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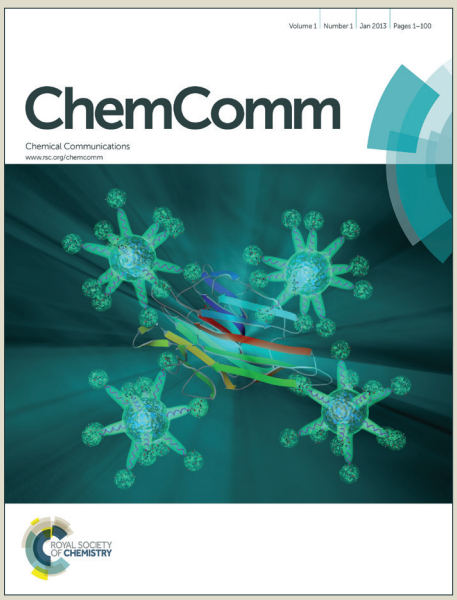

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COMMUNICATION

A NCS mediated oxidative C-H bond functionalization: direct esterification between C(sp^3)–H bond and carboxylic acids

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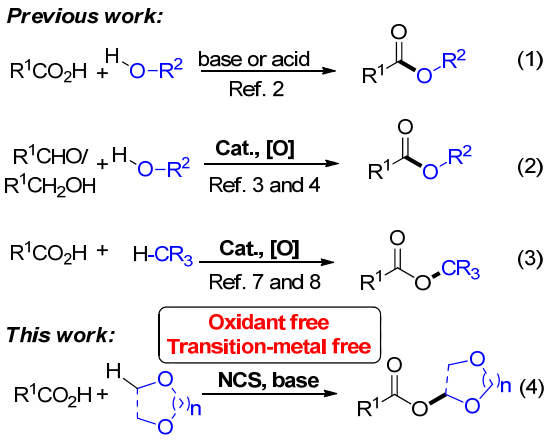
A transition metal free oxidative C-H bond functionalization/esterfication of α-alkoxy alkanes with acids is described in this report. This method is effectively mediated by NCS instead of traditional oxidants, like TBHP or its derivatives, and directly generates the esterification products in moderate to high yield under mild conditions. This tranformation constitute a practical and general approach toward various α-acyloxy ethers with broad substrates generality; alkyl-, aryl-, alkenyl- and alkynyl-carboxylic acids are all well tolerated.

Ester is an important motif and broad embodied in nature,[1] beside the traditional ester esterification process of alcohol with carboxylic acid or their derivatives (acyl chlorides or anhydrides) promoted by acid or base (Scheme 1, eq. 1),[1,2] alternative effective methodologies are reported: including direct esterification with aldehydes catalyzed with NHC-catalysts reported by Jiao and Connon independently,[3] oxidative esterification with alcohols by Lei and others (eq. 2),[4] C-H activation/esterification[5] and other variants.[6] All of these direct esterfication reactions provide a useful and convenient approach toward the ester motifs, especially the catalytic oxidative version of C(sp^3)-H bond with carboxylic acids discovered by Li and other groups (eq. 3).[7,8] However, oxidant is ineluctable in all these reported researches, and most of them need transition metal catalysts[4-7] or organo-catalysts in some cases.[3,8] Herein, we wish to report our recent discovery on the oxidative coupling reaction:[9] direct esterfication of carboxylic acid with C(sp^3)-H bonds mediated by NCS (*N*-chlorosuccinimide) in the presence of base (eq. 4). This transformation constitutes a practical and general access to form the corresponding ester under transition metal free and oxidant free conditions.

N-Chlorosuccinimide (NCS) is a versatile reagent, which is widely used in synthetic organic chemistry,[10-12] for examples, NCS is typical served as a halogenating reagent for chlorination[10] or used to generate the intermediates like the electrophilic *N*-chloroamines[11] and sulfenyl chloride.[12] Very recently, Tang and co-workers reported an iron-catalyzed NCS mediated radical oxidative cross-coupling reaction of 1,3-dithiane with aryl olefins.[13] In this report, NCS was thought to be essentical to promote the reaction in the pre-activation step, by which, the intermidate 2-chloro-1,3-dithiane was generated, and followed by a radical oxidative process to give the desired coupling product. Inspired by this work, we reasoned that the NCS may also promote the oxidative coupling esterfication of C(sp^3)-H bonds via similar initial radical step and followed by trapping the corresponding intermediate with carboxylate.



Scheme 1 General methods for the esterfication.

Initially, we investigated the coupling reaction of phenylpropiolic acid **1a** with 1,4-dioxane **2a** in the presence of NCS and sodium acetate under metal-free condition (Table 1, entry 1). To our best knowledge, direct esterfication of phenylpropiolic acid with C(sp^3)-H bond have not been reported, although procedures for other carboxylic acids have been well studied.[7,8] To our delight, the desired esterfication product **3a** was obtained, albeit in low yield (34%), and the generated α-acyloxy ether motif is important and useful in biological, medicinal and organic chemistry.[14] Then

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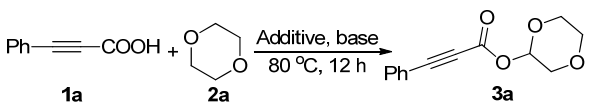
Table 1 Optimization of the reaction conditions[a]



Entry	Cat.	Additive	Base	Yield[b] (%)
1	—	NCS	K_2CO_3	34
2	$FeCl_2·4H_2O$	NCS	K_2CO_3	35
3	$FeCl_3$	NCS	K_2CO_3	36
4	CuBr	NCS	NCS	36
5	—	—	K_2CO_3	ND
6	—	NCS	—	ND
7	—	NBS	K_2CO_3	trace
8	—	NIS	K_2CO_3	ND
9	—	TCCA	K_2CO_3	ND
10	—	NCS	Na_2CO_3	27
11	—	NCS	^tBuOK	30
12	—	NCS	K_3PO_4	33
13	—	NCS	NaOAc	46
14	—	NCS	Et_3N	ND
15[c]	**—**	**NCS**	**NaOAc**	**74**
16[d]	—	NCS	NaOAc	64

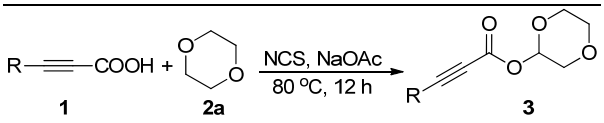
[a] Reaction conditions: Phenylpropiolic acid (**1a**, 0.30 mmol), catalyst (0.06 mmol), additive (0.36 mmol, 1.2 eq), base (0.36 mmol, 1.2 eq), 1,4-dioxane (**2a**, 2.0 ml), 80 °C, 12 h. [b] isolated yield. [c] 1.7 eq of NCS and 1.7 eq of NaOAc was used instead of 1.2 eq. [d] 2.0 eq of NCS and 2.0 eq of NaOAc was used instead of 1.2 eq. TCCA = Trichloroisocyanuric acid.

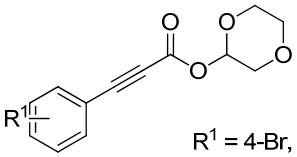
we proceeded to optimize the reaction conditions. Metal-catalysts, for examples, Fe(II),[11a] Fe(III)[13] and Cu(I)[11b,15] were tested, which were used as catalysts in previous radical processes in associated with NCS or NBS, and identical results were observed (entry 2-4). And the control reactions showed that no reaction occurs in the absence of additive or base (Table 1, entry 5, 6). Further optimization with various additives (entries 7-9) and different bases (entries 10-14) turned out that the combination of NCS (1.2 equiv) with sodium acetate (NaOAc, 1.2 equiv) was superior to others (entry 13). Subsequently, the amount of NCS and NaOAc was adjusted and 1.7 eq amounts gave the best isolated yield (entry 15, 74%).

With the optimized reaction conditions, the scope of this directly oxidative coupling esterfication reaction was then examined by using a series of phenylpropiolic acids **1** with **2a**. As shown in Table 2, this transformation proceeds smoothly over a wide range of substrates, providing the corresponding α-acyloxy ethers in moderate to high yield (55%-83%). The substitutions on the *ortho*-, *meta*-, and *para*- positions of the aryl ring, either with electronic rich or deficient ones, marginally affect this reaction. Besides, 1-naphthyl and 2-naphthyl propiolic acids also well tolerated under this condition and to give the desired products in 63% and 55% yield, respectively. It is worth mentioning that 2-butynoic acid also generates the corresponding product **3m** in 62% yield.

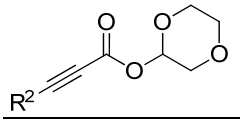
The reaction could be extended to other carboxylic acids, and only needs to switch the base with potassium carbonate (K_2CO_3) to ensure high yield. As illustrated in Table 3, benzoic acids, either with electronic rich or deficient substitutions, all work well under this condition and to give the desired products in high yield (60-94%).

Table 2 Direct esterfication of **2a** with various propiolic acid derivatives[a]





R^1 = H, **3a**, 77%
R^1 = 4-MeO, **3b**, 71%
R^1 = 4-Me, **3c**, 73%
R^1 = 4-^{t}Bu, **3d**, 83%
R^1 = 4-F, **3e**, 65%
R^1 = 4-Br, **3f**, 65%
R^1 = 4-Cl, **3g**, 62%
R^1 = 3-Cl, **3h**, 64%
R^1 = 2-Cl, **3i**, 77%
R^1 = 2-Br, **3j**, 71%
R^1 = 2-Me, **3k**, 70%

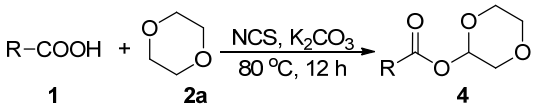


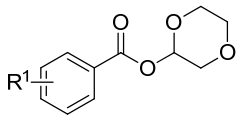
R^2 = 1-naphthyl, **3l**, 63%
R^2 = 2-naphthyl, **3m**, 55%
R^2 = Methyl, **3n**, 62%

[a] Reaction conditions: Propiolic acid derivatives (**1**, 0.30 mmol), 1,4-dioxane (**2a**, 2.0 ml), NCS (0.51 mmol), NaOAc (0.51 mmol), 80 °C, 12 h.

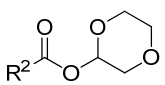
Notably, 2-furyl and 2-naphthyl carboxylic acids also afford **4h** and **4i** in 74% and 71% yield, respectively. Besides, the alkyl ones, including 3-phenylpropionic acid and cinnamic acid derivatives show good reactivity and produce the α-acyloxy ethers in high yield (60-83%).

Table 3 Direct esterfication of **2a** with various carboxylic acids[a]

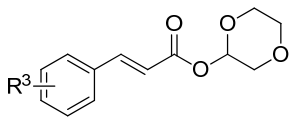




R^1 = H, **4a**, 74%
R^1 = 4-^{t}Bu, **4b**, 94%
R^1 = 4-MeO, **4c**, 60%
R^1 = 4-Me, **4d**, 80%
R^1 = 4-CF_3, **4e**, 85%
R^1 = Benzoyl, **4f**, 82%
R^1 = 4-F, **4g**, 65%



R^2 = 2-Furyl, **4h**, 74%
R^2 = 2-Naphthyl, **4i**, 71%
R^2 = 2-Phenylethanyl, **4j**, 83%



R^3 = 3-NO_2, **4k**, 70%
R^3 = H, **4l**, 60%
R^3 = 4-^{i}Pr, **4m**, 71%
R^3 = 3-Cl, **4n**, 64%

[a] Reaction conditions: carboxylic acid (**1**, 0.30 mmol), 1,4-dioxane (**2a**, 2.0 ml), NCS (0.51 mmol), K_2CO_3 (0.51 mmol), 80 °C, 12 h.

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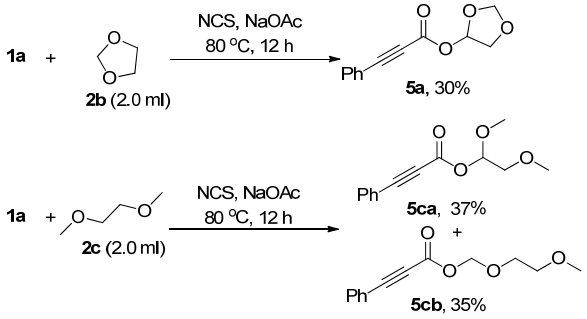
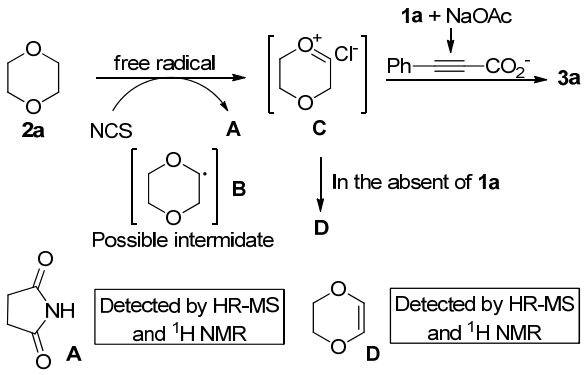
Have demonstrated the scope of carboxylic acids, we then tested the scope of ethers **2** by using phenylpropiolic acid **1a** as the coupling partner. Interestingly, the ethers containing only one oxygen atom cannot afford the corresponding products, for examples, THF or butyl ether. We are delighted to find out that 1,3-dioxolane **2b** and 1,2-dimethoxyethane **2c** (DME) generate the esterfication products in 30% and 72% yield, respectively, and the regioselectivity of the later is about 1:1 (Scheme 2).

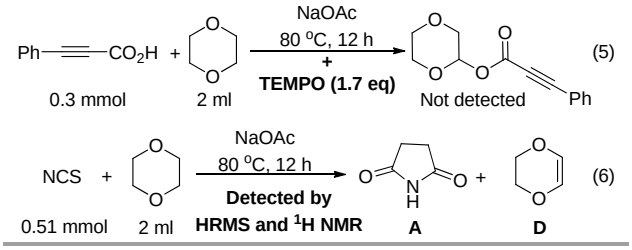


Scheme 2. Reaction of phenylpropiolic acid **1a** with ethers.

A possible mechanism for this NCS-mediated oxidative coupling esterfication reaction is proposed in Scheme 3. The reaction is initiated by NCS via a free radical process,[15] follows by the formation of active cationic intermediate **C** via probably the radical intermediate **B**, and generates the succinimide **A** as a by product, which is detected by HRMS and proton NMR in the crude reaction mixture.[16] The control reaction in the present of the free radical inhibitor TEMPO turn out to give no desired product at all, which suggests that the transformation proceed through a radical progress (eq. 5), although other pathways couldn't be ruled out so far. The final nucleophilic addition of the carboxylate to **C** leads to the desired product **3**, and this step is presented and studied by Wan and others.[7,8] It's noteworthy that the existence of intermediate **C** is further confirmed in our control reaction (eq. 6). In the absence of phenylpropiolic acid **1a** under standard conditions, product **D** is detected by HRMS and proton NMR analysis,[16] which is believed to derivate from **C** via addition/elimination process.[17]



Scheme 3. Possible reaction pathways.



Conclusions

In summary, we have developed a metal free oxidative coupling esterfication of α-alkoxy alkanes with acids. This transformation is effectively mediated by NCS instead of traditional oxidants under mild conditions, and provides a direct and general approach toward various α-acyloxy ethers in moderate to high yields with broad substrates generality. Moreover, the developed oxidant free system involving free radical process offers a practical alternate compared to the other oxidative coupling esterfication, and the modified NCS mediated system applies to other coupling reactions are undergoing in our lab.

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A direct esterfication of α-alkoxy alkanes with acids is reported under transition-metal-free conditions mediated by NCS with broad substrates generality.