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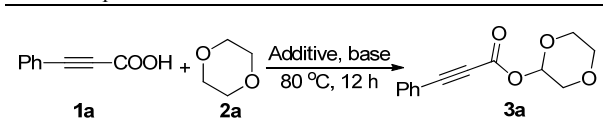


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Table 1 Optimization of the reaction conditions^a


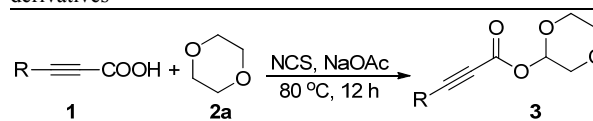
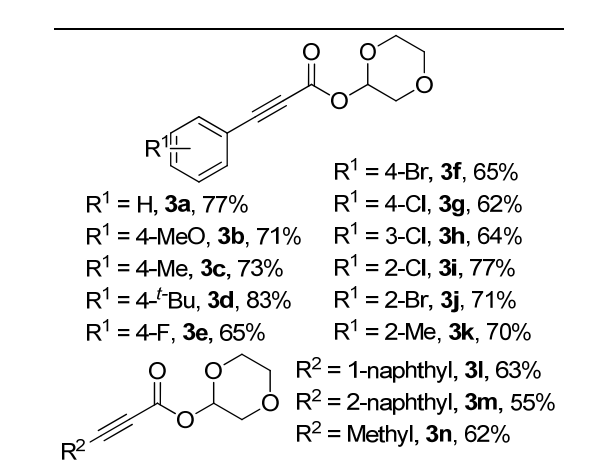
Entry	Cat.	Additive	Base	Yield ^b (%)
1	—	NCS	K ₂ CO ₃	34
2	FeCl ₂ ·4H ₂ O	NCS	K ₂ CO ₃	35
3	FeCl ₃	NCS	K ₂ CO ₃	36
4	CuBr	NCS	NCS	36
5	—	—	K ₂ CO ₃	ND
6	—	NCS	—	ND
7	—	NBS	K ₂ CO ₃	trace
8	—	NIS	K ₂ CO ₃	ND
9	—	TCCA	K ₂ CO ₃	ND
10	—	NCS	Na ₂ CO ₃	27
11	—	NCS	^t BuOK	30
12	—	NCS	K ₃ PO ₄	33
13	—	NCS	NaOAc	46
14	—	NCS	Et ₃ N	ND
15 ^c	—	NCS	NaOAc	74
16 ^d	—	NCS	NaOAc	64

^a Reaction conditions: Phenylpropionic 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 esterification reaction was then examined by using a series of phenylpropionic 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 propionic 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-butyric acid also generates the corresponding product **3m** in 62% yield.

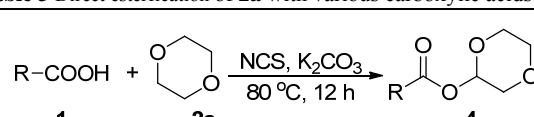
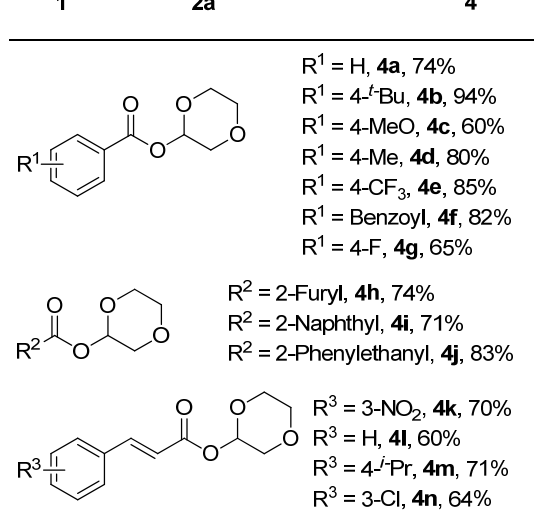
The reaction could be extended to other carboxylic acids, and only needs to switch the base with potassium carbonate (K₂CO₃) to ensure high yield. As illustrated in Table 3, benzoic acids, either with electronic rich or deficient substitutions, all work well under this condition and to give the desired products in high yield (60-94%).

Table 2 Direct esterification of **2a** with various propionic acid derivatives^a



$R^1 = \text{H}$, **3a**, 77%
 $R^1 = 4\text{-MeO}$, **3b**, 71%
 $R^1 = 4\text{-Me}$, **3c**, 73%
 $R^1 = 4\text{-}^t\text{Bu}$, **3d**, 83%
 $R^1 = 4\text{-F}$, **3e**, 65%
 $R^1 = 4\text{-Br}$, **3f**, 65%
 $R^1 = 4\text{-Cl}$, **3g**, 62%
 $R^1 = 3\text{-Cl}$, **3h**, 64%
 $R^1 = 2\text{-Cl}$, **3i**, 77%
 $R^1 = 2\text{-Br}$, **3j**, 71%
 $R^1 = 2\text{-Me}$, **3k**, 70%
 $R^2 = 1\text{-naphthyl}$, **3l**, 63%
 $R^2 = 2\text{-naphthyl}$, **3m**, 55%
 $R^2 = \text{Methyl}$, **3n**, 62%

^a Reaction conditions: Propionic 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.

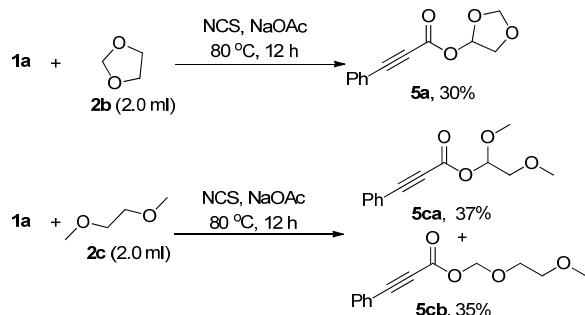
Notably, 2-furyl and 2-naphthyl carboxylic acids also afford **4h** and **4i** in 74% and 71% yield, respectively. Besides, the alkyl ones, including 3-phenylpropionic acid and cinnamic acid derivatives show good reactivity and produce the α -acyloxy ethers in high yield (60-83%).

Table 3 Direct esterification of **2a** with various carboxylic acids^a



$R^1 = \text{H}$, **4a**, 74%
 $R^1 = 4\text{-}^t\text{Bu}$, **4b**, 94%
 $R^1 = 4\text{-MeO}$, **4c**, 60%
 $R^1 = 4\text{-Me}$, **4d**, 80%
 $R^1 = 4\text{-CF}_3$, **4e**, 85%
 $R^1 = \text{Benzoyl}$, **4f**, 82%
 $R^1 = 4\text{-F}$, **4g**, 65%
 $R^2 = 2\text{-Furyl}$, **4h**, 74%
 $R^2 = 2\text{-Naphthyl}$, **4i**, 71%
 $R^2 = 2\text{-Phenylethanyl}$, **4j**, 83%
 $R^3 = 3\text{-NO}_2$, **4k**, 70%
 $R^3 = \text{H}$, **4l**, 60%
 $R^3 = 4\text{-}^i\text{Pr}$, **4m**, 71%
 $R^3 = 3\text{-Cl}$, **4n**, 64%

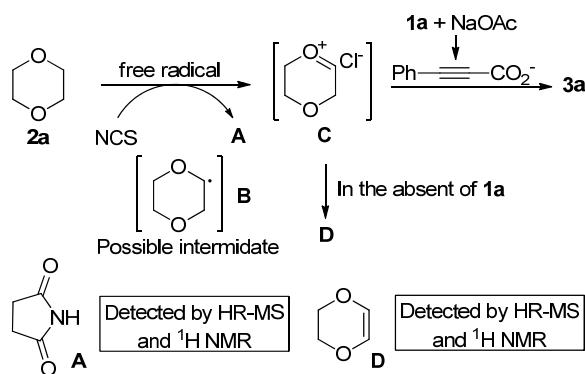
^a Reaction conditions: carboxylic acid (**1**, 0.30 mmol), 1,4-dioxane (**2a**, 2.0 ml), NCS (0.51 mmol), K₂CO₃ (0.51 mmol), 80 °C, 12 h.

Have demonstrated the scope of carboxylic acids, we then tested the scope of ethers **2** by using phenylpropionic 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 esterification products in 30% and 72% yield, respectively, and the regioselectivity of the later is about 1:1 (Scheme 2).

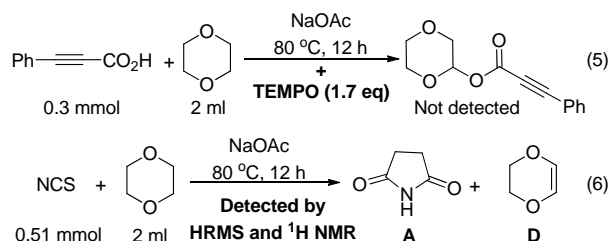


Scheme 2. Reaction of phenylpropionic acid **1a** with ethers.

A possible mechanism for this NCS-mediated oxidative coupling esterification 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 phenylpropionic 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 esterification 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 esterification, and the modified NCS mediated system applies to other coupling reactions are undergoing in our lab.

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Notes and references

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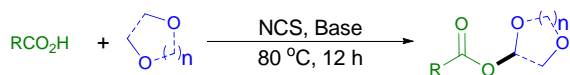


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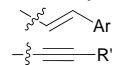
TOC

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



- 1. Transition Metal Free
- 2. Oxidant Free
- 3. Broad Scope

R = Ar, Alkyl,



n = 1, 2
30-94% yield
30 examples