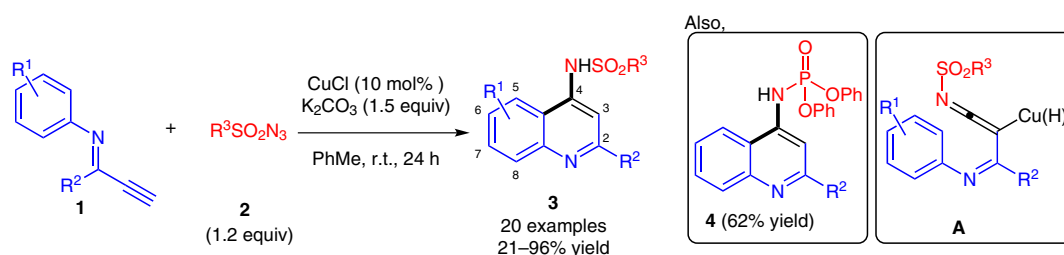


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Cu-Catalyzed Tandem Reactions of Fluorinated Alkynes with Sulfonyl Azides En Route to 2-Trifluoromethylquinolines
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Synthesis of 2-Trifluoromethylquinolines via a [2+3] Cycloaddition



R^1 = H, 6-Me, 6-NMe₂, 6-Br, 6-I, 6-CO₂Et, 5-Cl/7-Cl*, 5-Me/7-Me*, 8-F, 8-Me, 8-Ph, 6-OMe, 7,8-(CH=CH)₂
 R^2 = CF₃ (16 examples), C₂F₅, C₃F₇, CF₂Cl, CF₂Br, CF₂H (trace yield)
 R^3 = Ph, 4'-MeC₆H₄, 4'-ClC₆H₄, 4'-O₂NC₆H₄
 * ratio of regioisomers from 1:1.7 to 1:1.8

Significance: Reported is the synthesis of 2-trifluoromethyl quinolines **3** and **4** via a copper-catalyzed Huisgen [2+3]-cycloaddition reaction of sulfonyl azides **2** with terminal alkynes **1**. The starting material **1** was obtained by the reaction of 2,2,2-trifluoro-*N*-phenylacetimidoyl chloride with [(tri-methylsilyl)ethynyl]magnesium bromide, followed by trimethylsilyl deprotection. Optimum reaction conditions, as presented in the scheme, were used to obtain a variety of quinolines (**3**). Alkynes **1** containing electron-withdrawing groups as R^1 resulted in poor yield; those with electron-donating groups as R^1 resulted in moderate to good yields. Compound **3** was isolated as a mixture of isomers (C-5/C-7 from 1:1.7 to 1:1.8) when a *meta* substituent as R^1 on **1** was used. The method was also extended to the synthesis of 2-perfluoroalkylated quinolines (R^2 = C₂F₅, C₃F₇) and related analogous (R^2 = CF₂Br, CF₂Cl). Use of phosphoryl azide instead of **2** under similar conditions resulted in the formation of **4**. A mechanism involving a copper-catalyzed azide–alkyne cycloaddition, followed by the loss of N₂ to give intermediate aza-allene **A**, and followed by electrocyclic ring closure to quinolines **3** was proposed without experimental evidence.

Comment: The importance of the trifluoromethyl group in drug discovery programs has resulted in the development of new and improved methods for the introduction of CF₃ groups onto (hetero)arenes. Although recent focus has been on the transition-metal-mediated cross-couplings and direct C–H trifluoromethylations (see Reviews below), methods such as the present one provide competitive alternatives, especially when suitable starting material can be obtained easily. The current method can tolerate a wide range of functional groups, but the yield is lower with electron-poor alkynes. Also, this method was not tested on internal alkynes.

Reviews: X.-F. Wu, H. Neumann, M. Beller *Chem. Asian J.* **2012**, *7*, 1744–1754; H. Liu, Z. Gu, X. Jiang *Adv. Synth. Catal.* **2013**, *355*, 617–626; T. Besset, C. Schneider, D. Cahard *Angew. Chem. Int. Ed.* **2012**, *51*, 5048–5050.

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