A novel type of *N*-formylation and related reactions of amines *via* cyanides and esters as formylating agents†

Kai Bao, Weige Zhang,* Xiujuan Bu, Zhichun Song, Liang Zhang and Maosheng Cheng*

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A novel *N*-formylation and related reactions proceed from cyanides promoted by esters.

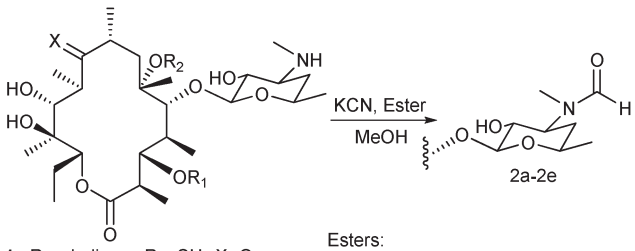
Cyanide ion catalysed aminolysis of esters is one of the useful methods for the conversion of amines into amides.[1] In our tentative preparation of de(*N*-methyl)-*N*-benzoyl-6-*O*-methyl erythromycin derivatives for the evaluation of their anti-inflammatory activity,[2] we applied this methodology by treating de(*N*-methyl)-6-*O*-methyl erythromycin **1a** with substituted benzoate **A**, **B** or **C** (1.2 equiv.) in the presence of potassium cyanide (1.0 equiv.) in methanol (containing 0.1% H_2O) under reflux for 48 h. To our surprise, the desired *N*-benzoyl derivatives were obtained in low yields (<10%). Instead, a common major product was isolated in these parallel reactions; the compound was subsequently confirmed to be de(*N*-methyl)-*N*-formyl-6-*O*-methyl erythromycin **2a** by the application of ^{1}H NMR, ^{13}C NMR and MS.

Intrigued by these results, we proceeded to repeat this reaction under different conditions and found that: (1) neither KCN nor benzoate alone could induce the reaction; (2) the moisture content of methanol played a positive role in the reaction; (3) the pH value of the reaction mixture rose from 7.5 to about 10.0 through the generation of an alkaline gas during these reactions. Furthermore, with the idea of optimizing the reaction conditions, we carried out the reactions of **1a** with KCN or NaCN and esters, including aliphatic esters **D** and **E**, respectively.

As indicated in Table 1: (1) the use of either aromatic esters or aliphatic esters in this reaction could generate the *N*-formylation products; (2) by increasing the quantity of KCN from 1 to 2 equiv. and decreasing of the amount of ester from 1.2 to 0.3 equiv., the yield was clearly improved, whereas further decreasing the amount of ester to 0.1 equiv. led to a lower yield; (3) the reaction was equally effective when KCN was replaced by NaCN. Our data also showed that dicarboxylic acid ester, dimethyl malonate **E**, was more efficient in promoting this reaction as compared with other esters. We also noted that the reaction was influenced to a considerable extent by the solvent utilized; methanol (containing 0.1% H_2O), in particular, was found to be more a favorable solvent than ethanol. The following reactions using diverse *N*-demethyl erythromycin derivatives **1b–1e** as the substrates, under the standardized condition [KCN (2.0 equiv.), dimethyl malonate **E** (0.3 equiv.)] were efficiently transformed to give *N*-formyl erythromycin derivatives **2b–2e**, respectively. Taking the above results into account, we realized that an unusual ester promoted *N*-formylation of amines using cyanide as formylating agent, instead of the normal *N*-acylation catalysed by KCN, had occurred as the main reaction path.

In order to assess its generality, the same reaction was investigated for several other aliphatic secondary amines

Table 1 Ester-promoted *N*-formylation of *N*-demethyl erythromycin derivatives[a]



1a R_1=cladinose,R_2=CH_3,X=O
1b R_1=cladinose,R_2=H,X=O
1c R_1=H,R_2=CH_3,X=O
1d R_1=cladinose,R_2=H,X=(E)-NOH
1e R_1=cladinose,R_2=H,X=(E)-NOMEM

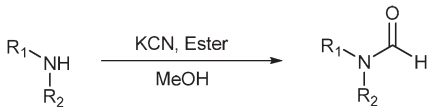
Esters:
A=methyl 3,4,5-trihydroxybenzoate
B=methyl 3,4,5-trimethoxybenzoate
C=methyl 4-methoxy-3-nitrobenzoate
D=ethyl acetate
E=dimethyl malonate

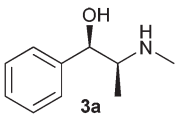
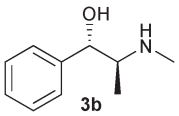
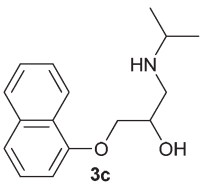
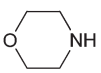
Entry	Substrate	MCN (eq)	Ester (eq)	Product	Yield (%)
1	**1a**	KCN (1.0)	**A** (1.2)	**2a**	49
2	**1a**	KCN (1.0)	**B** (1.2)	**2a**	55
3	**1a**	KCN (1.0)	**C** (1.2)	**2a**	53
4	**1a**	KCN (2.0)	**A** (0.3)	**2a**	62
5	**1a**	KCN (2.0)	**B** (0.3)	**2a**	60
6	**1a**	KCN (2.0)	**C** (0.3)	**2a**	76
7	**1a**	KCN (2.0)	**D** (0.3)	**2a**	58
9	**1a**	KCN (2.0)	**E** (0.3)	**2a**	79
10	**1a**	KCN (2.0)	**C** (0.1)	**2a**	45
11	**1a**	KCN (2.0)	**E** (0.1)	**2a**	65
12	**1a**	NaCN (2.0)	**C** (0.3)	**2a**	72
13	**1a**	NaCN (2.0)	**E** (0.3)	**2a**	77
14	**1b**	KCN (2.0)	**E** (0.3)	**2b**	82
15	**1c**	KCN (2.0)	**E** (0.3)	**2c**	70
16	**1d**	KCN (2.0)	**E** (0.3)	**2d**	69
17	**1e**	KCN (2.0)	**E** (0.3)	**2e**	65

[a] Reactions performed in MeOH (containing 0.1% H_2O) at 45 °C for 4 h, then under reflux for 48 h.

School of Pharmaceutical Engineering, Shenyang Pharmaceutical University, Shenyang, 110016, China.
E-mail: zhangweige2000@sina.com; mscheng@263.net;
Fax: +86(24)-23995043; Tel: +86(24)-23986422
† Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, and scans of NMR spectra. See DOI: 10.1039/b810086a

Table 2 Ester-promoted *N*-formylation of aliphatic secondary amines

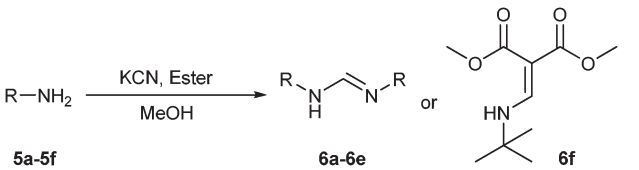


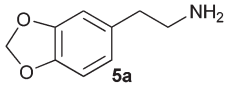
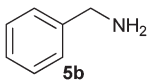
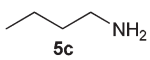
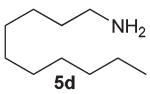
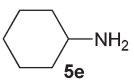
Substrate	Ester	Product	Yield (%)
 3a	**A**	**4a**	75
	C	**4a**	68
	D	**4a**	62
	E	**4a**	83
 3b	**E**	**4b**	57
 3c	**E**	**4c**	62
 3d	**E**	**4d**	60
 3e	**E**	**4e**	66
 3f	**E**	**4f**	55

3a–3f under the standardized conditions, and the results are summarized in Table 2. The reactions of ephedrine **3a**, a β-hydroxyl secondary amine similar to the desosamine moiety of erythromycin derivatives, with KCN promoted by aromatic esters **A**, **C** or aliphatic esters **D**, **E**, furnished the *N*-formylation product **4a** at a 62–83% yield. Other β-hydroxyl secondary amines, including pseudoephedrine **3b** and propranolol **3c**, and five- or six-membered cyclic amines **3d–3f**, were also employed in the reaction, successfully generating the expected products. Unfortunately, any attempt to transform hindered amines, dibenzylamine and dicyclohexylamine into the corresponding *N*-formylation products under our conditions failed, even under reflux for more than 96 h and only the unreacted starting materials were recovered.

Unexpectedly, standard treatment of aliphatic primary amines **5a–5f** (Table 3) did not form the desired *N*-formylation products, rather a set of (*E*)-*N*,*N*′-disubstituted formamidines **6a–6e** was encountered, with the exception that dimethyl 2-((*tert*-butylamino)methylene) malonate **6f** was obtained at a low yield (44%), which can be explained by the steric hindrance of *tert*-butyl.

Table 3 Reactions of aliphatic primary amines

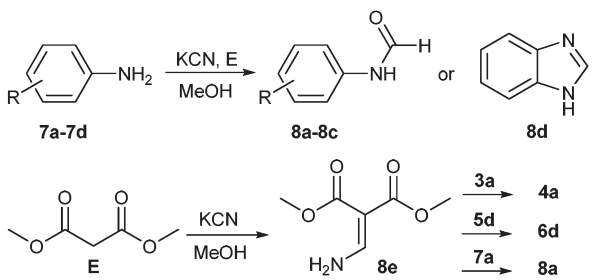


Substrate	Ester	Product	Yield (%)
 5a	**C**	**6a**	41
	E	**6a**	56
 5b	**C**	**6b**	46
	E	**6b**	70
 5c	**E**	**6c**	77
 5d	**C**	**6d**	65
	D	**6d**	60
	E	**6d**	81
 5e	**E**	**6e**	75
 5f	**E**	**6f**	44

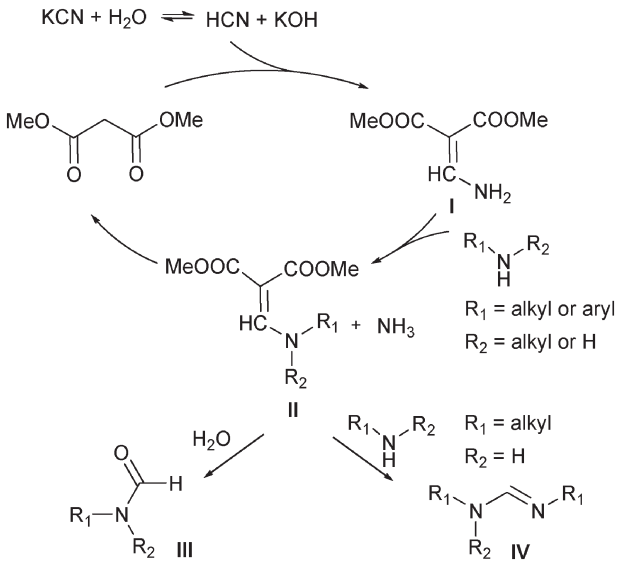
Aromatic primary amines, **7a–7c** were also utilized in the reaction, generating the expected *N*-formylation products **8a–8c** at moderate to high yields (Table 4). Treatment of *o*-phenylenediamine **7d** gave the expected product, benzimidazole **8d**, which could be regarded as an analog of formamidine to a certain extent, at a 78% yield.

Notably, the above reactions were highly insensitive for ester **A**, **B**, **C** and **D**, and no *N*-formylation products or *N*,*N*′-disubstituted formamidines were generated. In contrast, the reaction of aromatic primary amines substituted by

Table 4 Reactions of aromatic primary amines



Substrate	Product	Yield (%)
7a R = H	**8a**	66
7b R = *p*-OCH_3	**8b**	82
7c R = *p*-OCH_2CH_3	**8c**	85
7d R = *o*-NH_2	**8d**	78



Scheme 1 Mechanism of the *N*-formylation and related reactions.

electron-withdrawing groups, such as 4-chloroaniline, 3-nitroaniline, 3-aminopyridine and 2-aminothiazole, failed to give the desired *N*-formylation products either the use of aromatic esters **A**, **B**, **C** or that of aliphatic esters **D**, **E**; whereas the same product dimethyl 2-(aminomethylene) malonate **8e**, was obtained exclusively in the presence of **E** and the unreacted aromatic primary amines could be recovered.

These phenomena indicated that ester **E** exhibited a behavior that deviated from esters **A**, **B**, **C** and **D**; **E** might have utilized a unique mechanism, compared with the other esters. We therefore carried out the following experiments to gain some mechanistic insight into ester **E**. Treatment of **E** with KCN in methanol (containing 0.1% H_2O) at 45 °C for 3 h gave **8e** at a 86% yield, whereas **4a**, **6d** or **8a** (63%, 52% or 56% yield) could form if **3a**, **5d** or **7a** was subsequently added to the reaction mixture, respectively. No *N*-formylation products were obtained when **E** was replaced by dimethyl 2,2-diethylmalonate, in the case of **7a**. In addition, the unique mechanism of **E** was indirectly supported by the formation of **6f** (Table 3). To better understand the above reactions and the role of **E**, we proposed the following reaction mechanism (Scheme 1) to account for the *N*-formylation and related reactions.

Accordingly, the existence of a trace amount of HCN that acted as a formic acid equivalent, condensed with the malonate to form intermediate **I** (**8e**), which then subjected to a nucleophilic additon of amine, followed by elimination of ammonia to give **II**. Hydrolysis or aminolysis of **II** would afford the corresponding *N*-formylated product **III** or formamidine **IV**.

In summary, we describe a novel *N*-formylation and related reactions proceed from cyanide promoted by dimethyl malonate and other esters. These results led to a general and efficient access to the synthesis of formamides, *N*,*N*′-disubstituted formamidines, benzo-imidazole, 2-(aminomethylene) malonate and its derivative. Efforts are currently underway in our research group to apply this method to the construction of other potentially valuable organic molecules.

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Notes and references

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