PhIOA(O)2 and the Ruppert–Prakash reagent (TMSCF3) was used at room temperature to obtain similar derivatives.

**Equation:**

\[ R^1 = H, 2-Me, 2-F, 3-Cl, 3-Me, 4-Me, 2,4-Me_2 \\
R^2 = H, 8-Me, 8-t-Bu, 8-OMe, 8-Cl, 8-F, 8-Ph, 8-Ac, 8-NC, 10-Me, 9-Me/7-Me*, 9-Cl/7-Cl*, 7,8-(CH=CH-)2/8,9-(CH=CH-)2*, 8,9-OCH2O/7,8-OCH2O* \\
X = CH, N (1 example) \\
C_{nF_{2n+1}} = CF_3, C_2F_5 (1 example), C_3F_7 (1 example) \\
Bu_4NI (5 mol%) (1.5 equiv) \\
1,4-dioxane, 80 °C, 3 h \\
24 examples 52–86% yield \\
(* ratio of regioisomers from 1:1 to 7.4:1) \\
4 (54% yield) \\
5 (77% yield) \\
A
B
C
D
E
F
G
H
I
J
K
L
M
N
O
P
Q
R
S
T
U
V
W
X
Y
Z

**SYNFACTS Contributors:** Victor Snieckus, Suneel P. Singh (Snieckus Innovations)

SYNFACTS 2014, 10(1), 0016 Published online: 13.12.2013 DOI: 10.1055/s-0033-1340419; Reg-No. V15013SF

This document was downloaded for personal use only. Unauthorized distribution is strictly prohibited.