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 substituent, 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 Ph(OAc)₂ and the Ruppert–Prakash reagent (TMSCF₃) was used at room temperature to obtain similar derivatives.