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2-Trifluoromethylated Indoles via Radical Trifluoromethylation of Isonitriles

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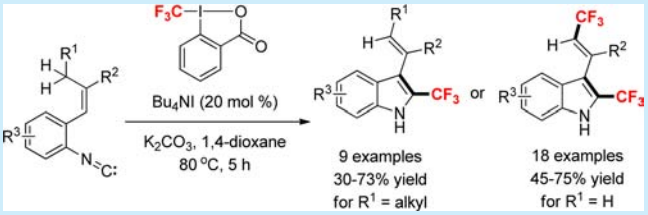
Supporting Information

ABSTRACT: Either two or three C−C bonds are formed in the synthesis of 2-trifluoromethylindoles starting with readily prepared isonitriles and the Togni reagent as CF_3 radical precursor. These transformations occur in the absence of transition metal, and products are obtained in moderate to good yields with excellent diastereoselectivity.

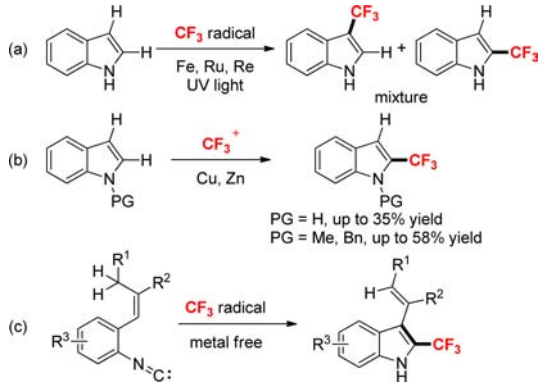


The indole scaffold is a prominent and privileged chemical entity that is found in numerous natural products and drug candidates.[1] Therefore, there is continuing interest in the development of synthetic methods for the construction and chemical modification of indoles.[2] New synthetic routes to 2-trifluoromethylated indoles are particularly attractive owing to their potential pharmaceutical application.[3] In medicinal chemistry, the incorporation of a CF_3 group into a lead compound is an important strategy for improvement of the biological activity due to enhanced lipophilicity, metabolic stability, and bioavailability of the fluorinated derivatives.[4] Therefore, it is important to develop synthetic methods for the construction of 2-trifluoromethylated indoles and their derivatives.

Recently, several methods for the construction of 2-trifluoromethylated indoles have been developed.[5] However, these approaches also revealed some drawbacks such as limited availability of the starting materials, multistep reaction processes, or harsh reaction conditions. Transition-metal-catalyzed[6] and radical indole trifluoromethylation,[7] which offer a direct approach to 2-trifluoromethylated indoles, have been studied intensively. However, in radical indole trifluoromethylation,[7] a regioselectivity problem occurs leading to a mixture of the 2- and 3-trifluoromethylated indoles (Scheme 1, a). Transition-metal-catalyzed electrophilic trifluoromethylation[6] of (NH)-indoles provided 2-trifluoromethylated indoles with complete regiocontrol but poor yields. An N-substituent had to be installed in order to get improved yields. This results in two extra steps (N-protection and deprotection after trifluoromethylation) (Scheme 1, b). Therefore, the development of methods for construction of 2-trifluoromethylated (NH)-indoles is important.

Encouraged by our recent work on the use of arylisonitriles as CF_3 radical acceptors,[8a] we became interested in constructing 2-trifluoromethylated indoles via trifluoromethylation of isonitriles (Scheme 1, c). These studies were inspired by reports on the preparation of indoles using arylisonitriles as substrates.[9] The significance of the chemistry presented here is

Scheme 1. Different Strategies for the Preparation of 2-Trifluoromethylated Indoles



3-fold: (1) First examples for the construction of 2-trifluoromethylated indoles via trifluoromethylation of isonitriles are reported. (2) In contrast to the intensively studied indole trifluoromethylation where fluoroalkylation generally occurs at an intact indole core, the presented chemistry comprises a trifluoromethylation with concomitant indole formation. (3) The novel process does not require the help of any transition metal, and an N-protecting (directing) group is not necessary.

Extensive optimization studies revealed that trifluoromethylated indoles of type **3** can be obtained from isonitriles **1** (1.2 equiv) using the commercially available Togni reagent **2**[10,11] (1.0 equiv) as CF_3 radical source in the presence of K_2CO_3 (2 equiv) at 80 °C in 1,4-dioxane (Scheme 2). Bu_4NI[12] (20 mol %) in combination with **2** can be used as radical initiator as previously shown by us.[8a] 2-Trifluoromethylindole **3a** was isolated in 67% yield with excellent *E*-selectivity (17:1) from **1a**. The *E*/*Z* ratio and the relative configuration were readily

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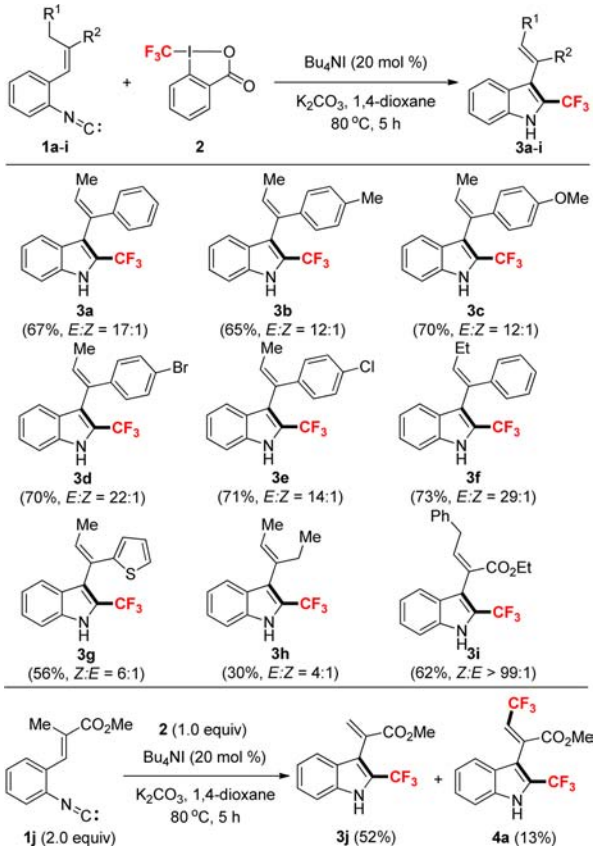
Scheme 2. 2-Trifluoromethylated Indoles via Radical Trifluoromethylation of Isonitriles



assigned by NMR spectroscopy. Electronic effects of the R^2-phenyl group are weak since similar yields were achieved for systems bearing electron-donating as well as electron-accepting substituents at the para position of the phenyl ring (see **3b–e**). Longer alkyl chains as R^1-substituents are tolerated as documented by the transformation of **1f** to **3f** (73%). As compared to the methyl congener **3a**, *E*/*Z* selectivity increased to 29:1 likely for steric reasons. The thiophene-substituted alkene **1g** underwent trifluoromethylation/cyclization to give **3g** in 56% yield with lower *E*-selectivity (6:1). We also tested an isonitrile bearing an alkyl group as R^2-substituent (see **1h**) and found the reaction to work in moderate yield and selectivity (**3h**: 30%, *E*/*Z* = 4:1). A high yield was obtained for the ester-activated alkene **1i** and **3i** was isolated in 62% yield with complete selectivity. We also reacted alkene **1j** lacking the R^1-substituent (R^2 = CO_2Me) with **2** and noted that the targeted indole **3j** underwent further trifluoromethylation to give the bis-CF_3-indole **4a** as side product. Under slightly modified conditions we were able to get the monotrifluoromethylated indole **3j** in 52% yield as major product.

We found the double trifluoromethylation interesting and valuable and optimized reaction conditions toward formation of **4a**. The highest yield (72%) and complete *Z*-selectivity were achieved by using 3.0 equiv of **2** (1.5 fold excess) and 20 mol % of Bu_4NI with K_2CO_3 as base in 1,4-dioxane at 80 °C (Figure 1).[12,13] Under these conditions, the scope and limitations of the bistrifluoromethylation were investigated.

Variation of the arene moiety carrying the isonitrile functionality was studied first (see **4b–i**). Reactions with substrates bearing electron-withdrawing (halides and methoxycarbonyl) and also electron-donating (methyl) substituents at different positions proceeded well, and products **4b–i** were isolated in moderate to good yields (45–72%; Figure 1) and excellent diastereoselectivity. The lowest yield (45%) was obtained with the methoxycarbonyl-substituted isonitrile, likely because of the reduced reactivity of the electron-deficient isonitrile in the reaction with the electrophilic CF_3 radical (see **4h**). Next, we examined the scope of the reaction with respect to the nature of the R^2-substituent in the substrate (see Scheme 1, c). Various esters, such as the ethyl, propyl, isopropyl, *tert*-butyl, and phenyl ester, underwent bistrifluoromethylation smoothly to generate **4j–n** with excellent stereocontrol (48–68%). A substrate bearing an amide moiety in place of the ester group was also applicable to this reaction, and **4o** was isolated in good yield (65%). Importantly, the ester group R^2 can be replaced by an aryl group. Phenyl-, *p*-tolyl-, and *β*-naphthyl-substituted systems were converted to the corresponding indoles **4p–r** in good yields (64–75%) and excellent diastereoselectivity.

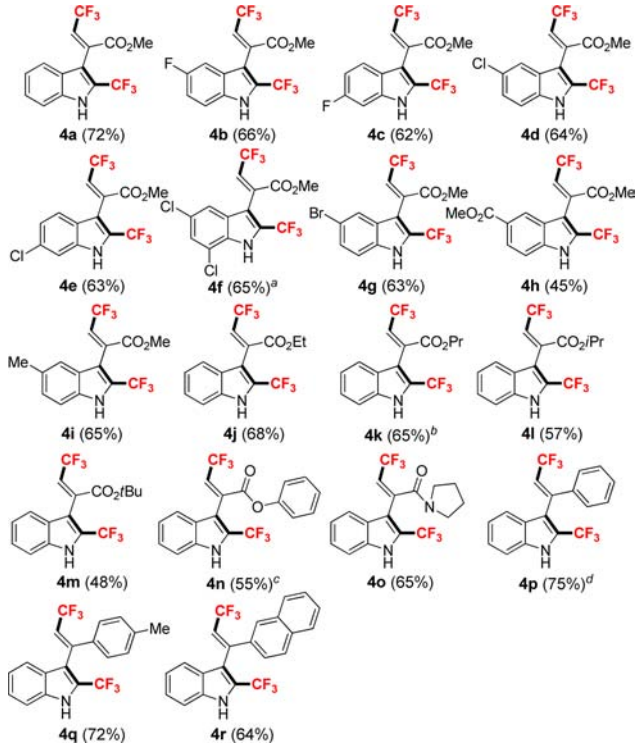


Figure 1. Various 2-trifluoromethylated indoles prepared (diastereoisomer ratio *Z*/*E*: (a) 36:1, (b) 47:1, (c) 32:1; (d) *E*/*Z* = 42:1; selectivity was determined by ^{19}F NMR spectroscopy).

As the first followup reaction on model compound **4a**, the C–C double bond was readily reduced by treatment with Pd/C and H_2 (1 atm) in EtOH at room temperature to provide indole **5** in near-quantitative yield (Scheme 3). In analogy, indole **3a** was reduced to **7**. Double-bond reduction along with ester reduction in **4a** with $CeCl_3/NaBH_4$ in EtOH afforded indole **6**.[14]

Preliminary mechanistic studies revealed that CF_3 radicals are likely involved in these reactions. Under optimized conditions, formation of **4a** from **1j** was completely suppressed in the presence of TEMPO as a radical scavenger, and TEMPO-CF_3 was detected in the reaction mixture by ^{19}F NMR spectroscopy. Considering this experiment and our previous report,[8a] a plausible mechanism is proposed in Scheme 4. In the initiation

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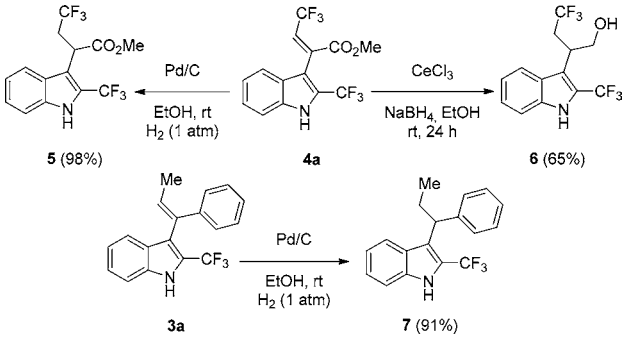
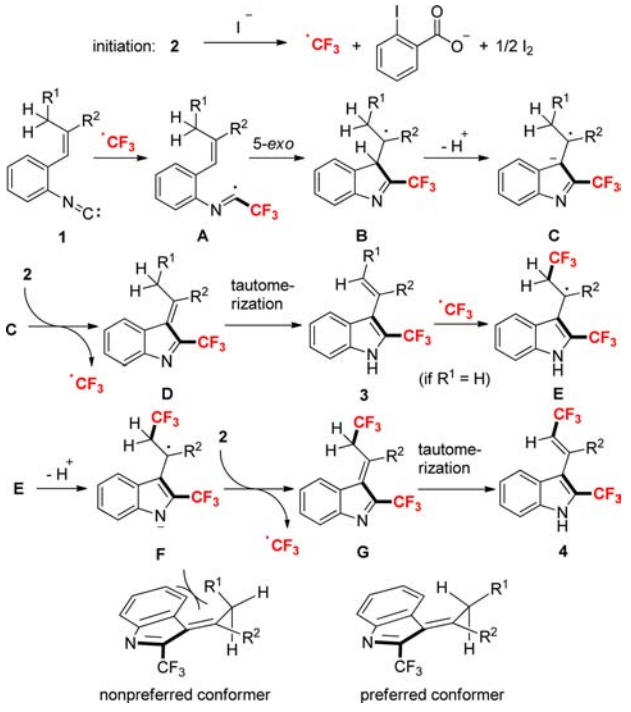
Scheme 3. Reduction of 3a and 4a



Scheme 4. Proposed Reaction Mechanism



step, Bu_4NI is oxidized by **2** to generate the CF_3 radical, *o*-iodobenzoate, and iodine. Addition of the CF_3 radical to **1** provides the imidoyl radical **A**,[15] which undergoes 5-*exo* cyclization to give radical **B**. We assume that **B** gets deprotonated by K_2CO_3 to radical anion **C**, which then further reacts with **2** via single-electron transfer (SET) to **D** and the CF_3 radical, thereby sustaining the radical chain.[16−18] Tautomerization of **D** generates the targeted monotrifluoromethylated indole **3**. If R^1 is a H-atom, **3** acts as CF_3 radical acceptor to afford adduct **E**, which is deprotonated by K_2CO_3 to radical anion **F**.[19] SET from **F**, which is electronically similar to radical anion **C**, to **2** leads to **G** along with the generation of the CF_3 radical. Finally, product **4** is formed by tautomerization of **G**. The stereochemistry for formation of **3** and **4** is set for steric reasons (minimization of allylic $A_{1,3}$-strain, R^1 = alkyl or CF_3) in the tautomerization step as indicated in Scheme 4.

In summary, we have demonstrated a novel approach for the synthesis of 2-trifluoromethylindoles starting with readily prepared isonitriles and the commercially available trifluoromethylation reagent **2** as a precursor of the CF_3 radical. Experiments that are easy to conduct occur with excellent stereocontrol. Importantly, trifluoromethylation occurs without the help of any transition metal. In contrast to current intensively investigated indole trifluoromethylations, in which C−CF_3 bond formation occurs at an intact indole ring, our process comprises a trifluoromethylation with concomitant indole framework and C−C double-bond formation. Depending on the substitutents at the alkene acceptor, mono- or bistrifluoromethylated products are obtained.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(15) We observed the coupling product from 2-iodobenzoic acid and 1,4-dioxane. The result indicates the CF_3 radical is able to abstract hydrogen from 1,4-dioxane. Oxidation of the α-oxy radical and ionic trapping of the corresponding oxycarbenium ion with 2-iodobenzoic acid provides the coupling product.

(16) Alternatively, radical **B** is iodinated with I_2 followed by base-mediated elimination of HI to give **D**.

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(19) The pK_a of indole is 21.0 in DMSO, see: Bordwell, F. G.; Drucker, G. E.; Fried, H. E. *J. Org. Chem.* **1981**, *46*, 632. The radical species **E** will have a far lower NH pK_a value than the parent indole. As an alternative route, CH deprotonation next to the CF_3 group in **E** would lead to a radical anion which upon SET to **2** directly delivers product **4**. We currently disfavor the CH deprotonation pathway because the excellent diastereoselectivity obtained (in particular for the aryl-substituted substrates R = aryl leading to **4p**−**r**) would be difficult to explain for the deprotonation of radical **E**.