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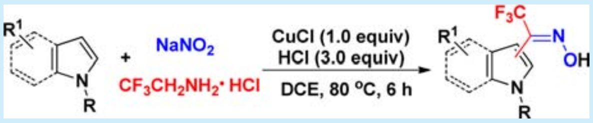
A Direct Copper-Promoted Three-Component Entry to Trifluoromethylketoximes

Shuai Wang, Jing Nie, Yan Zheng, and Jun-An Ma*

Department of Chemistry, Key Laboratory of Systems Bioengineering (the Ministry of Education), Tianjin University, and Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Tianjin 300072, P. R. of China

Supporting Information

ABSTRACT: A new copper-promoted three-component method for constructing ketoximes has been developed. This transformation can be achieved using indoles/pyrroles with the in situ generated 2,2,2-trifluorodiazoethane and nitrite species under mild conditions, thus offering a direct pathway to (*E*)-3-indolyl/2-pyrrolyl trifluoromethylketoximes.



Ketoximes are common structural motifs in both chemical and biological contexts.[1] Among them are Cyclohexanone-oxime (precursor to Nylon 6),[2] Thiofluoximate (insecticide),[3] Alloxydim (herbicide),[4] Cymoxanil (fungicide),[5] Risperidone (antipsychotic),[6] and Fluvoxamine (antidepressant)[7] (Figure 1). Traditional methods for the synthesis of ketoximes have usually focused on two-component condensations, including the oximation of ketones with hydroxylamine (eq 1)[8] and the reaction of nitrites with compounds containing the active methylene group (eq 2).[9] Moreover, the corresponding ketones or reactants containing the active methylene group have to be prepared beforehand. It is striking, however, that the three-component reaction in one pot for ketoxime construction has not been reported to date. Through our attempts to use 2,2,2-trifluorodiazoethane as a C2-synthon for the preparation of organofluorines,[10] we have discovered a new three-component route to trifluoromethylketoximes involving a copper-promoted reaction of indoles/pyrroles with the in situ generated 2,2,2-trifluorodiazoethane[11] and nitrite species (eq 3). Herein, we report our preliminary results on this subject.

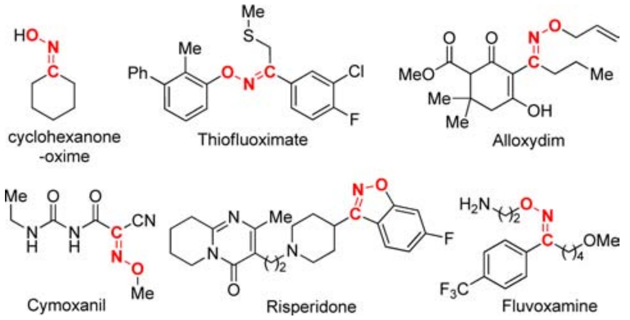
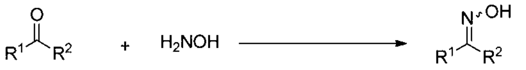


Figure 1. Ketoxime-based chemical and biological compounds.



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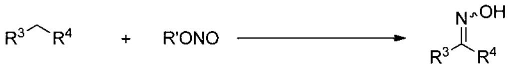

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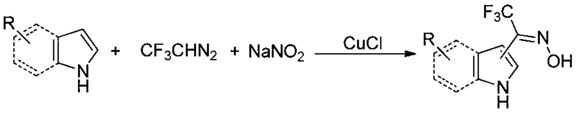

(3)

In an initial study, we explored the reaction of *N*-methylindole **1a** with the in situ generated 2,2,2-trifluorodiazoethane and nitrite species. In the presence of CuI at room temperature, no product was observed (Table 1, entry 1). Subsequently, the reaction was conducted at higher temperatures (60 and 80 °C), and (*E*)-3-indolyl trifluoromethylketoxime **2a** was obtained in 18−33% yield (entries 2 and 3). The structure of **2a** was further confirmed by means of X-ray crystallographic analysis (see the Supporting Information). Then, a series of copper salts were screened for this model reaction (entries 4−7), and CuCl was found to deliver the desired product in 37% yield. When the amount of CuCl was increased, the reaction proceeded to afford the product **2a** in moderated to good yields (entries 8−10). The solvent was found to have an important effect on the reactivity (entries 11−16). Among the solvents tested, dichloroethane (DCE) was found to be the choice of solvent for this three-component reaction (entry 16). The use of an excess of the $CF_3CH_2NH_2\cdot HCl$ reagent was essential for this transformation, but 4.0 equiv of $CF_3CH_2NH_2\cdot HCl$ did not improve the yield when compared to that obtained with 3.0 equiv of $CF_3CH_2NH_2\cdot HCl$ (entries 17 and 18). It was noteworthy that in all cases cyclopropanation or cross-coupling of indole with 2,2,2-trifluorodiazoethane was not a detectable side reaction for these copper-promoted processes.

Having established an optimal protocol for this three-component reaction, we examined the scope of the indole substrates, and the results are summarized in Scheme 1. A series

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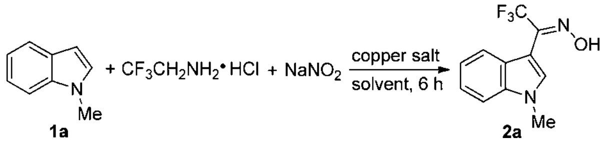
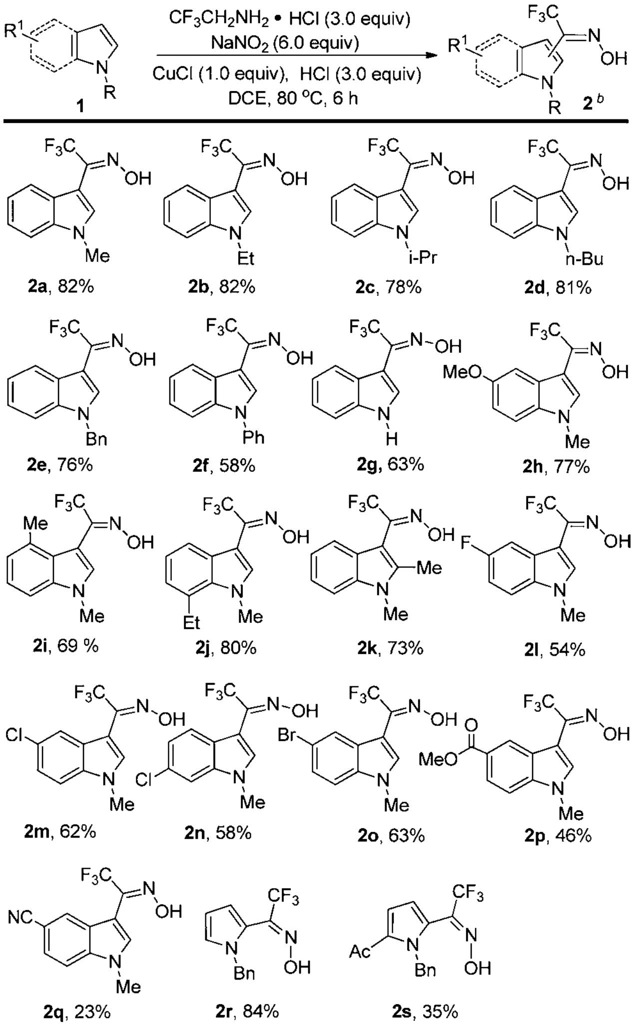
Table 1. Screening Optimal Conditions[a]



entry	copper salt (*x* equiv)	solvent/temp (°C)	yield (%)[b]
1	CuI (0.2)	benzene/25	0
2	CuI (0.2)	benzene/60	18
3	CuI (0.2)	benzene/80	33
4	CuBr (0.2)	benzene/80	28
5	CuCl (0.2)	benzene/80	37
6	$Cu(OAc)_2$ (0.2)	benzene/80	22
7	$Cu(acac)_2$ (0.2)	benzene/80	17
8	CuCl (0.5)	benzene/80	44
9	CuCl (1.0)	benzene/80	59
10	CuCl (1.5)	benzene/80	60
11	CuCl (1.0)	toluene/80	67
12	CuCl (1.0)	toluene/110	59
13	CuCl (1.0)	1,4-dioxane/80	23
14	CuCl (1.0)	CH_3CN/80	0
15	CuCl (1.0)	DMF/80	0
16	CuCl (1.0)	$ClCH_2CH_2Cl$/80	71
17[c]	CuCl (1.0)	$ClCH_2CH_2Cl$/80	82
18[d]	CuCl (1.0)	$ClCH_2CH_2Cl$/80	83

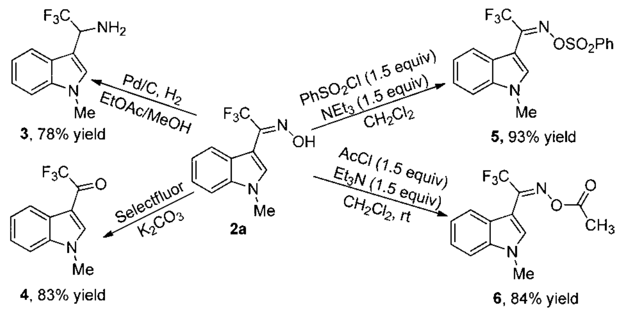
[a] General reaction conditions: **1a** (0.3 mmol), Cu salt (0.2−1.5 equiv), $CF_3CH_2NH_2\cdot HCl$ (2.0 equiv), $NaNO_2$ (5.0 equiv), and 36% HCl (3.0 equiv) in solvent (4 mL) were conducted in one pot for 6 h. [b] Isolated yield. [c] $CF_3CH_2NH_2\cdot HCl$ (3.0 equiv) and $NaNO_2$ (6.0 equiv) was used. [d] $CF_3CH_2NH_2\cdot HCl$ (4.0 equiv) and $NaNO_2$ (7.0 equiv) was used.

Scheme 1. Substrate Scope of CuCl-Promoted Three-Component Reaction[a]



[a] General reaction conditions: **1** (0.3 mmol), CuCl (1.0 equiv), $CF_3CH_2NH_2\cdot HCl$ (3.0 equiv), $NaNO_2$ (6.0 equiv), and 36% HCl (3.0 equiv) were conducted in 4 mL of DCE at 80 °C for 6 h. [b] Isolated yield.

Scheme 2. Further Synthetic Transformation of Trifluoromethylketoxime 2a



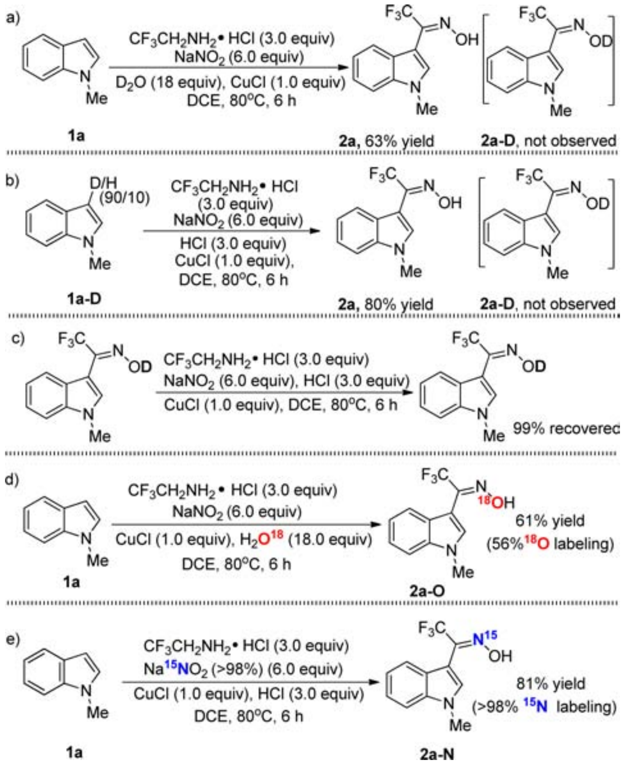
of N-substituted indoles were employed in this one-pot transformation, and the corresponding trifluoromethylketoximes **2a**−**2f** were obtained in 58−82% yields. For example, the reaction worked well with the indoles bearing N-alkyl protecting groups to afford (*E*)-3-indolylketoximes **2a**−**2e** in good yields. When N-alkyl protecting groups were replaced with a phenyl substituent, the yield was reduced to 58%. In addition, when indole without an N-protecting group was subjected to this three-component transformation under the same conditions, the desired product **2g** was obtained in 63% yield without any detectable quantities of the N−H insertion product. Four *N*-methylindoles bearing electron-donating groups on the aromatic ring could also participate in this transformation, affording the trifluoromethylketoximation products **2h**−**2k** in good yields. The substrates bearing electron-withdrawing groups on the aromatic ring delivered the desired products **2l**−**2o** in 54−63% yields. Unfortunately, ester- and cyano-substituted indoles were poor substrates, providing the corresponding products **2p** and **2q** in lower yields. Accordingly, the reaction worked well with *N*-benzylpyrrole under our current reaction conditions to afford the regioselective product **2r** in 84% yield, whereas 2-acetyl-*N*-benzylpyrrole furnished the product **2s** in 35% yield. In addition, it was found that the use of other electron-enriched arenes, such as anisole, *N*,*N*-dimethylaniline, and 3-dimethylaminoanisole, did not deliver any desired products, even when the reaction time is prolonged to 48 h.

The products obtained here can be readily transformed into other trifluoromethylated compounds, and some examples are illustrated in Scheme 2. Direct hydrogenation of **2a** using a Pd/C catalyst and H_2 at atmospheric pressure gave rise to 2,2,2-trifluoro-1-(1-methyl-1*H*-indol-3-yl)ethanamine **3** in 78% yield. Treatment of **2a** with Selectfluor and K_2CO_3 at room temperature afforded the corresponding ketone **4** in 83% yield. Also, the reaction of **2a** with benzenesulfonyl chloride and acetyl chloride in the presence of triethylamine delivered

O-phenylsulfonylated and acetylated oximes **5** and **6** in 93% and 84% yield, respectively.

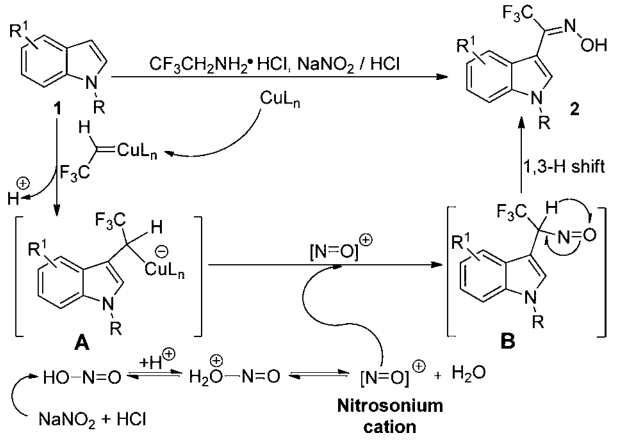
With the aim of providing preliminary mechanistic insight into this transformation, we conducted the following isotopic labeling experiments. Reaction of **1a** with the in situ generated 2,2,2-trifluorodiazoethane and nitrite species in the presence of D_2O gave the corresponding trifluoromethylketoxime **2a** in 63% yield upon isolation (Scheme 3a), and 3-deuterated indole **1a-D** delivered the product **2a** in 80% yield under the standard reaction conditions (Scheme 3b). In these two cases, however, the deuterated product **2a-D** was not detected by ^1H NMR spectroscopy. Furthermore, in the control experiment (Scheme 3c), we did not observe any proton exchange when the OD-labeled ketoxime was refluxed under our current conditions. Therefore, the reaction could not proceed by an O_{water}−H or C_{indole}−H insertion process. Subsequently, by using ^{18}O-labeled H_2O and ^{15}N-labeled $NaNO_2$, we were delighted to find compelling evidence that both oxygen and nitrogen atoms are derived from water and/or the nitrite salt, as the ^{18}O and ^{15}N labels were effectively incorporated into the products **2a-O** and **2a-N**, respectively (Scheme 3d and 3e).

Scheme 3. Isotopic Labeling Experiments



With these results taken into consideration, a plausible mechanism for this three-component reaction is shown in Scheme 4. Initially, the copper carbenoid is formed by the reaction of the in situ generated 2,2,2-trifluorodiazoethane with copper(I). Then, the indole **1** attacks the copper carbenoid to give the intermediate **A**, which is trapped by a nitrosonium cation (in situ generated from $NaNO_2$ and HCl) to form the intermediate **B**. The subsequent step is the intramolecular 1,3-hydrogen shift of **B**, thus giving rise to the ketoxime **2**. In addition, a zwitterionic species formed from the indole and the copper carbenoid is not excluded as the intermediate involved in this process (see the Supporting Information).[12] Further analysis will be necessary to elucidate the nature of this three-component reaction more accurately.

Scheme 4. Proposed Mechanism for This Copper-Promoted Three-Component Reaction



In summary, we have developed a new Cu-promoted three-component reaction of indoles/pyrroles with the in situ generated 2,2,2-trifluorodiazoethane and nitrite species. This strategy enables rapid access to a series of (*E*)-3-indolyl and 2-pyrrolyl trifluoromethylketoximes. In addition, we proposed a mechanistically novel C−N bond-forming reaction of nitrosonium species utilizing $NaNO_2$ as the sole nitrogen source. A more detailed mechanistic investigation and extension of the present chemistry to the synthesis of other ketoximes are currently ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, spectral data of all the new compounds, and the CIF information of **2a**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: majun_an68@tju.edu.cn.

Notes

The authors declare no competing financial interest.

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