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PII: S0040-4039(18)30906-7
DOI: https://doi.org/10.1016/j.tetlet.2018.07.032
Reference: TETL 50141

To appear in: *Tetrahedron Letters*

Received Date: 23 May 2018
Revised Date: 27 June 2018
Accepted Date: 11 July 2018

Please cite this article as: Zhu, M., Chen, D., Zeng, S., Xing, C., Deng, W., Xiang, J., Wang, R-J., Synthesis of *(Z)*-Nitroalkene Derivatives through Oxidative Dehydrogenation Coupling of α-Aminocarbonyl Compounds with Nitromethane by Copper Catalysis, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.07.032

Tetrahedron Letters
journal homepage: www.elsevier.com

Synthesis of *(Z)*-Nitroalkene Derivatives through Oxidative Dehydrogenation Coupling of *α*-Aminocarbonyl Compounds with Nitromethane by Copper Catalysis

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
α-Amino carbonyl compounds
Nitromethane
(Z)-Nitroalkene
Cross-dehydrogenative coupling

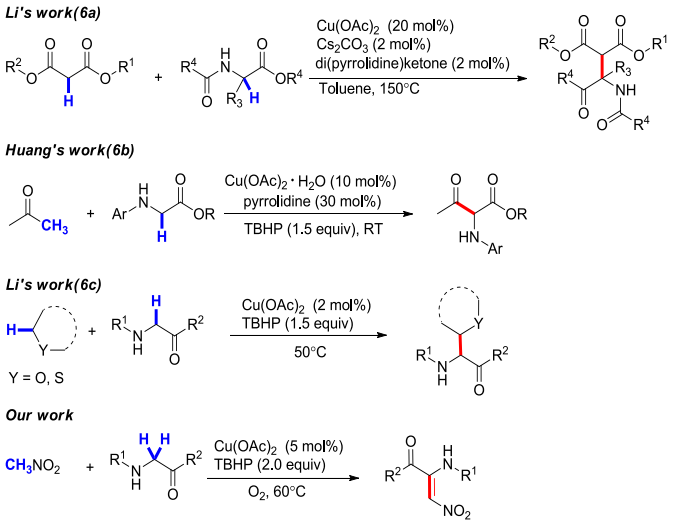
ABSTRACT

A novel copper-catalyzed cross-dehydrogenative coupling reaction of *α*-amino carbonyl compounds with nitromethane to synthesis of *(Z)*-nitroalkene derivatives has been established. *(Z)*-Nitroalkene derivatives are achieved through the cleavage of sp^3 C-H bonds and formation of C-C double bond, with mild reaction conditions and excellent stereoselectivity.

Introduction

The direct cross-dehydrogenative coupling (CDC) of C-H processes is the most efficient and straightforward method in building complex molecules starting from easily available materials[1]. Among the various CDC reactions[2], the direct formations of C-C bonds by the cleavage of C(sp^3)-H bond has been a long standing challenges in organic and bioorganic synthesis, because of their low reactivity and selectivity problems[3]. Under the circumstances, C(sp^3)-H bond adjacent to heteroatoms or double bonds has been used to construct C-C bonds due to their special activity, direction and site-specificity over the past decades [4].

α-Amino carbonyl compounds is one kind of important bioactive compounds[5], and the oxidative functionalization of their C-H bond at the α-position by C-C single bond has been investigated for some times. For example, in 2008, Li and co-workers firstly reported that copper-catalyzed oxidative cross-coupling of N-aryl glycine amides derivatives with malonates formed C-C bond at α-position[6a]. Subsequently, the oxidative α-alkylation of N-aryl glycine esters/amino ketones with unmodified ketones/ethers have been reported respectively by Huang and Li[6b, 6c]. After some investigations[7], the *α*-amino carbonyl compounds and nitromethane may also react under certain conditions to form C-C single bond at the α-position. However, to the best of our knowledge, the example of oxidation of functionalized *α*-aminocarbonyl compounds with nitromethane to form C-C double bonds by CDC reactions has not been exploited.Because of the strong electron-deficient property in their alkene part and simple conversion of nitro group to amino or other heterocycles, Synthesis of six-membered saturated heterocycles such as piperidines, tetrahydropyrans, piperidinones, piperazines, tetrahydro-1,2-oxazines and thiopyrans are conveniently accessible using nitroalkenes.Therefore, nitroalkenes are regarded as one of the most common and important intermediates in modern synthetic organic chemistry[8].



Scheme 1. Cross-Dehydrogenative Coupling using *α*-Amino carbonyl compounds as the raw materials

Herein, we wish to report our preliminary results on the synthesis of *(Z)*-nitroalkene derivatives through CDC reaction by copper catalyst and *tert*-butyl hydrogen peroxide (TBHP).

Results and discussion

To begin our study, we examined various copper salts, oxidants, the amount of catalysts and oxidants, the reaction temperature, and the atmosphere for the desired CDC reaction between 2-(phenylamino)-1-(p-tolyl)ethanone (**1a**) and nitromethane (**2a,** CH_3NO_2) (Table 1). Among the copper salts tested, they all showed catalytic activity, and results indicated that the $Cu(OAc)_2$ has the best catalytic activity, which gave 58% yield of the desired product (Z)-3-nitro-2-(phenylamino)-1-(p-tolyl)prop-2-en-1-one (**3a**), using CH_3NO_2 as solvent and TBHP as oxidant at 60°C under air (entries 1-8). It was also found that no reaction was observed in the absence of the copper salt or oxidant (entries 9-10). The reactions using other oxidants are less effective (entries11-13). Then, a screening of the amount of both $Cu(OAc)_2$ and TBHP revealed that a combination of $Cu(OAc)_2$ (5 mol%) with TBHP (2 equiv) is the best choice (entries 14-17). It is worth noting that the highest yield could be achieved under oxygen atmosphere (entry 19), however, the reaction almost stopped under the nitrogen atmosphere(entry 18). Finally, decreasing or increasing the reaction temperature all lowered the product yield (entries 20-21). The structure of **3a** was unambiguously identified by single-crystal X-ray diffraction analysis (Figure1).

Figure 1. X-ray crystal structure of **3a**.

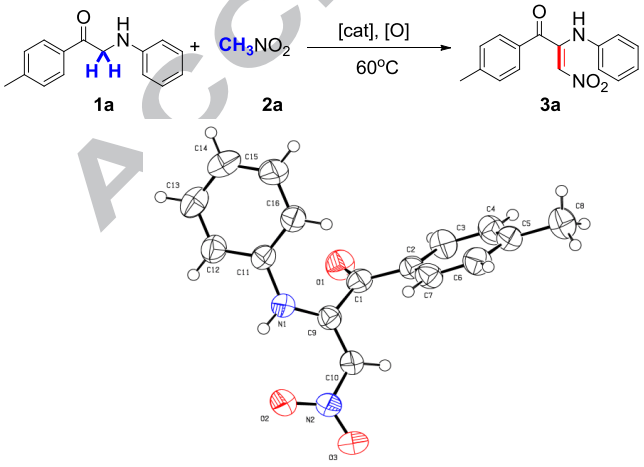
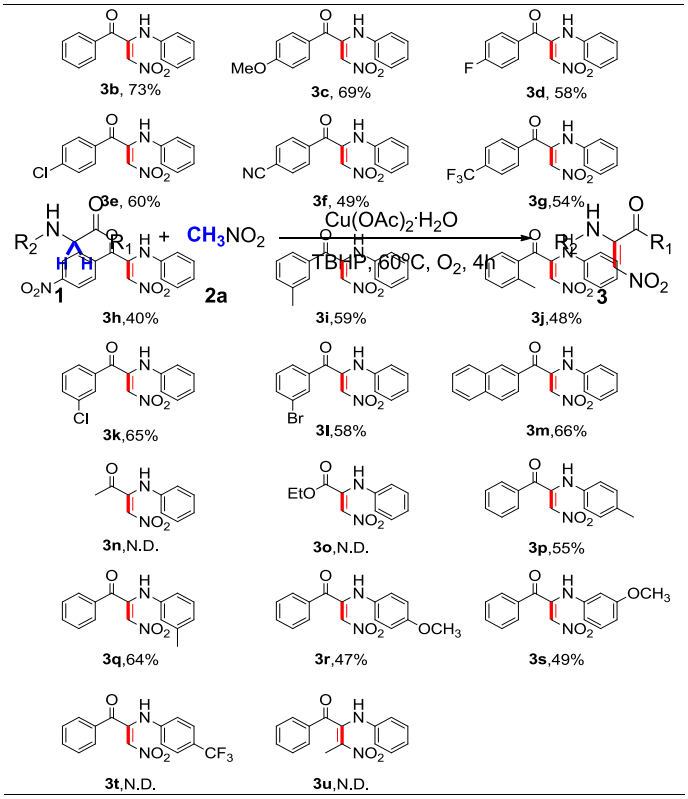


Table 1. Optimization of the reaction conditions [a]

Entry	Catalyst (mol %)	Oxidant (equiv)	T(°C)	Yield(%) [b]



1[a]	CuI (10)	TBHP[c] (1)	60	42
2[a]	CuBr (10)	TBHP (1)	60	30
3[a]	CuCl (10)	TBHP (1)	60	28
4[a]	$CuCl_2$ (10)	TBHP (1)	60	25
5[a]	$CuBr_2$ (10)	TBHP (1)	60	38
6[a]	$Cu(acac)_2$ (10)	TBHP (1)	60	35
7[a]	$Cu(OTf)_2$ (10)	TBHP (1)	60	15
8[a]	$Cu(OAc)_2·H_2O$ (10)	TBHP (1)	60	58
9	--	TBHP (1)	60	trace
10	$Cu(OAc)_2·H_2O$ (10)	--	60	trace
11	$Cu(OAc)_2·H_2O$(10)	DTBP (1)	60	21
12	$Cu(OAc)_2·H_2O$(10)	H_2O_2 (1)	60	28
13	$Cu(OAc)_2·H_2O$(10)	$K_2S_2O_8$ (1)	60	7
14	$Cu(OAc)_2·H_2O$(10)	TBHP (2)	60	63
15	$Cu(OAc)_2·H_2O$(10)	TBHP (3)	60	44
16	$Cu(OAc)_2·H_2O$ (5)	TBHP (2)	60	65
17	$Cu(OAc)_2·H_2O$ (20)	TBHP (2)	60	52
18[d]	$Cu(OAc)_2·H_2O$ (5)	TBHP (2)	60	trace
19[e]	**$Cu(OAc)_2·H_2O$ (5)**	**TBHP (2)**	**60**	**75**
20	$Cu(OAc)_2·H_2O$ (5)	TBHP (2)	25	47
21	$Cu(OAc)_2·H_2O$ (5)	TBHP (2)	80	59

[a] Reaction conditions: **1a** (0.3 mmol), [cat.], [O] and **2a** (2 mL) at 60°C under air atmosphere for 4 h . [b] Isolated yields. [c] TBHP (70% aqueous solution). [d] under N_2 atmosphere. [e] under O_2 atmosphere.

Table 2. **Reaction scope for the formation of (Z)-3-nitro-prop-2-en-1-one** [a,b]

[a] Reaction conditions: **1a** (0.3 mmol), $Cu(OAc)_2$, H_2O (5 mol%), TBHP(2 equiv,70% aqueous solution) and **2a** (2 mL) under O_2 atmosphere at 60 °C for 4 h. [b] Isolate yield. [c] N.D.= not detected.

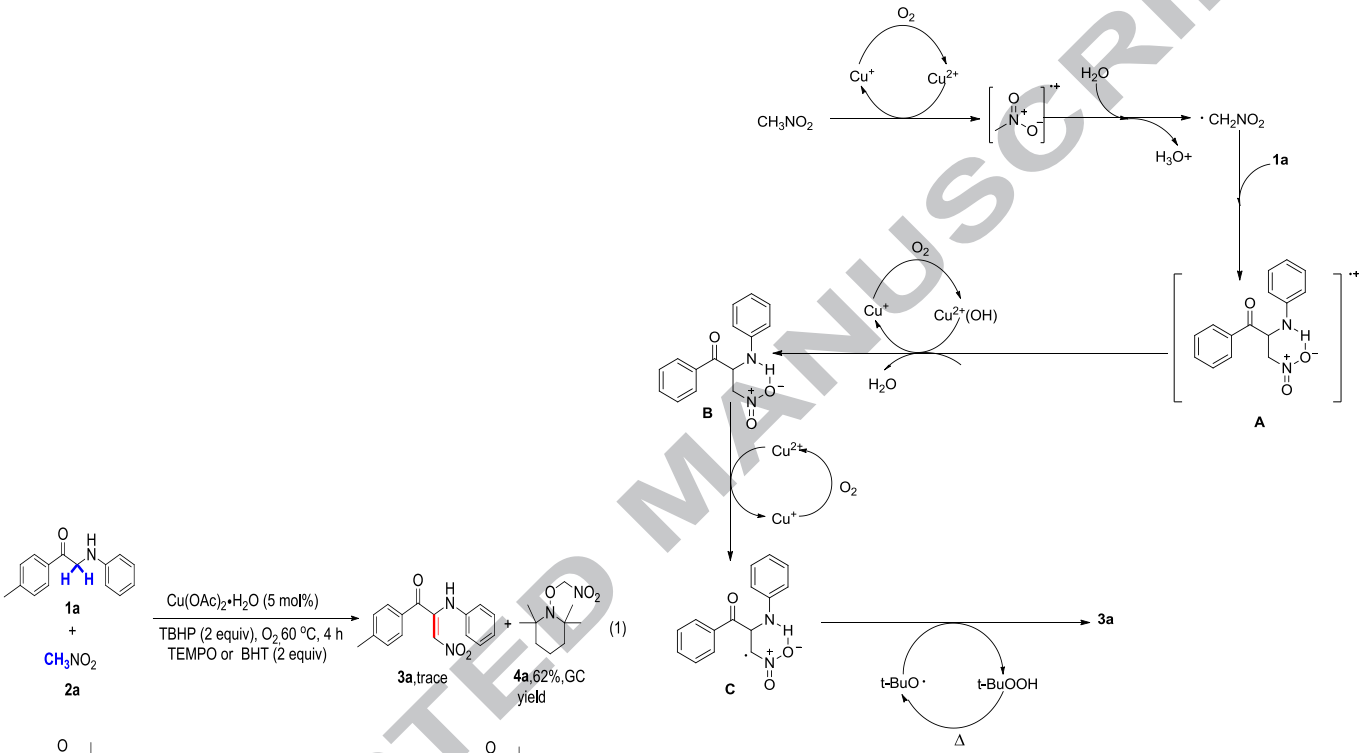
With the optimal reaction conditions in hand (Table 1, entry 19), different sets of experiments were carried out to investigate the scope and limitations of this reaction. Initially, the electronic and steric factors of the aryl group of 1-aryl-ethanone moiety did not affect the reaction significantly under the standard reaction conditions (Table 2, **3b–3l).** They could smoothly furnish the desired products in 40%-73% yields. In addition, when the naphthyl replaced aryl group of 1-aryl-ethanone moiety, the reaction could still be done to give the desired product **3m** in 66% yield. Unfortunately, the 1-alkyl-ethanone (**3n**) and *N*-aryl-glycine ester (**3o**) were unsuitable substrate for this reaction. Then, steric and electronic variations in the N-aryl moiety were tested. The results showed that the steric factors of the aryl group of N-aryl moiety also have no obvious effect on the reaction (**3p-3s**). However, the electron-withdrawing substituent could obviously prevent this reaction (**3t**). Finally, we attempted to use the less active nitroethane to synthesize desired product 3u, but failed.

To understand the reaction mechanism, the following control experiments were designed. Firstly, the process of optimization reaction conditions disclosed that the $Cu(OAc)_2$, TBHP and oxygen were all necessary for the conversion of **1a** into **3a** (Table 1, entry 9, 10, 18, 19). Furthermore, when a radical inhibitor TEMPO (2,2,6,6-tetramethylpiperidyloxy) was added to the reaction system, the yield of the coupling product **3a** decreased dramatically from 75% to less than 5%. Nitromethane radical, the key intermediate in this transformation, was captured by TEMPO which was identified through GC-MS. This means that the reaction may proceed by a radical mechanism (Scheme 2 Eq. (1)). Then, when the nitrogen was substituted, the desired product was not detected (Scheme 2 Eq. (2)). Finally, the result in Eq.(3)(4) demonstrate that no imine intermediates were formed during the

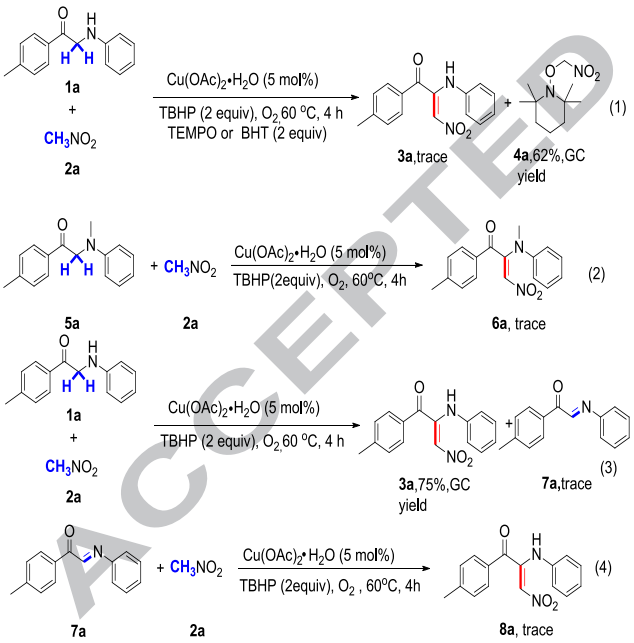
reaction..

Scheme 2. Control Experiments

Based on our experimental results and previous reports[1-4, 6-7,10], we speculate that the reaction may be nitromethane radical direct attack **1a** through the intermediates A and B to get the final product. the mechanism of the reaction is proposed, as shown in Scheme 3. Single-electron transfer from copper (II) species to CH_3NO_2 in the presence of molecular oxygen forms nitromethane cation radical. Water deprotonates this cation radical to produce nitromethane radical, which attacks **1a** to result intermediate **A**, followed by hydrogen atom abstraction from intermediate **A** with $Cu^{2+}(OH)$ which takes place to afford the intermediate **B**.Subsequently, the formed intermediate **B** is split by copper (II) into an alkyl radical intermediate **C**, Finally, tert-butoxy radical acts on radical intermediate **C** synthesize the desired product **3a.**



Scheme 3. Plausible Mechanism



Conclusion

In summary, a simple and mild approach to the formation of the new compound *(Z)*-3-nitro-prop-2-en-1-one by the *α*-aminocarbonyl compound with nitromethane has been reported. The reaction is characterized by forming a carbon-carbon double bonds through oxidative cross coupling between the C(sp^3)-H bond of nitromethane and the α-C-H bond of the *α*-aminocarbonyl compound to generate a new *α*-amino group carbonyl nucleus. Most importantly, the synthesis of this novel nitroalkene compound broadens the use value of *α*-aminocarbonyl compounds, making it more research significance.

Acknowledgment

We are grateful for financial support from the National Natural Science Foundation of China (Nos. 21502049 and 51573040), the Planned Science and Technology Project of Hunan Province, China (No. 2015WK3003).

Supplementary data

Supplementary data associated with this article can be found, in

the online version

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Highlights:

Synthesis of new bioactive compound (Z)-Nitroalkene Derivatives.
A novel method for constructing double C-C bonds through cross coupling of C(sp3)-H bond.
The direct cross-dehydrogenative coupling between Nitromethane and α-Aminocarbonyl Compounds.
The reaction conditions are mild and have excellent stereoselectivity.

Graphical Abstract

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