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The modified trifluoromethylation protocol applicable to electronically deficient iodopyridinones

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ABSTRACT

Utilization of a mixed solvent system of DMF/HMPA=1/1 (v/v) to the KF/CuI/TMSCF$_3$ reagent system proved to significantly affect the reaction, realizing convenient introduction of a trifluoromethyl (CF_3) group not only to electron-deficient iodopyridinones with quite a few previous successful examples but also to aliphatic vinylic iodides.

1. Introduction

The pyridin-2(1*H*)-one structure is widely found in a variety of biologically active naturally occurring compounds (Fig. 1).

For example, camptothecin,[1] isolated from *Camptotheca acuminate* in 1966, and its derivatives, topotecan and irinotecan, are known to show prominent anticancer activity like the case of lyconadin A.[2] Significant attention to huperzine A[3] from *Huperzia serrata* has been recently paid for its pharmaceutical activity to the Alzheimer's disease. Pirfenidone has been employed against fibrotic disorder and its derivatives with a CF_3 group were disclosed as promising antiasthma compounds.[4] 3-Iodo-4-phenoxypyridin-2(1*H*)-ones were also reported as a new family of highly potent non-nucleoside inhibitors of HIV-1 reverse transcriptase.[5] Thus, it is easily understood that pyridinone compounds are wide-spread in nature and some of them display attractive activities for a variety of diseases.

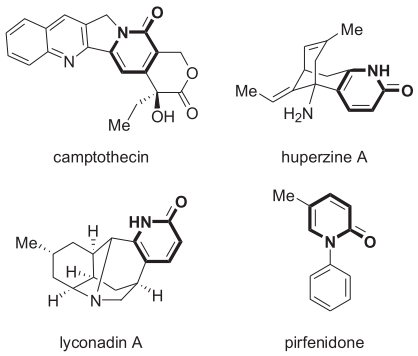

Fig. 1. Bioactive pyridinone derivatives.

Until now, although introduction of a CF_3 group to bioactive lead compounds has been performed in diverse manners for modification of original activities,[6] a scarce number of methods have been developed for electron-deficient pyridinones. One route to access 3-(trifluoromethyl)pyridin-2(1*H*)-one derivatives is substitution of an iodine atom for a CF_3 group by means of methyl 2,2-difluoro-2-(fluorosulfonyl)acetate in the presence of copper(I) iodide.[7] Another known process is direct installation of CF_3 radical to pyridin-2(1*H*)-ones, which is realized either by CF_3CO_2H/XeF_2[8] or CF_3CO_2Na/CuI[9] systems, and the more attractive generation of this radical was devised by Yamakawa et al. using a combination of CF_3I, a Fe(II) catalyst, and H_2O_2 in DMSO.[10] Recently, the Baran's group attained very practical C–H trifluoromethylation of heterocycles by CF_3SO_2Na[11] or $(CF_3SO_2)_2Zn$[12] with focusing on various heteroaromatics as substrates, however this protocol sometimes suffers from low regioselectivity.

Extension of our interest to pyridines allowed to find out a relatively larger number of precedented work in the literature. For

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example, copper-mediated oxidative trifluoromethylation towards boronic acids was utilized by Buchwald et al.,[13] where 3-(trifluoromethyl)quinoline and 3,6-dimethoxy-4-(trifluoromethyl) pyridazine were readily constructed.

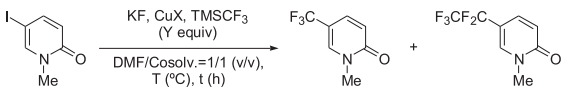
The Grushin's group succeeded in the synthesis and isolation of $[(Ph_3P)_3Cu(CF_3)]$ from $[(Ph_3P)_3CuF]\cdot MeOH$ and the Ruppert–Prakash reagent ($TMSCF_3$), whose ability was exemplified towards useful iodine-CF_3 exchange reactions of electron-deficient aromatics with successful formation of 2-(trifluoromethyl)pyridine in 75% yield.[14] They also revealed that a mixture of CF_3H, CuCl, and *t*-BuOK in DMF smoothly generated $CuCF_3$, which afforded trifluoromethylated pyridines in high yields by coupling with the corresponding boronic acids.[15] Moreover, other CF_3 sources like the Togni's reagent,[16] 2,2,2-trifluoroacetophenone,[17] or $AgCF_3$[18] were alternative choices for this purpose when appropriate copper reagents were employed. A significantly important role of 1,10-phenanthroline was demonstrated by Amii et al.[19] in trifluoromethylation, enabling catalytic usage of CuI. The possible intermediate (phen)$CuCF_3$ in this process was independently synthesized and isolated by the Hartwig's group, and they proved usefulness of this species.[20]

As mentioned above, in spite of relatively a larger number of procedures for constructing CF_3-possessing pyridines, only a very few routes have been published for incorporation of this intriguing group to electronically deficient pyridinones. Moreover, some previous methods exploited for pyridines were found not to be applicable to this specific system.[21] For such reasons, our work has been devoted to development of an efficient protocol for this purpose, and we would like to report our successful modification of the KF/CuI/$TMSCF_3$ reagent system originally reported by Schlosser et al.,[22] which offered a new option to readily prepare desired compounds in good to excellent chemical yields.

2. Results and discussion

Investigation of reaction conditions was performed in detail by using 5-iodo-1-methylpyridin-2(1*H*)-one **1**[23] as a model substrate (Table 1). With reference to the Schlosser's original recipe (entry 1),[22] we changed the stoichiometry of KF, CuI, and $TMSCF_3$ from 1.1 to 2.6 equiv but only disappointing result was obtained at room temperature (Table 1, entry 2). Clear improvement was recognized by heating the mixture and the product **2** was detected in 43 and 65% yields at 50 and 80 °C, respectively (entries 3 and 4). Increase of reagent amounts to 3.9 equiv further improved the yield of **2** to 77%, while this change affected formation of the undesired as well as chromatographically inseparable pentafluoroethylated byproduct **3** in 28% yield (entry 5). Cu-promoted trifluoromethylation sometimes led to construction of this compound **3** by the CuC_2F_5 species, which was formed as a result of insertion of in situ generated difluorocarbene to the *Cu*-CF_3[15,21] bond. Addition of an identical volume of *N*-methylpyrrolidin-2-one (NMP) or *N*,*N*-dimethylpropyleneurea (DMPU) to DMF lowered the yields of **2** (entries 6 and 7), while hexamethylphosphoric triamide (HMPA) was the exception and this mixed solvent system recorded quantitative construction of **2**[24] at 80 °C (entry 8). The effect of this additive was remarkable even when only 1 equiv of HMPA to CuI was introduced (entries 9 vs 4). Efficiency of this additive was lowered by shorter reaction period (entries 10 and 11 vs 8), and other copper halides were found not to work appropriately with formation of the byproduct **3** in about 10% yields (entries 12 and 13). *t*-BuOK or CsF instead of KF also afforded the desired trifluoromethylated product **2** in moderate yields (entries 14 and 15). Thus, we eventually

Table 1
Optimization of reaction conditions



Entry	X (CuX)	Y (equiv)	Cosolv.[a]	T (°C)	t (h)	Yield[b] (%)	
						2	**3**
1	I	1.1	—	rt	6	0	0
2	I	2.6	—	rt	6	0	0
3	I	2.6	—	50	6	43	0
4	I	2.6	—	80	6	65	3
5	I	3.9	—	80	6	77	28
6	I	2.6	NMP	80	6	25	0
7	I	2.6	DMPU	80	6	49	0
8	I	2.6	HMPA	80	6	>99	0
9	I	2.6	HMPA[c]	80	6	89	0
10	I	2.6	HMPA	80	3	67	0
11	I	2.6	HMPA	80	1	70	0
12	Br	2.6	HMPA	80	6	30	10
13	Cl	2.6	HMPA	80	6	29	9
14[d]	I	2.6	HMPA	80	6	67	0
15[e]	I	2.6	HMPA	80	6	74	0

[a] Cosolv.: cosolvent. In the case of HMPA, this amount corresponded to 5.5 equiv to CuI.
[b] Yields were determined by ^{19}F NMR spectroscopy.
[c] CuI/HMPA=1/1 (mol/mol).
[d] *t*-BuOK was employed instead of KF.
[e] CsF was used instead of KF.

Table 2
Introduction of a CF_3 group to pyridinone derivatives

Entry	R	X	Substrates	Products	Isolated yield (%)
1	Me	I	**1**	**2**	3 h; [67][a] 6 h; 84
2	PMB	I	**3**	**4**	68
3	Ph	I	**6**	**7**	78
4	MOM	I	**8**	**9**	68
5	Allyl	I	**10**	**11**	76
6	H	I	**12**	**13**	0
7	Me	Br	**14**	**2**	3
8			**15**	**16**	3 h; [92][a] 6 h; 87 [98][a]
9[b]			**17**	**18** **19**	70[c] (**18**:**19**=2:1)
10			**20**	**21**	98
11			**22**	**23**	99
12			**24**	**25**	87

[a] The yield in brackets were determined by ^{19}F NMR spectroscopy.
[b] The reaction was performed at room temperature for 48 h.
[c] Total yield of mono- and bis-trifluoromethylated compounds.