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Oxidative Esterification

Sterically Congested Ester Formation from α-Substituted Malononitrile and Alcohol by an Oxidative Method Using Molecular Oxygen

Yujiro Hayashi,*[a] Jing Li,[a] Hirotaka Asano,[a] and Daisuke Sakamoto[a]

Abstract: A metal-free oxidative esterification or thio-esterification of readily available substituted malononitrile and alcohol or thiol has been developed by simply mixing α-substituted malononitrile and alcohol or thiol in the presence of base under a molecular oxygen atmosphere. Sterically hindered ester or thioester can be prepared efficiently.

Introduction

Esters are one of the most important units in organic synthesis.[1] Classical methods for ester synthesis are based on nucleophilic substitution of carboxylic acid derivatives such as carboxylic acid halides, anhydrides, and activated esters with alcohols.[2] In spite of the many synthetic methods for the generation of esters, the ester formation of the sterically hindered carboxylic acid is still a challenging transformation because of its difficulty based on steric reason.

On the other hand, acyl cyanide is a reactive species and it can be widely utilized in organic synthesis. In spite of its high reactivity as an activated carboxylic acid equivalent, it is not widely used in the synthesis of ester because of the limitation of the generation of acyl cyanides.[3] Generally, acyl cyanides can be prepared by the reactions of acid halides with a variety of metal cyanides or trimethylsilyl cyanide.[4a] An alternative method is the oxidation of cyanohydrins or phenyl cyanide with strong oxidants or using transition metals.[4b,4c] The oxidation of α-substituted malononitrile using strong oxidation reagents such as MCPBA, H_2O_2, or Oxone is also widely used to generate acyl cyanide, but there is a limitation in the substrate scope.[5] In addition, while the protected hydroxyl malononitriles are known as masked acyl cyanides, these methods still have a limitation of the substrate scope for sterically hindered systems.[6] An efficient and simple procedure to construct a sterically hindered ester without a transition metal catalyst, elaborate reagent, and strong oxidants is still urgently required.

We have already developed a series of novel transition metal-free oxidative generations of ketones,[7] amides,[8] and esters[9] from nitroalkane by the use of molecular oxygen. Recently, we developed an efficient method to generate sterically hindered amide from α-substituted malononitrile and amine in the presence of base under a molecular oxygen atmosphere.[10] A mechanistic study proved that acyl cyanide is a key intermediate, which reacts with amine to generate sterically hindered amide (Figure 1). It was anticipated that sterically hindered ester would be formed when alcohol was employed as a nucleophile instead of amine. In this communication, we disclose the successful realization of this scenario.

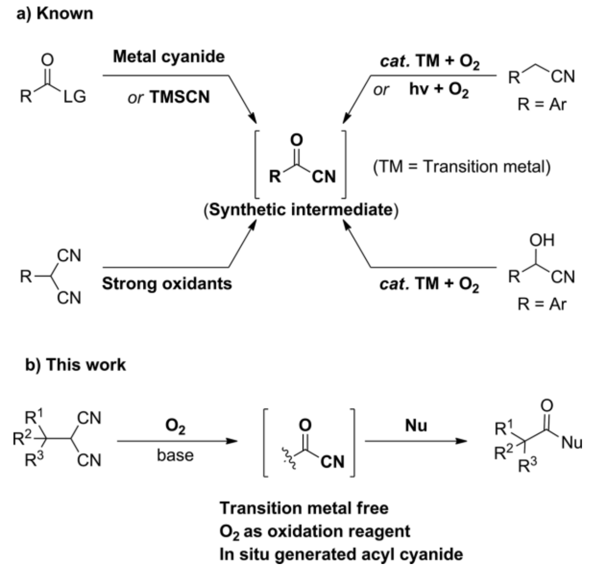

Figure 1. a) Known methods to generate acyl cyanide, b) the present method to make ester or thioester using in situ generated acy cyanide.

We selected a readily prepared α-substituted malononitrile **1a** and benzyl alcohol **2a** as a model system for the optimization of the formation of sterically hindered ester **3aa** (Table 1). Based on our previous procedures for sterically hindered amide synthesis,[10] Cs_2CO_3 was selected as a base in CH_3CN under O_2 atmosphere at 50 °C as an initial study. To our delight, malononitrile **1a** was completely consumed and the desired ester **3aa** was generated in 82 % yield after 2 h (entry 1). In order to further improve the chemical yield, other carbonate bases such as Na_2CO_3 (entry 2) and K_2CO_3 (entry 3) were screened, but the

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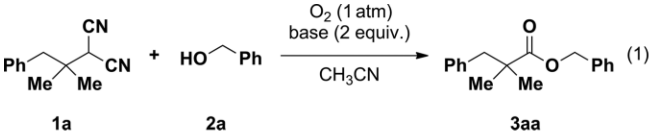
[a] *Graduate School of Science, Tohoku University,*
6-3 Aramaki-Aza, Aoba-ku, Sendai 980-8578, Japan
E-mail: yhayashi@m.tohoku.ac.jp
http://www.ykbsc.chem.tohoku.ac.jp

Supporting information and ORCID(s) from the author(s) for this article are available on the WWW under https://doi.org/10.1002/ejoc.201800984.

reaction was slow with a lower yield. The decrease of the reaction temperature to room temperature increased the yield of ester to 90 % with a longer reaction time (entry 4).

Table 1. Optimization of oxidative esterification of **1a** and **2a**.[a]

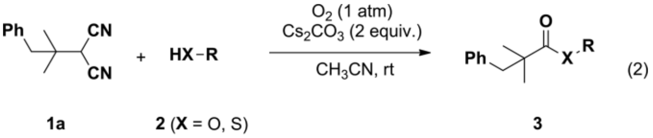


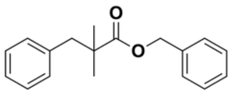
Entry	Base	Time [h]	Temp. [°C]	Yield [%]
1	Cs_2CO_3	2	50	82
2	Na_2CO_3	66	50	21
3	K_2CO_3	57	50	71
4[b]	Cs_2CO_3	11	r.t.	90

[a] Reactions were conducted with **1a** (0.5 mmol), benzyl alcohol **2a** (0.5 mmol) under O_2 (1 atm). [b] Cs_2CO_3 was dried under a flame.

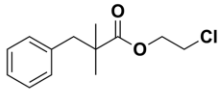
Next, the scope of the esterification of alcohol moiety was investigated with the optimized conditions using 2,2-dimethyl-3-phenylpropane-1,1-dicarbonitrile (**1a**) as a representative malononitrile (Table 2). MeOH and BnOH are suitable nucleophiles (**3aa**, **3ac**). In the case of 2-chloro-1-ethanol, which might generate oxirane, the ester was obtained in good yield (**3ab**). Phenol is also employed very well (**3ad**). Alcohols such as allyl and propynyl alcohols displayed high reactivity to generate the corresponding esters (**3ae**, **3af**). In addition, an unprotected 1,3-diol with primary and secondary alcohol moieties afforded the corresponding ester chemoselectively in primary alcohol site in 95 % yield (**3ag**). The alcohol reacted selectively without reaction of *N*-Boc-protected amine moiety (**3ah**). Even sterically hindered *i*PrOH is a suitable alcohol (**3ai**). *tert*-Butylthiol, which is easily oxidized, worked very well to afford the desired thioester in 68 % yield (**3aj**).

Table 2. Coupling reaction of sterically hindered malononitrile **1a** with various alcohols.[a]

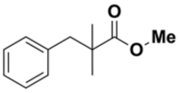




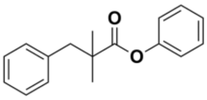
3aa (90%, 9 h)



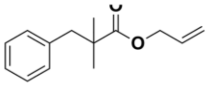
3ab (80%, 9 h)



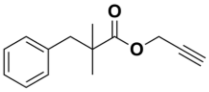
3ac : (95%, 7 h)[b]



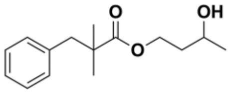
3ad (78%, 11 h)



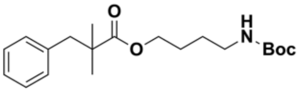
3ae (81%, 6 h)



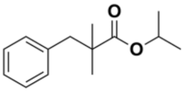
3af (95%, 10h)



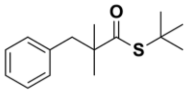
3ag (95%, 16 h)



3ah (77%, 7 h)



3ai (75 %, 15.5 h)[c]

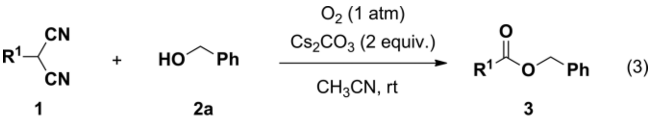


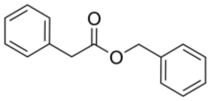
3aj (68%, 24 h)[d]

[a] Unless noted otherwise, all reactions were conducted with **1a** (0.5 mmol), alcohol **2** (0.5 mmol), Cs_2CO_3 (1.0 mmol) in CH_3CN at rt under O_2 (1 atm.). [b] MeOH (1.0 mmol) was used. [c] Alcohol (0.55 mmol) was used at 60 °C. [d] *t*BuSH (1.0 mmol) was used.

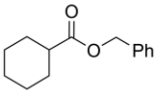
The generality in the malononitrile moiety[11,12] was examined using benzyl alcohol **2a** as a representative alcohol (Table 3). α-Substituted malononitriles such as α-benzyl or α-cyclohexyl were excellent substrates to provide esters in good yield (**3ba**, **3ca**). As for the substrates having aromatic groups at the α-position of malononitrile, the reaction proceeded to

Table 3. Coupling reaction of sterically hindered malononitriles **1** with benzyl alcohol **2a**.[a]

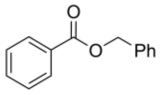




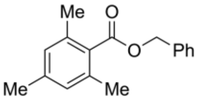
3ba (67%, 12.5 h)



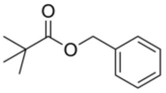
3ca (78%, 6.5 h)



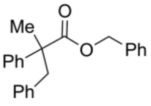
3da (95%, 172.5 h)
(68%, 5 h)[b]



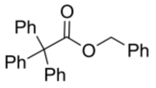
3ea (74%, 43.5 h)



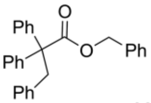
3fa (96%, 17 h)



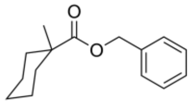
3ga (95%, 21 h)
(91%, 5 h)[b]



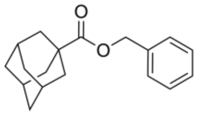
3ha (68%, 66 h)[c]



3ia (86%, 66 h)[c]



3ja (88%, 15.5 h)



3ka (93%, 19.5 h)

[a] Unless noted otherwise, all reactions were conducted with **1** (0.5 mmol), benzyl alcohol **2a** (0.5 mmol), Cs_2CO_3 (1.0 mmol) in CH_3CN (0.1 M) at room temperature under O_2 (1 atm.). [b] Reaction was conducted in CH_3CN at 100 °C. [c] Reaction was conducted at 70 °C.

afford the esters (**3da**, **3ea**) with a longer reaction time. When the α-position of malononitrile are sterically congested quaternary carbon, the reaction proceeded as well to provide the corresponding esters in good yield (**3fa**–**3ka**).

Based on our previous mechanistic studies of making amides[10] from malononitriles, a possible reaction mechanism is illustrated in Figure 2. The α-substituted malononitrile is firstly deprotonated to generate an anion, which reacts with molecular oxygen to form a peroxide adduct **4**. Peroxide **4** would fragment into acylating species **5**, which is intercepted by the alcohol or thiol nucleophiles to afford ester **3** or thioester.

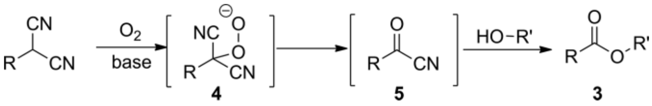


Figure 2. Proposed oxidative conversion of α-substituted malononitrile into ester.

In summary, we have developed an efficient and practical method for the synthesis of esters or thioesters from α-substituted malononitriles and alcohols or thiol under molecular oxygen. Sterically congested ester, which is difficult to synthesize using the conventional methods, can be prepared successfully in good yield. The reaction is simple, and requires only mixing malononitrile derivative, alcohol, or thiol and base under an O_2 atmosphere without a transition metal catalyst, strong oxidant, or elaborate reagent.

Acknowledgments

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Keywords: Esters · Malononitrile · Oxygen · Esterification · Steric hindrance

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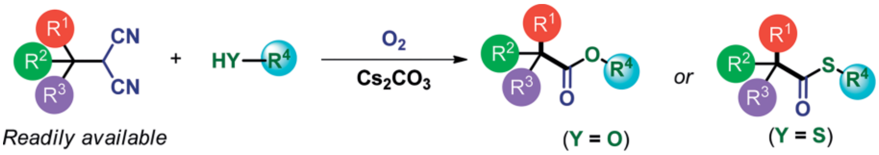
Y. Hayashi, J. Li, H. Asano, D. Sakamoto* 1–4

Sterically Congested Ester Formation from α-Substituted Malononitrile and Alcohol by an Oxidative Method Using Molecular Oxygen



A metal-free oxidative esterification or thio-esterification of readily available substituted malononitrile and alcohol or thiol has been developed by simply mixing α-substituted malononitrile and alcohol or thiol in the presence of base under a molecular oxygen atmosphere.

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