Journal of Fluorine Chemistry 174 (2015) 88–94

Contents lists available at ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

[3 + 2] Cycloaddition of arynes with CF_3CHN_2: Access to 3-trifluoromethyl-1*H*-indazoles

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ARTICLE INFO

Article history:
Received 29 April 2014
Received in revised form 1 June 2014
Accepted 3 June 2014
Available online 20 June 2014

Keywords:
Cycloaddition reaction
Arynes
2,2,2-Trifluorodiazoethane
Indazoles
Synthesis

ABSTRACT

Efficient [3 + 2] cycloaddition reactions of arynes and CF_3CHN_2 were developed in the presence of fluoride in conjunction with TEBAC. Structurally distinct 3-trifluoromethyl-1*H*-indazoles were obtained in good to high yields with moderate regioselectivities. This experimentally simple process facilitates the access to potential biologically active 3-trifluoromethyl-indazoles from readily available starting materials.

1. Introduction

Indazole derivatives, an important class of nitrogen-containing heterocycles, have exhibited a variety of applications as pharmaceutical candidates and biologically active structural components [1–9]. In particular, 3-substituted-1*H*-indazoles frequently set up the core frame of numerous pharmaceutically active compounds, such as Lonidamine and Granisetron. Indubitably, trifluoromethyl compounds are receiving increasing attention because of the unusual and profound effects on physical properties imparted by the introduction of the trifluoromethyl group into organic molecules [10–15]. In this context, indazoles featuring a trifluoromethyl substitution are attractive targets with regard to their potential bioactivities. Although a large number of methods have been developed for the syntheses of the 3-substituted-indazole derivatives [16], the efficient construction of 3-trifluoromethyl indazoles is still underdeveloped [17]. One known method involved the reductive cyclization of ortho-nitro trifluoromethylketoximes with CO catalyzed by $[Cp^*Fe(CO)_2]_2$, which suffered from harsh reaction conditions of high-pressure and high-temperature (Scheme 1a) [17a]. An alternative methodology for accessing these compounds required a multiple-steps sequence, in which the overall yield was only 8% (Scheme 1b) [17b]. Therefore, the development of a general and efficient method for the synthesis of 3-trifluoromethyl-indazoles is highly desirable.

The reactions of CF_3CHN_2 have emerged as powerful tools for the construction of diverse trifluoromethylated building blocks [18]. Among these, we employed CF_3CHN_2 as a 1,3-dipole in the cycloaddition with terminal alkynes to afford functionalized 3-trifluoromethyl-pyrazoles [19b]. As a part of our continued interest in synthetic utility of CF_3CHN_2, we envisioned that 3-trifluoromethyl-indazoles could be constructed by [3 + 2] cycloaddition of CF_3CHN_2 with arynes *in situ* generated from *O*-(trimethylsilyl)aryl triflates (Scheme 1c). Meanwhile, CF_3CHN_2 is easily accessible by a diazotization of trifluoroethylamine hydrochloride in the presence of sodium nitrite. We anticipated that this method could be an attractive strategy in accessing structurally distinct 3-trifluoromethyl-indazoles with potential biological and pharmaceutical utility. Herein, we report our preliminary results on this subject.

2. Results and discussion

Considering that the arynes are easily accessed *in situ* by a fluoride induced de-trimethylsilylation of *O*-(trimethylsilyl)phenyl triflates and subsequent elimination, we initiated our study by evaluating the reactions of *O*-(trimethylsilyl)phenyl triflate **1a** and 2,2,2-trifluorodiazoethane **2** in the presence of 1.2 equiv of tetra-*n*-butylammonium fluoride (TBAF) in THF at room temperature. As shown in Table 1, 3-trifluoromethyl-indazole **3a** could only be obtained in moderate yield (Table 1, entry 1). The reaction did not

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http://dx.doi.org/10.1016/j.jfluchem.2014.06.002
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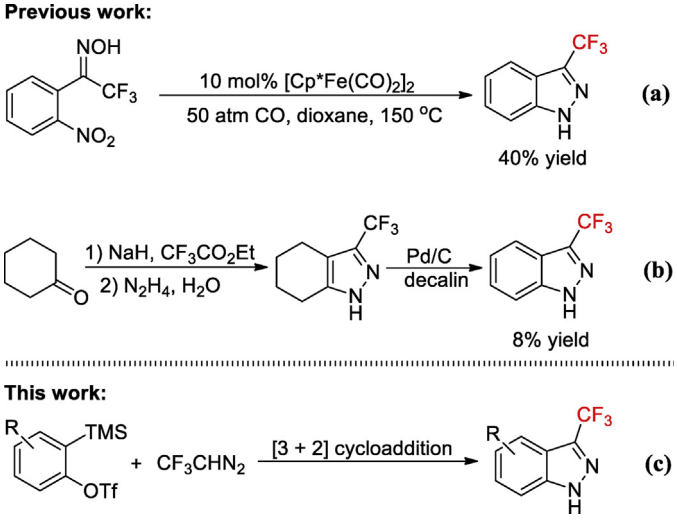
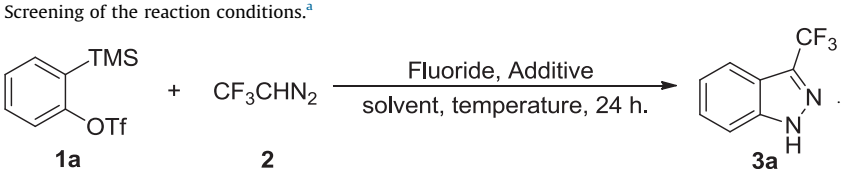


Scheme 1. Strategies for synthesis of 3-trifluoromethyl-1*H*-indazoles.

proceed as fluoride was switched to CsF (Table 1, entry 2). Next, several phase-transfer catalysts (PTC) were introduced into the cycloaddition reaction (Table 1, entries 3–5). Addition of 18-crown-6 resulted in the formation of **3a** in 33% yield (Table 1, entry 3). Noteworthy, the use of CsF in conjunction with TEBAC ($[Et_3NBn]^+Cl^-$) increased the yield to 56% (Table 1, entry 4). To our delight, a two-fold increase of the amount of CsF and TEBAC gave **3a** with a dramatically improved yield of 81% (Table 1, entry 6). The activity of this cycloaddition reaction was sensitive to the quantity of PTC, since decreasing the quantity of TEBAC led to a significantly lower yield (Table 1, entry 7). With the optimal combination of fluoride and PTC established, we next investigated the influence of the solvent and temperature (Table 1, entries 8–11). It was found that CH_3CN and toluene could also deliver the products as well, albeit in lower yields (Table 1, entries 8 and 9). However, only trace product was detected by using CH_2Cl_2 as the solvent instead (Table 1, entry 10). Furthermore, a slightly decreased yield was obtained at higher temperature (Table 1, entry 11).

To explore the generality of this practical approach, the [3 + 2] cycloadditions of various 2-(trimethylsilyl)aryl triflates **1** with 2,2,2-trifluorodiazoethane **2** were performed under the optimized conditions. As summarized in Table 2, good to high yields for the cycloadducts **3a**–**f** were achieved regardless of the steric or electronic properties of the substituents on the aromatic ring. The cycloaddition was effective even with sterically hindered 4,6-di-*tert*-butyl substituted aryne precursor **1g**, albeit with slightly lower reactivity (Table 2, entry 7). It was shown that two regioisomers were obtained as the unsymmetrical *O*-silylaryl triflates were employed in this reaction. Cycloaddition of *O*-silylaryl triflates bearing an electron-donating group on the aromatic ring with CF_3CHN_2 favored nucleophilic attack at the meta-position over para-position in 1.2:1 ratio (Table 2, entries 2–4, 6, 7). In contrast, the corresponding reaction of *O*-silylaryl triflates substituted with electron-withdrawing group displayed a preference for nucleophilic attack at more distant position of "triple bond" (Table 2, entries 8–13). 6-Methyl-substituted 2-silylaryl triflates **1e** displayed a reversal in regioselectivity compared to other electron-donating group substituted counterpart (Table 2, entry 5), which implied considerable steric hindrance arising from the 6-methyl group of **1e**. Notably, the transformations of the unsymmetrical 4,6-di-*tert*-butyl-, 4-methoxy-, and 6-methoxy-substituted aryne precursors proceeded with high regioselectivity, leading to the formation of only one regioisomer (Table 2, entries 7–9). The regioselectivity could be ascribed to the more favorable electronic and steric factors during the nucleophilic attack of the CF_3CHN_2. Additionally, treatment of **1m** with CF_3CHN_2 led to a 3.5:1 mixture of products favoring attack at *para*-position of the methoxy group (Table 2, entry 13). This result indicated that the bromo and methoxy substitutents could permit the simultaneous stabilization of the developing negative charge. The regioselectivity observed for **1n** was attributed to a more prominent electronic and steric effect imposed by the methyl group (Table 2, entry 14). Finally, the naphthyl-derived *O*-silylaryl triflate **1o** was also a variable substrate, affording the desired product in 82% yield with a 1:1 ratio of two regioisomers (Table 2, entry 15).

Table 1
Screening of the reaction conditions.[a]



1a 2 3a

Entry	Fluoride (equiv)	Additive (equiv)	Solvent	Temp. (°C)	Yield (%)[b]
1	TBAF (1.2)	–	THF	25	43
2	CsF (1.2)	–	THF	25	0
3	CsF (1.2)	18-crown-6 (1.5)	THF	25	33
4	CsF (1.2)	TEBAC (1.5)	THF	25	56
5	KF (1.2)	TEBAC (1.5)	THF	25	41
6	CsF (2.4)	TEBAC (3.0)	THF	25	81
7	CsF (2.4)	TEBAC (2.4)	THF	25	67
8	CsF (2.4)	TEBAC (3.0)	CH_3CN	25	60
9	CsF (2.4)	TEBAC (3.0)	Toluene	25	56
10	CsF (2.4)	TEBAC (3.0)	CH_2Cl_2	25	13
11	CsF (2.4)	TEBAC (3.0)	THF	70	78

[a] The reactions were carried out with *o*-(trimethylsilyl)phenyl triflate (0.2 mmol, 1.0 equiv) and 2,2,2-trifluorodiazoethane (0.8 mmol, 4.0 equiv).
[b] Isolated yield.