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Copper-Catalyzed Aerobic Oxidation of Azinylmethanes for Access to Trifluoromethylazinylols

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A copper-catalyzed oxygenation of methylazaarenes was found to occur in the absence of both ligand and additive, and has been successfully employed for the synthesis of trifluoromethylazinylketols. This synthetic strategy incorporates aerobic oxidation and a trifluoromethylation in one-pot and provides a novel method for the trifluoromethylation of aliphatic C—H bond.

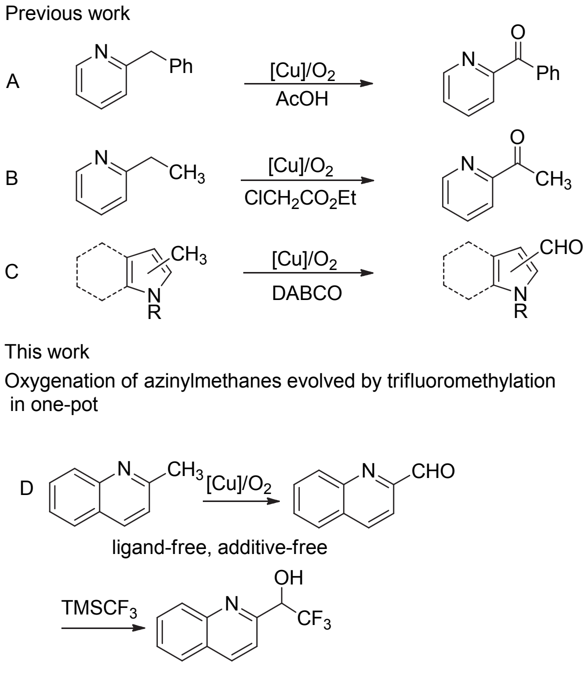
Keywords aerobic oxidation, azinylmethanes, copper catalysis, synthetic methods, trifluoromethylation

Introduction

The direct oxidation of sp^3 C—H bonds provides the most straightforward way for the functionalization of hydrocarbons.[1] Due to the low reactivity of the aliphatic C—H bonds, however, stoichiometric and hazardous oxidants or severe reaction conditions have to be usually utilized for this purpose.[2] On the other hand, copper catalyst in combination with molecular oxygen as the ultimate oxidant has been recognized as an ideal oxidative system due to their environmental benign and economy.[3] Yet few examples in the oxidations of hydrocarbons are fit for this simple and sustainable oxidation system to date.[4-6]

Maes and co-workers[4a] reported an aerobic oxidation of arylazinylmethanes to aryazinyl ketones in the presence of a catalytic amount of CuI (Scheme 1A) in 2012. Acidic additive, such as AcOH or TFA, was required for their oxidation protocol. The acidity of the methylene of substrates was also proven to be crucial, for example 2-methylpyridine was difficult to oxidize under the identical conditions. Recently, Lei[4b] developed a chloroacetate-promoted oxidation of *N*-heterobenzylic methylenes for the synthesis of hereoarylmethylketones under copper catalysis in dioxygen atmosphere (Scheme 1B). The strong activation of the benzylic methylene C—H bonds, which resulted from the formation of pyridium salts in the presence of chloroacetate led the oxidation process occurring smoothly. Comparatively, the acid-assisted CuI/O_2 oxidation system developed by Maes was ineffective for those substrates tested by Lei. Also in 2012, Chiba *et al*.[4c] found that 2- or 3-methyl indoles/pyrroles could be oxidized by O_2 leading to the corresponding aldehydes under the copper catalysis, while the process required DABCO to form Cu(I)-DABCO complex for efficient oxidations (Scheme 1C). During preparing for this work, Yin and Deng groups[6] independently reported a kind of copper-catalyzed amidation of 2-methylquinolines with amines in the absence of ligand and additive, in which the *in situ* generation of aldehyde intermediate was proposed to be involved. By comparison, we here report an alternative ligand-free and additive-free copper-catalyzed oxygenation of azinylmethanes by using O_2 as

Scheme 1 Cu-catalyzed aerobic oxygenation of benzylic C—H bonds of heteroarenes



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oxidant (Scheme 1D). Encouraged by the achievements obtained in trifluoromethylations[7] and our investigations on the applications of (trifluoromethyl) trimethylsilane ($TMSCF_3$, Ruppert-Prakash reagent),[7a,8,9] the oxygenation has been successfully evolved by the trifluoromethylation to afford trifluoromethylazinylols in one-pot.

Experimental

Materials

All commercially available compounds were used as received unless otherwise noted. All reactions were carried out under dioxygen atmosphere (1 atm). Reactions were monitored through thin layer chromatography [TLC, silica gel 60 F254]. Subsequent to elution, spots were visualized using UV radiation (254 nm). Flash column chromatography was performed on silica gel 60 (particle size 200—400 mesh, purchased from Qingdao, China). Hydrogen nuclear magnetic resonance spectra (^1H NMR), carbon nuclear magnetic resonance spectra (^{13}C NMR) and fluorine nuclear magnetic resonance spectra (^{19}F NMR) were recorded at 25 ℃ on a Varian 500, 125 and 470 MHz spectrometer, respectively, and $CDCl_3$ was purchased from J&K. Chemical shifts for ^1H NMR spectra are reported as δ downfield from $SiMe_4$ (δ 0.0) and relative to the signal of $SiMe_4$ (δ 0.00, singlet). ^{13}C NMR are reported as δ downfield from $SiMe_4$ (δ 0.0) and relative to the signal of chloroform-*d* (δ 77.00, triplet). ^{19}F spectra are recorded using fluorobezene (δ –113.5) as external standard. High-resolution mass spectra (HRMS) were obtained on a Bruker micro TOF II focus spectrometer (ESI).

General procedure for the copper-catalyzed aerobic oxidation of aliphatic $C(sp^3)$—H bond of *N*-heterocyclic compounds

Under an oxygen atmosphere (1 atm), $CuCl_2{\bullet}2H_2O$ (0.05 mmol) was added to a 25 mL sealed tube. Subsequently, azinylmethanes **1** (0.5 mmol) and DMF (3.0 mL) were injected via a syringe. Finally, the sealed tube was allowed to stir at 130 ℃ and monitored by thin layer chromatography. After complete consumption of substrates, the resulting mixture was poured into water, extracted with CH_2Cl_2 (15 mL×3). Then the combined organic extracts were washed with saturated aqueous solution of ammonium chloride (15 mL×3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, *V*∶*V*=19∶1) to give the desired aldehydes **2**.

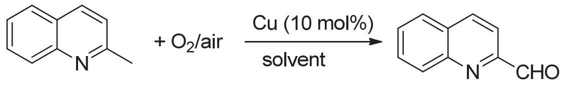
General procedure for the copper-catalyzed one-pot aerobic oxidation and trifluoromethylation of aliphatic $C(sp^3)$—H bond of *N*-heterocyclic compounds for access to trifluoromethylazinyl alcohols

Under an oxygen atmosphere (1 atm), $CuCl_2{\bullet}2H_2O$ (0.05 mmol) was added to a 25 mL sealed tube. Subsequently, azinylmethanes **1** (0.5 mmol) and DMF (3.0 mL) were injected via a syringe. Finally, the sealed tube was allowed to stir at 130 ℃ and monitored by thin layer chromatography. After complete consumption of **1**, Me_3SiCF_3 (2.0 mmol) and K_2CO_3 (0.5 mmol) were sequentially added to the sealed tube. Then the reaction mixture was stirred at atmosphere temperature and monitored by thin layer chromatography. After complete consumption of **2**, the reaction was quenched by saturated aqueous solution of ammonium chloride, the resulting mixture was poured into water, extracted with CH_2Cl_2 (15 mL×3). The combined organic extracts were washed with saturated aqueous solution of sodium chloride (15 mL×3), dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to yield the crude product, which was purified by silica gel chromatography (eluent: petroleum ether/ethyl acetate, *V*∶*V*=10∶1) to give the desired trifluoromethylazinylols **3**.

Results and Discussion

A survey of reaction conditions was carried out using 2-methylquinoline (**1a**) as the model substrate and the selected experimental results are listed in Table 1. As we expected, when **1a** was treated with 10 mol% CuI in DMF at 130 ℃ under O_2 atmosphere, the desired product quinoline-2-carbaldehyde (**2a**) was formed

Table 1 Aerobic oxidative of 2-methylquinoline[a]



1a **2a**

Entry	[Cu]/mol%	Solvent	*T*/℃	Yield[b]/%
1	CuI	DMF	130	66
2	CuBr	DMF	130	54
3	CuCl	DMF	130	43
4	CuOAc	DMF	130	57
5	Cu_2O	DMF	130	34
6	$Cu(MeCN)_4PF_6$	DMF	130	51
7	$CuSO_4{\bullet}5H_2O$	DMF	130	33
8	$Cu(OAc)_2$	DMF	130	63
9	Cu	DMF	130	33
10	$CuCl_2{\bullet}2H_2O$	DMF	130	82
11[c]	—	DMF	130	0
12	$CuCl_2{\bullet}2H_2O$	DMF	100	81
13	$CuCl_2{\bullet}2H_2O$	DMF	50	27
14	$CuCl_2{\bullet}2H_2O$	DMSO	130	42
15	$CuCl_2{\bullet}2H_2O$	1,4-Dioxane	130	38
16	$CuCl_2{\bullet}2H_2O$	Toluene	130	32
17	$CuCl_2{\bullet}2H_2O$	NMP	130	67
18	$CuCl_2{\bullet}2H_2O$	MeCN	130	24
19[d]	$CuCl_2{\bullet}2H_2O$	DMF	130	10

[a] Reaction conditions: **1a** (0.3 mmol), solvent (3.0 mL), 1 atm O_2. [b] Isolated yield. [c] No Cu salt was added. [d] The reaction was conducted in the air.

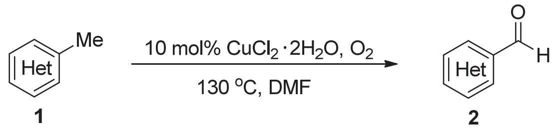
in 66% yield after 12 h (Table 1, Entry 1). Subsequently, various Cu$^{I/II}$ salts including CuBr, CuCl, CuOAc, Cu_2O, Cu[(MeCN)$_4$PF$_6$], $CuSO_4$•$5H_2O$, Cu(OAc)$_2$, $CuCl_2$•$2H_2O$ and Cu were examined and $CuCl_2$•$2H_2O$ was proven to be more efficient (Table 1, Entries 2—10). A control experiment revealed that copper catalyst was essential for the reaction (Table 1, Entry 11). Lower temperature or air condition decreased the reaction yield (Table 1, Entry 13 and Entry 19), while 81% yield of **2a** performed at 100 ℃ could be obtained by prolonging reaction time to 12 h (Entry 12). Further screening of the solvents revealed that DMF was the best solvent for this transformation (Table 1, Entries 14—18). As a result, the oxidation of 2-methylquinoline **1a** could give **2a** in 82% yield in 4 h by using 10 mol% $CuCl_2$•$2H_2O$ as catalyst and O_2 as oxidant in DMF at 130 ℃.

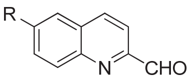
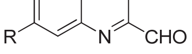
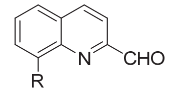
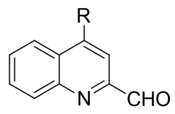
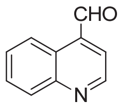
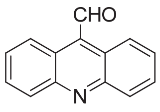
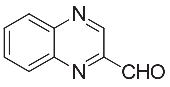
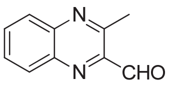
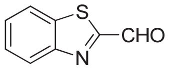
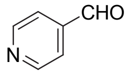
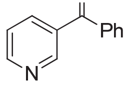
With the optimized conditions in hand, various substituted quinolines were subjected to the copper-catalyzed oxidation of aliphatic C—H bond. The results are summarized in Table 2. Both electron-donating and electron-withdrawing groups at the 6, 7, 8, or 4-position of quinoline ring afforded the corresponding aldehydes in 38%—87% yields (Table 2, **2a**—**2m**). But the reaction does not work for compound **1** containing a strong electron-withdrawing group, such as NO_2, at its 6-position. The reaction was also successful with 4-methylquinoline **1n** leading to **2n** in 91% yield. Other heterocycles, including 9-methylacridine (**1o**), 2-methylquinoxaline (**1p**), 2,3-dimethylquinoxaline (**1q**), and 2-methylbenzo[*d*]-thiazole (**1r**) also worked well leading to the corresponding aldehydes **2o**—**2r** in good yields (56%—89%). Compared to Lei's work,[4b] our methodology is compatible with 4-methylpyridine (**1s**) and 2-benzylpyridine (**1t**) to give corresponding carbonyl products in 45% and 78% yields, respectively. By comparison, the requirement of longer reaction time for the formation of ketone **2t** indicates a lower reactivity of "methylene" in **1t** than those of other substrates.

Recently, our interest focuses on developing new trifluoromethylation reagent and trifluoromethylation reactions,[8,9] especially exploring the applications of $TMSCF_3$ in trifluoromethylations. Considering the importance of trifluoromethylated compounds, we turned to combine the above oxygenation of azinylmethanes with further nucleophilic trifluoromethylation of these aldehydes with $TMSCF_3$[7a,10-12] for the synthesis of trifluoromethylazinylols in one-pot. As presented in Table 3, all tested substrates **1** are suitable for the present one-pot reaction and trifluoromethylazinylols **3** were obtained in good to excellent yields.

On the basis of the related work,[4,6] a reaction mechanism was proposed as described in Scheme 2. Initially, the isomer of **1a** is oxidized by Cu(II) in the presence of O_2 to afford a peroxycupric intermediate **I** along with the release of a proton. Then, peroxycuprous intermediate **II** was formed by an intramolecular reaction of oxygen radical with benzyl followed by an elimination of CuOH to give aldehyde product **2a**. Cu(II) is recovered by the oxidation of Cu(I) in the presence of O_2 and proton. In the combined transformations, the nucleophilic addition of $TMSCF_3$ onto the *in situ* generated carbonyl group of **2a** affords trifluoro-

Table 2 Copper-catalyzed aerobic oxidation of azinylmethanes[a]

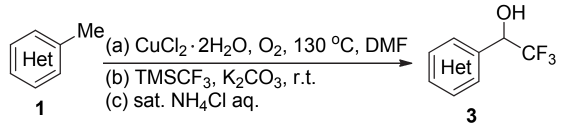


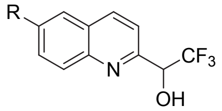
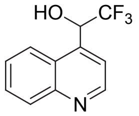
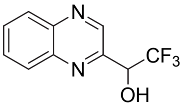
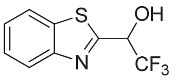
Entry	Product **2**		*t*/h	Yield[b]/%
1		**2a**, R=H	4	82
2		**2b**, R=F	7	64
3		**2c**, R=Cl	6	87
4		**2d**, R=Br	3	73
5		**2e**, R=Me	5	82
6		**2f**, R=OMe	8	84
7		**2g**, R=F	3	43
8		**2h**, R=Cl	5	62
9		**2i**, R=Cl	6	64
10		**2j**, R=OAc	4	71
11		**2k**, R=4-NH_2	4	38
12		**2l**, R=4-NHAc	10	76
13		**2m**, R=4-Cl	5	47
14		**2n**	4	91
15		**2o**	4	81
16		**2p**	6	89
17		**2q**	4	71
18		**2r**	36	56
19		**2s**	12	45
20		**2t**	24	78

[a] Conditions: **1** (0.3 mmol), DMF (3.0 mL), 1 atm O_2. [b] Isolated yield.

methylazinylol (**3a**) as the final product.

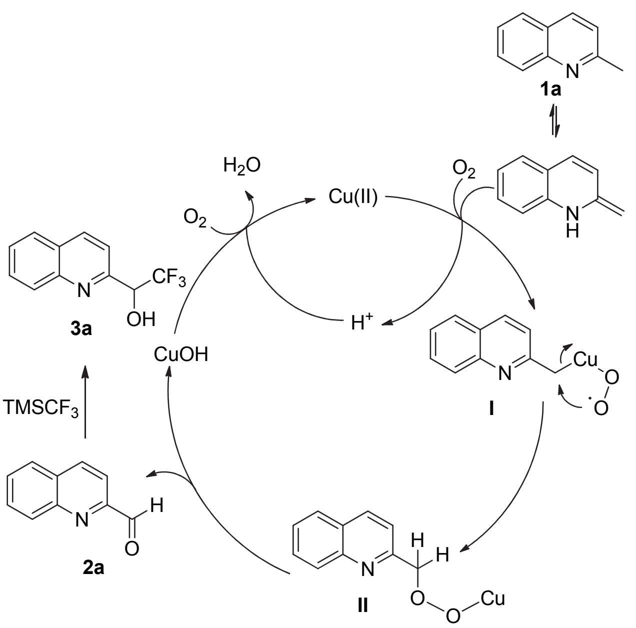
Table 3 One-pot synthesis of trifluoromethylazinyl methanols[a]



Entry	Product **3**	*t*/h	Yield[b]/%
1	 **3a**, R=H	8	70
2	**3b**, R=F	12	53
3	**3c**, R=Cl	11	83
4	**3d**, R=Br	7	67
5	**3e**, R=Me	12	76
6	**3f**, R=OMe	15	79
7	 **3n**	8	88
8	 **3p**	7	87
9	 **3r**	40	51

[a] Conditions: **1** (0.3 mmol), $CuCl_2•2H_2O$ (10 mol%), DMF (3.0 mL), 1 atm O_2. Then, $TMSCF_3$ (1.2 mmol), K_2CO_3 (0.3 mmol). [b] Isolated yield.

Scheme 2 Proposed reaction mechanism



Conclusions

In conclusion, we have developed a direct oxidation of sp^3-hybridized C—H bond by using cheap copper salts as the catalyst and molecular oxygen as the ultimate oxidant under ligand-free and additive-free conditions. The study of the substrate scope showed that various *N*-heterocyclic compounds were converted into the corresponding aldehydes with good to excellent yields. Additionally, a well combination of oxidations of heterobenzylic methylenes with trifluoromethylation in one-pot was realized to synthesize a set of trifluoromethylazinylketols which are valuable synthon in organic chemistry.

Acknowledgement

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