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FULL PAPER

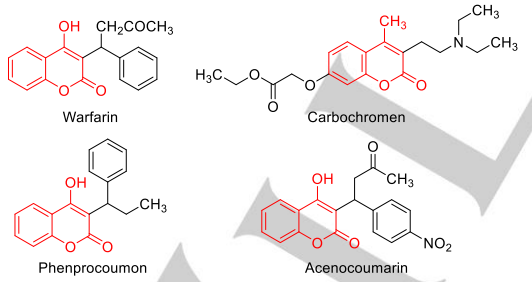
Copper-Catalyzed C-H Difluoroalkylation of Coumarins with Fluoroalkyl Bromides

Min Rao,*[a] [b] Zhenwei Fan,[a] Yaofeng Yuan*[a] and Jiajia Cheng[a]

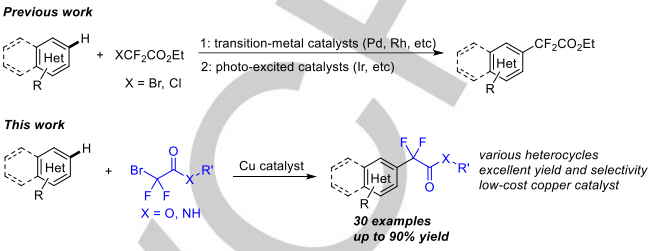
Abstract: An efficient method for the copper-catalyzed selective C-H difluoroalkylation of coumarins and with low cost and readily available ethyl bromodifluoroacetate and *N*-phenyl bromodifluoroacetamide has been reported. This reaction exhibits good functional group tolerance with respect to coumarins and difluoroalkylation reagents, and several redox-sensitive substrates have been successfully C-H difluoroalkylated in good to high yield. This design could further expand the scope to other heteroarenes, including furan, benzofuran, pyrrole, pyridinone, chromenone, indole, and quinolinone. A mechanism involving copper-catalyzed in-situ generation of fluoroalkyl radical is proposed.

Introduction

As an important structural motif widely existed in natural products and active pharmaceutical ingredients,[1] coumarin derivatives have been extensively applied in the fields of organic synthesis, pharmaceutical industry and materials due to their outstanding bioactivity, photoelectric properties, and fluorescent properties.[2] Many coumarin derivatives exhibit excellent biological properties and pharmaceutical activities.[3] For example, Warfarin, Acenocoumarin, Phenprocoumon, and Carbochromen have been well-known as anticoagulants for the prevention and treatment of thromboembolism, angina pectoris and myocardial infarction, respectively (**Scheme 1**).[4] During the past years, several methods have been developed for the modification of the coumarin derivatives to further expand their application scope, including phosphonylation,[5] halogenation,[6] sulfonylation,[7] and arylation.[8] However, high cost, poor selectivity, tedious and



Scheme 1. Examples of coumarins as key structures of human medicine.



Scheme 2. Fluoroalkylation of coumarins.

energy-consuming purification process, and multiple reactions steps made these structure modification methods inefficient for practical/industrial applications. As a consequence, embedding functional groups into π acceptors of heterocycles via direct C-H functionalization has attracted considerable interest from worldwide researchers in pursuing the prospects for practical application.

Incorporation of fluorine atom(s) into organic molecules may lead to dramatic changes in their chemical, physical and biological properties such as the binding affinity, lipophilicity, and pharmacokinetics.[9] Since the late 1950s, fluorine-containing structural motifs has played a central role in pharmaceuticals, agrochemicals, functional materials, and PET (positron emission tomography) imaging technology; roughly 5%–15% of newly launched pharmaceuticals and agrochemicals on the market are fluorinated compounds yearly.[10] Thus, the development of efficient methods for the preparation of structurally diverse fluorinated compounds, especially molecules containing a difluoromethylene unit, is of great importance in the drug design and screening.[11] Traditional deoxy fluorination of ketones for the preparation of organofluorines necessitate the utilization of the highly toxic fluorine reagent amino sulfur trifluoride (Et_2NSF_3 or (diethylamino)sulfur trifluoride). Alternatively, besides transition metal-mediated cross-coupling reactions,[12] direct C-H functionalization catalyzed by transition-metals has also emerged as a straightforward tool for the preparation of organofluorines. The advantages of this method include the excellent activity and selectivities.[13] However, the wide application of the C-H fluoroalkylation strategies may be severely limited by the expensive noble metal catalysts or photocatalysts. In recent years, copper-catalyzed radical difluoroalkylation strategy has attracted growing attention because of its simple reaction conditions and environmentally benign reaction process.[14] Copper-catalyzed C-H fluoroalkylation has been recognized as a powerful method to access complex fluorinated molecules and biomolecules.[15] On the other hand, direct C-H fluoroalkylation of coumarin derivatives by photo-excited catalysis,[16] palladium catalysis,[17] Rh(III) catalysis[18] and EDA complexes or halogen bond initiator[19] has proved to be capable for the post-modification of pharmaceutical significant molecules. Nevertheless, Cu-catalyzed C-H fluoroalkylation of heteroarenes, e.g. coumarin derivatives, has not been

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systematically investigated previously and the reaction yield was not satisfying (**Scheme 2**),[20] especially considering the appealing fact of utilizing fluoroalkylated heteroarenes as pharmacophores. Therefore, developing the highly efficient and practical catalytic systems for the efficient introduction of difluoroalkyl groups to the framework of heterocycles under the low-cost copper catalyst is of great significance.

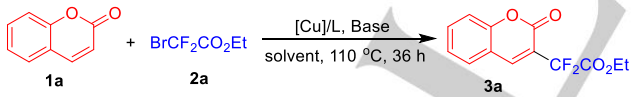
Herein, we disclose one radical C-H 3-fluoroalkylation of coumarin and other heteroarenes. This reaction utilizes inexpensive copper salt as the catalyst and commercially available ethyl bromodifluoroacetate and *N*-benzyl-bromodifluoroacetamide as the difluoromethylene group (CF_2) source, and several redox-sensitive substrates have been successfully C-H difluoroalkylated with this method in good to high yield. This design further expands the scope of copper-mediated difluoroalkylation to other heteroarenes, including furan, benzofuran, pyrrole, pyridinone, chromenone, indole, and quinolinone, thus providing a facile and general access to a wide range of difluoroalkylated molecules.

Results and Discussion

Initial studies were focused on the difluoroalkylation of coumarin **1a** with ethyl bromodifluoroacetate **2a** in the presence of CuI (10 mol %), 1,10-phenanthroline (phen), and K_2HPO_4 under N_2 atmosphere at 110 °C (**Table 1**). We were delighted to observe that the corresponding product **3a** could be obtained when using toluene as the reaction solvent, albeit lower 24% NMR yield was obtained (**entry 1**). Further screening of the solvents revealed that MeCN was most suitable for this reaction with an excellent 83% yield (**entries 2-4**). The performance of the other bases in the fluoroalkylation was next examined. However, the use of other organic or inorganic base, such as $N(Et)_3$ and KOAc, all resulted in reduced yield (**entries 5-6**). Further investigation on various copper catalysts revealed that CuBr, $Cu(acac)_2$ and $Cu(OTf)_2$ could also be utilized as a qualified partner in this catalytic system to deliver the desired fluoroalkylation product (**entries 7-9**). Finally, in comparison with bipy and phen-5,6-dione, screening of the ligand effect confirmed the superior performance of phen in promoting the reaction, affording **3a** in 80% isolated yield (**entries 10−11**).

With the optimal reaction conditions in hand, the scope of the difluoroalkylation reaction of coumarins was then evaluated, and the results are shown in **Table 2**. Generally, coumarins with both electron-withdrawing groups and electron-donating groups all worked well with **2a**, affording the desired difluoroalkylation products **3** in 70-90% yields. The halogen-substituted substrates (R = F, Cl, or Br) were tested under the standard conditions, which gave the desired products in good yields (**3b-3d**). Coumarin substituted with a methyl group in the 6-position of the phenyl ring provided the desired product **3e** in 76% yield. It is noteworthy that coumarins with a variety of alkoxy groups at 7-position of the aromatic ring were difluoroalkylated smoothly to deliver the target products (**3f-3j**). Additionally, *N*, *N*-diethyl amino group at the 7-position of the aromatic ring proceeded cleanly to furnish the desired product **3k** in excellent yield. Moreover, the multi-substituted substrate also proved to be suitable for the reaction to provide the corresponding product **3l** in good yield. Gratifyingly, the installation of an additional methyl group to the adjacent position of the olefin moiety did not have a big impact on the

Table 1. Optimization of the reaction conditions.[a]

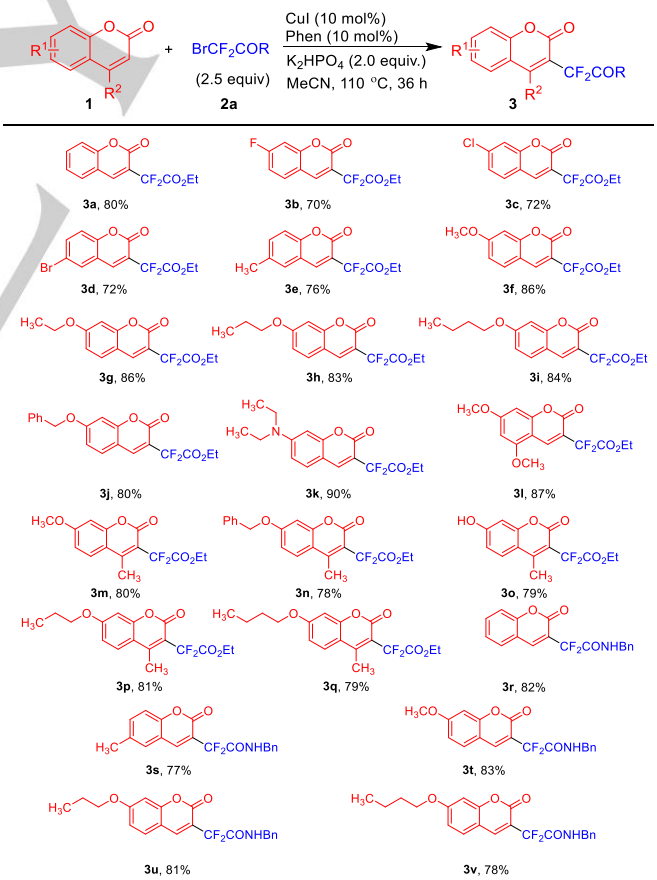


1a 2a 3a

Entry[a]	Catalyst	Ligand	Base	Solvent	Yield(%)[b]
1	CuI	Phen	K_2HPO_4	Toluene	24
2	CuI	Phen	K_2HPO_4	MeCN	83 (80[c])
3	CuI	Phen	K_2HPO_4	DMF	9
4	CuI	Phen	K_2HPO_4	THF	9
5	CuI	Phen	NEt_3	MeCN	21
6	CuI	Phen	KOAc	MeCN	4
7	CuBr	Phen	K_2HPO_4	MeCN	69
8	$Cu(acac)_2$	Phen	K_2HPO_4	MeCN	62
9	$Cu(OTf)_2$	Phen	K_2HPO_4	MeCN	74
10	CuI	bipy	K_2HPO_4	MeCN	64
11	CuI	L[d]	K_2HPO_4	MeCN	43

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (2.5 equiv), catalyst (10 mol%), ligand (10 mol%), base (2.0 equiv) in anhydrous solvent (3 mL), N_2, 110 °C, 36 h. [b] Determined by ^{19}F NMR analysis with trifluoromethoxybenzene as the internal standard. [c] Isolated yield. [d] 10 mol % of phen-5,6-dione was added as ligand.

Table 2. Substrate scope for coumarins. [a] [b]

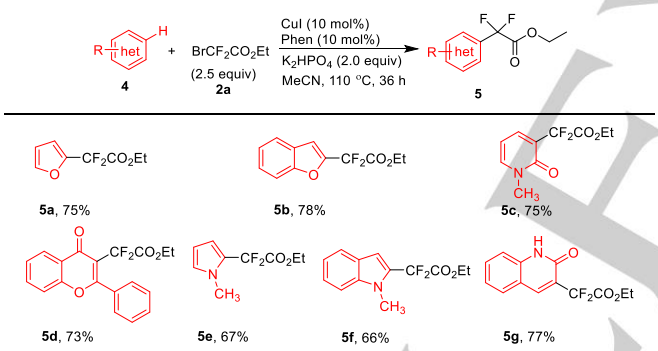


[a] Reaction conditions: **1** (0.2 mmol), **2a** (2.5 equiv), CuI (10 mol%), 1,10-phenanthroline (10 mol%), K_2HPO_4 (2.0 equiv) in anhydrous acetonitrile (3 mL), N_2, 110 °C, 36 h. [b] Isolated yield.

reaction efficiency, affording the desired products in moderate to good yields (**3m-3q**). Notably, redox-sensitive hydroxyl-substituted substrate, which has seldom been utilized in previous studies, could also be successfully direct C-H difluoroalkylated under the standard reaction condition (**3o**). When the alkylation agent was changed from ethyl bromodifluoroacetate to *N*-phenyl bromodifluoroacetamide, coumarin that contains a range of functional groups on the aromatic ring, such as RO− and Me−, underwent the intended transformation cleanly to give the corresponding products in moderate to good yields (**3r−3v**).

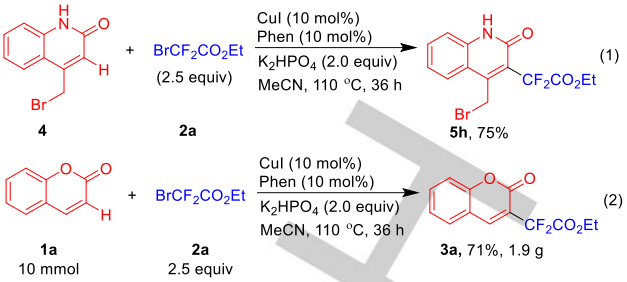
We next turned our attention to a wider range of heterocycles since difluoroalkylated heterocycles may be a valuable candidate for drug discovery and development (**Table 3**). The array of suitable substrates has been extended to include other important heterocycles, providing the corresponding products in moderate yields and excellent regioselectivities (**5a**-**5g**). Furan and benzofuran reacted smoothly to afford the difluoroalkylated products in 75% and 78% yield respectively under our reaction conditions(**5a** and **5b**). Both pyridone and chromenone could be efficiently and highly selectively difluoroalkylated at specific positions (**5c** and **5d**). *N*-methylpyrrole and *N*-methylindole were well tolerated under the standard conditions, giving the desired products in 67% and 66% yield (**5e** and **5f**). Finally, it was found that 2-quinolinone was also applicable for the reaction, which provided feasible access to the preparation of the 2-quinolinone derivative (**5g**).

Table 3. Substrate scope for aromatic heterocycles.[a] [b]

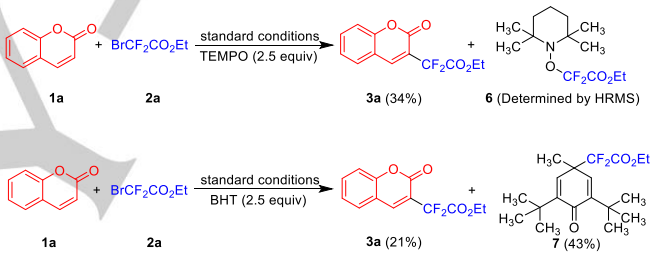


[a] Reaction conditions: **4** (0.2 mmol), **2a** (2.5 equiv), CuI (10 mol%), 1,10-phenanthroline (10 mol%), K_2HPO_4 (2.0 equiv) in anhydrous acetonitrile (3 mL), N_2, 110 °C, 36 h. [b] Isolated yield.

To further demonstrate the application of the methodology, attempts to expand the reaction scope to the steric hindered substrate 4-(Bromomethyl)-2-quinolinone resulted in the production of **5h** in good yield (eq. 1). Importantly, a multigram-scale experiment has been demonstrated using coumarin as a model substrate. Remarkably, gram-scale synthesis of **3a** in the presence of 10 mol% copper catalyst proceeded smoothly with moderate yield. Thus, this general, facile, and cost-effective method may offer a practical access to highly functionalized fluoroalkylated molecules (eq. 2).

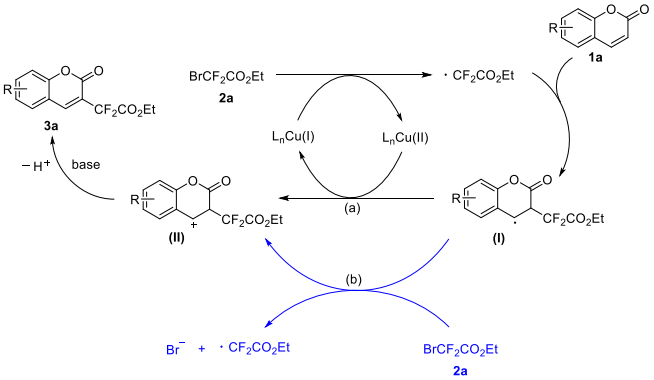


To gain a deeper insight into the reaction mechanism, some control experiments were conducted (**Scheme 3**). When 2.5 equiv of 2,2,6,6-tetramethyl piperidine-1-oxyl (TEMPO) was added to the reaction as a radical scavenger, the difluoroalkylation was partly inhibited and the desired product was generated in 34% yield. Furthermore, the radical-trapping product TEMPO-CF_2CO_2Et was observed by HRMS, indicating the generation of fluoroalkyl radicals during the reaction process. In line with the above result, when the radical scavenger butylated hydroxytoluene (BHT, 2.5 equiv) was added to the standard reaction mixture of **1a** and **2a**, the C-H alkylation product **3a** was obtained in only 21% yield. Meanwhile, the radical-trapping product **7** was could by isolated in 43% yield.



Scheme 3. Mechanism studies.

In light of this result, a plausible mechanism was proposed as illustrated in **Scheme 4**. The reaction was initiated by a single-electron-transfer (SET) from Cu(I) to ethyl bromodifluoroacetate. The resulted difluoroalkyl radical subsequently reacted with coumarins **1a** to generate a new radical intermediate **I** which could undergo two possible pathways. First, a one-electron transfer from **I** to Cu(II) regenerates Cu(I) and forms a carbocation intermediate **II**. Subsequent the desired product **3a** could be



Scheme 4. Proposed reaction pathway.

afforded through the elimination of one proton with the assistance of one base [pathway (a)].[20, 21] Alternatively, the radical chain reactions could occur to regenerate a carbocation intermediate **II** and difluoroalkyl radical by addition of **I** radical to $BrCF_2CO_2Et$ followed by electron transfer [pathway (b)].[22]

Conclusions

In conclusion, we have disclosed an efficient method for the synthesis of difluoroalkylated coumarins through Cu-catalyzed. The reaction was found to tolerate a wide range of functional groups. Other heteroarenes, such as furan, benzofuran, pyrrole, pyridinone, chromenone, indole, and quinolinone could also be successfully C-H difluoroalkylated in good to high yield. This method will not only provide a cost-effective and facile approach to access a wide range of difluoroalkylated molecules but also prompt the research in low-cost transition-metal-catalyzed fluoroalkylation reaction of valuable functional organic compounds.

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Keywords: Copper-Catalysis • C-H Perfluoroalkylation • Radicals • Coumarin

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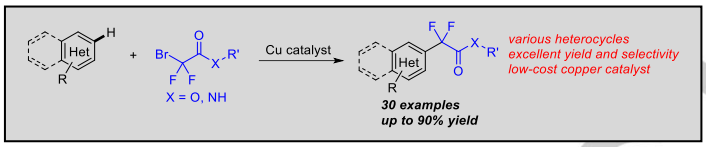

A novel copper-catalyzed selective C-H difluoroalkylation of coumarins and with low cost and readily available ethyl bromodifluoroacetate and N-phenyl bromodifluoroacetamide has been presented. This reaction exhibits good functional group tolerance with respect to coumarins and difluoroalkylation reagents, and a number of redox-sensitive substrates have been successfully C-H difluoroalkylated in good to high yield. This design could further expand the scope to other heteroarenes, including furan, benzofuran, pyrrole, pyridinone, indole and quinolinone.