

DBU-Promoted Trifluoromethylation of Aryl Iodides with Difluoromethyltriphenylphosphonium Bromide

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DBU-promoted trifluoromethylation of aryl iodides with difluoromethyltriphenylphosphonium bromide (DFPB) in the presence of copper source is described. In this transformation, DBU not only acts as base to deprotonate the difluoromethyl group in DFPB to generate difluoromethylene phosphonium ylide $\text{Ph}_3\text{P}^+\text{CF}_2^-$, but also converts the difluorocarbene generated from ylide $\text{Ph}_3\text{P}^+\text{CF}_2^-$ into trifluoromethyl anion, finally resulting in the trifluoromethylation of aryl iodides. The reactions proceeded smoothly to afford expected products in moderate to good yields.

Keywords difluorocarbene, trifluoromethylation, difluoromethyltriphenylphosphonium bromide, copper

Introduction

As the introduction of a trifluoromethyl group into a molecule usually results in profound modifications of the physiochemical properties, trifluoromethylated compounds have found widespread application in a variety of research areas, such as polymers, agrochemicals, and pharmaceuticals.^[1] Consequently, determined efforts have been devoted to the exploration of efficient methods for trifluoromethylation. Although the past years have witnessed the significant advances in this research area, those studies usually employ CF_3 -containing reagents for trifluoromethylation.^[2] Recently, the use of difluorocarbene precursors as trifluoromethylating reagents has received a great deal of attention.^[3] In these studies, the addition of external fluoride is usually necessary. As part of our research interest in the chemistry of fluoroalkylation,^[4] we have now investigated the trifluoromethylation of aromatic iodides with difluoromethyltriphenylphosphonium bromide (DFPB), a potential difluorocarbene precursor, without the addition of external fluoride.

Previously, we disclosed that difluoromethylene phosphobetaine ($\text{Ph}_3\text{P}^+\text{CF}_2\text{CO}_2^-$, PDFA) can generate difluoromethylene phosphonium ylide reagent via decarboxylation.^[5] Interestingly, the *in situ* generated ylide can further dissociate to produce difluorocarbene,^[6] meaning that PDFA is a difluorocarbene precursor and can be used in trifluoromethylation reactions. Our at-

tempts at trifluoromethylation with PDFA were successful, but the presence of external fluoride in this transformation was mandatory.^[3b] Soon afterwards, we found that DBU can promote the decomposition of difluorocarbene to give fluoride, resulting in the discovery of a novel method for trifluoromethylation with difluorocarbene precursor without the addition of external fluoride.^[7] PDFA was found to be applicable in this conversion, whereas the reaction always produces trace amount of pentafluoroethylation by-products, which is difficult to be separated from the trifluoromethylated products. On the basis that deprotonation of DFPB by DBU can generate difluoromethylene phosphonium ylide^[8] and that this ylide can further dissociate to form difluorocarbene, it is reasonable to envision that this phosphonium salt can be used in DBU-promoted trifluoromethylation reaction without the addition of external fluoride. Surprisingly, our examination showed that the reaction can occur smoothly without producing pentafluoroethylation by-products.

Experimental

General procedure for the trifluoromethylation of aromatic iodide

Into the solution of 4-iodobiphenyl (56 mg, 0.2 mmol) and DFPB (236 mg, 0.6 mmol) in DMF (2 mL) were added $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (373 mg, 1.0 mmol) and DBU (213 μL , 1.4 mmol) under N_2 . The resulting mix-

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ture was stirred at 100 °C for 5 h. After the mixture was cooled to room temperature, the yield of the reaction was determined by ^{19}F NMR with the addition of 2,2,2-trifluoroethanol as an internal standard.

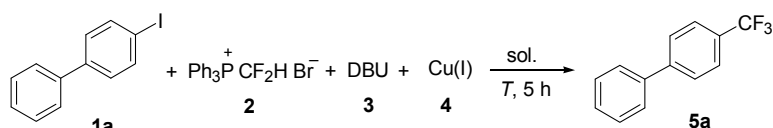
Results and Discussion

Our initial attempts at the Cu-promoted trifluoromethylation of 4-phenyl iodobenzene with DFPB **2** in the presence of DBU showed that the reaction temperature was crucial to the conversion (Table 1, Entries 1–4). The solubility of the copper source was also quite important (Entries 5–6). Superior results obtained with $\text{Cu}(\text{MeCN})_4\text{PF}_6$ prompted us to further screen various reaction conditions by using this copper source. DMF was found to be a good solvent, probably because it can stabilize trifluoromethyl anion (Entry 3 vs. Entries 7–11). The effect of the molar ratio of the substrate and

reagents was examined (Entries 12–20), and the molar ratio 1 : 3 : 7 : 5 of **1a** : **2** : **3** : **4** was determined to be a suitable ratio (Entry 16). Interestingly, the concentration also affected the yield of the reaction. Slightly decreasing the concentration led to the increase in the yield (Entry 21 vs. Entry 16), but further decreasing the concentration resulted in lowering the yield (Entries 22–24).

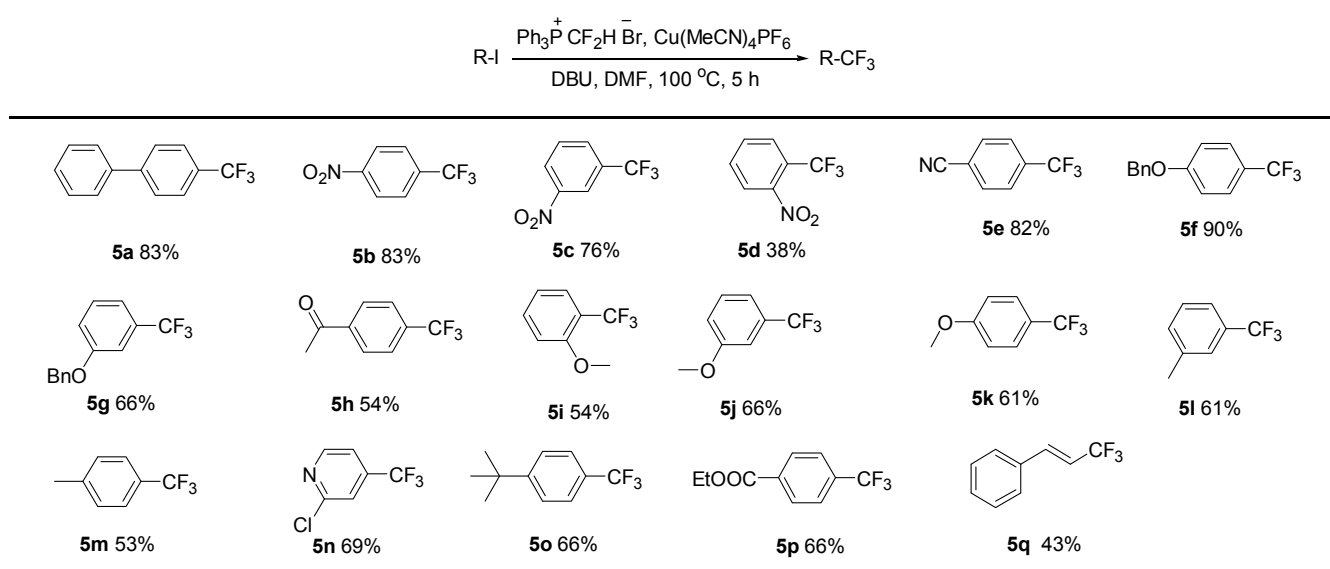
With the optimized reaction conditions in hand (Entry 21, Table 1), we then investigated the substrate scope of the DBU-promoted trifluoromethylation of aromatic iodide with DFPB in the presence of copper source (Table 2). Irrespective of whether the phenyl group was substituted by an electron-withdrawing or -donating group, the transformations proceeded smoothly to furnish the expected products in moderate to good yields. To our surprise, for nitro-substituted

Table 1 Screening of reaction conditions for the trifluoromethylation with DFPB^a



Entry	Temp./°C	Solv.	Equiv. ^b	Cu(I)	Yield ^c /%
1	60	DMF	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	N.D.
2	80	DMF	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	Trace
3	100	DMF	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	34
4	120	DMF	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	30
5	100	DMF	1 : 3 : 6 : 3.5	CuI	N.D.
6	100	DMF	1 : 3 : 6 : 3.5	CuBr	N.D.
7	100	DMSO	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	Trace
8	100	CH_3CN	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	6
9	100	DMA	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	32
10	100	THF	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	N.D.
11	100	NMP	1 : 3 : 6 : 3.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	Trace
12	100	DMF	1 : 3 : 5.5 : 3	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	24
13	100	DMF	1 : 3 : 6.5 : 4	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	53
14	100	DMF	1 : 3 : 7 : 4.5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	55
15	100	DMF	1 : 3 : 7.5 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	66
16	100	DMF	1 : 3 : 7 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	68
17	100	DMF	1 : 3 : 6.5 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	41
18	100	DMF	1 : 3 : 6 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	47
19	100	DMF	1 : 3 : 5.5 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	57
20	100	DMF	1 : 3 : 5 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	46
21 ^d	100	DMF	1 : 3 : 7 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	83
22 ^e	100	DMF	1 : 3 : 7 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	72
23 ^f	100	DMF	1 : 3 : 7 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	70
24 ^g	100	DMF	1 : 3 : 7 : 5	$\text{Cu}(\text{MeCN})_4\text{PF}_6$	31

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.6 mmol), **3** (1.4 mmol), **4** (1.0 mmol), solvent (1.5 mL); ^b Molar ratio of **1a** : **2** : **3** : **4**; ^c Determined by ^{19}F NMR with 2,2,2-trifluoroethanol as an internal standard; ND=not detected; ^d DMF (2 mL); ^e DMF (2.5 mL); ^f DMF (3 mL); ^g DMF (4 mL).

Table 2 Cu-promoted trifluoromethylation of aromatic iodide with DFPB^a

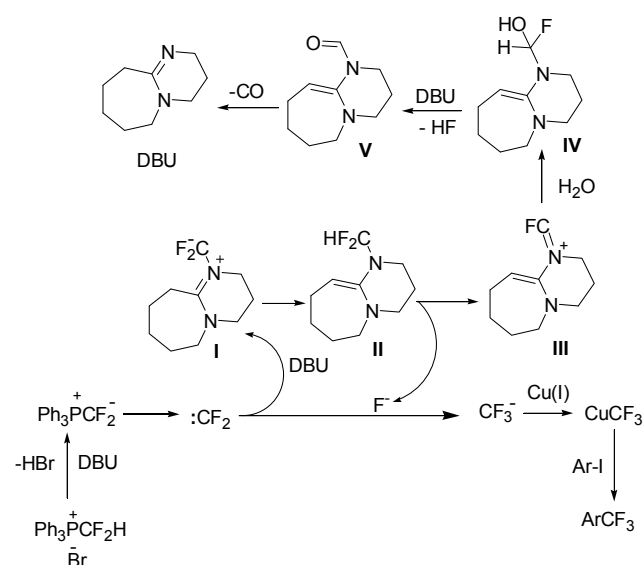
^a The yields were determined by ¹⁹F NMR with 2,2,2-trifluoroethanol as an internal stand.

substrates, the position of the nitro group shows strong effect on the reaction (**5b–5d**). *ortho*-Nitro substrate (**5d**) can not be converted well into the desired product. But for methoxy-substituted substrates (**5i–5k**), the position of methoxy group does not obviously affect the yield. The reaction can also be applied to alkenyl iodide even though lower yield was obtained (**5q**).

Combined with our previous report^[7,8] and the reported literatures,^[9] we propose the reaction mechanism as shown in Scheme 1. Deprotonation of the phosphonium salt by DBU produces phosphonium ylide, in which the dissociation of P–CF₂ bond generates difluorocarbene. Difluorocarbene would be readily trapped by DBU to give nitrogen ylide **I**, followed by the rearrangement of this ylide to afford difluoromethyl amine **II**. **II** is unstable due to the negative hyperconjugation between lone pair electrons on the nitrogen atom and the C–F bond, indicating that it would readily decompose to give intermediate **III** and fluoride ion (F[−]). The trap of fluoride by difluorocarbene forms trifluoromethyl anion, the ligand exchange of which with copper source produces [CF₃Cu], an important intermediate for trifluoromethylation. Intermediate **III** is highly unstable, and would be decomposed in the presence of water, giving intermediate **IV** and then **V** after the elimination of HF. Decarbonylation of **V** regenerates DBU. It should be mentioned that intermediate **II**, **V** and carbon monoxide were detected in our previous work.^[7]

Conclusions

In conclusion, we have described the DBU-promoted trifluoromethylation of aromatic iodide with DFPB (Ph₃P⁺CF₂HBr[−]) in the presence of copper source. This transformation occurs through the conversion of difluorocarbene to trifluoromethyl anion without the addition of external fluoride. The reactions afforded the

Scheme 1 The plausible reaction mechanism

desired products in moderate to high yields, without producing pentafluoroethylation by-products.

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