Tetrahedron 70 (2014) 7100–7105

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Kinetics and mechanism of base catalysed ethyl cyanoformate addition to aldehydes

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ARTICLE INFO

Article history:
Received 2 January 2014
Received in revised form 2 February 2014
Accepted 4 February 2014
Available online 8 February 2014

Dedicated to the memory of Professor Sandy McKillop

Keywords:
Cyanohydrin
Ethyl cyanoformate
Base
Catalysis
Kinetics

ABSTRACT

The mechanism by which tertiary amines catalyse the formation of cyanohydrin carbonates from aldehydes and alkyl cyanoformates is investigated by means of a kinetic study. The reaction rate shows a second order dependence on amine concentration unless the amine is sterically hindered, when the rate has a first order dependence on amine concentration. The catalytic activity of the amine correlated with its pK_{aH}. On the basis of these results, a mechanism is proposed in which the amine acts as a base to activate a water molecule, which reacts with the ethyl cyanoformate generating cyanide in situ.

1. Introduction

The base catalysed addition of cyanide to aldehydes to form a cyanohydrin was one of the first reactions to be mechanistically studied[1] and is still an important carbon–carbon bond forming reaction for organic synthesis.[2] Although cyanide salts are still used in cyanohydrin synthesis,[3] other cyanide sources such as trimethylsilyl cyanide,[4–7] ethyl cyanoformate,[7,8] diethyl cyanophosphonates[7,9] and acyl cyanides[7,10] are now often preferred to avoid side reactions,[11] render cyanohydrin synthesis irreversible and directly produce protected cyanohydrins. Another advantage of these cyanide sources is that they permit the asymmetric synthesis of cyanohydrin derivatives.[12] We have previously developed metal(salen) complexes as highly effective catalysts for asymmetric cyanohydrin synthesis[13] and have also studied the mechanism of asymmetric cyanohydrin synthesis using trimethylsilyl cyanide as the cyanide source.[14] During this work, we realised that very little work had been reported on the mechanism of racemic cyanohydrin synthesis using cyanide sources other than alkali metal cyanides. Thus, Umani-Ronchi and co-workers had studied the indium tribromide catalysed reactions between ketones and trimethylsilyl cyanide,[5] and Denmark and Chung had studied the use of various amines and phosphines as Lewis base catalysts for the reaction between aldehydes and trimethylsilyl cyanide.[6] Therefore, we initiated a project to investigate the mechanism of cyanohydrin formation using various cyanide sources and have previously reported our results on the Lewis base catalysed addition of trimethylsilyl cyanide to aldehydes.[15]

Cyanoformates such as ethyl cyanoformate **1** are also good cyanating agents and react with aldehydes and ketones to form cyanohydrin carbonates (Scheme 1). This reaction does not occur spontaneously, but has been shown to be catalysed by homogeneous catalysts including: triethylamine **2**,[16,17] DMAP,[8e,f] secondary amines,[18] triarylphosphines,[4k] DMSO,[19] *N*-heterocyclic carbenes,[20] ionic liquids,[8d] 1-methoxy-2-methyl-1-(trimethylsiloxy)propene[8a] and tributyltin cyanide.[10c] Heterogeneous catalysts including 4 Å molecular sieves[21] and silica-alumina supported tertiary amines[8b,c] have also been used. These compounds are, or are sources of, Lewis basic, nucleophilic catalysts, and therefore, where the authors have proposed a mechanism for the reaction[8b–f,19,20] in the absence of any mechanistic evidence, this has generally been of the form shown in Scheme 2. In this mechanism, the nucleophilic catalyst reacts with the cyanoformate to form a cyanide ion. The cyanide then reacts with the carbonyl compound to form a cyanohydrin alkoxide, which reacts with the nucleophile–formate adduct to form the cyanohydrin carbonate and regenerate the nucleophile.

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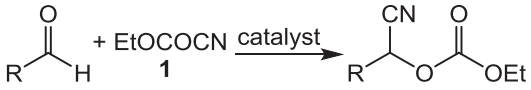
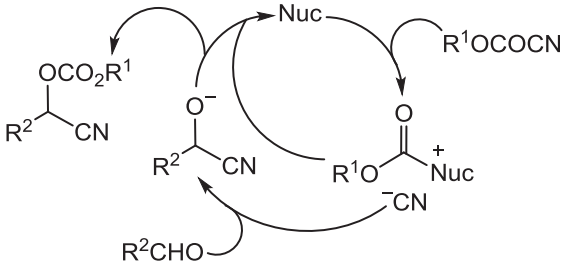
0040-4020/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2014.02.009

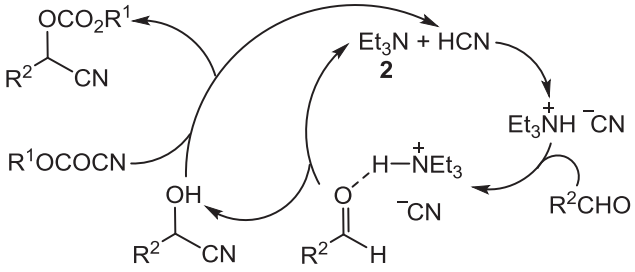


Scheme 1. Synthesis of cyanohydrin ethyl carbonates.



Scheme 2. Lewis-base catalysed mechanism proposed for cyanohydrin carbonate synthesis.

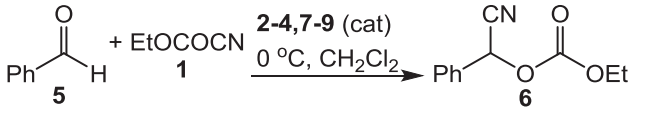
The one exception is Najera et al.[17] who on the basis of DFT calculations on a related asymmetric process[22] proposed the mechanism shown in Scheme 3 for the triethylamine catalysed addition of cyanoformates to carbonyl compounds. In this mechanism, the triethylamine acts as a Brønsted-base catalyst for the addition of hydrogen cyanide to the carbonyl compound. It is proposed that traces of hydrogen cyanide are present in the cyanating agent[17] and that subsequent reaction of the initially formed cyanohydrin with the cyanoformate forms the cyanohydrin carbonate and regenerates the hydrogen cyanide. In view of the lack of experimental evidence as to the mechanism of base catalysed cyanohydrin carbonate synthesis we decided to carry out a kinetic study of the reaction to distinguish between the proposed mechanisms and in this paper we report the results of this study.



Scheme 3. Brønsted-base catalysed mechanism proposed for cyanohydrin carbonate synthesis.

2. Results and discussion

Initially, we selected triethylamine **2**, tetrabutylammonium thiocyanate **3** and tetrabutylammonium cyanide **4** as catalysts for the addition of ethyl cyanoformate **1** to benzaldehyde **5** at 0 °C in dichloromethane (Scheme 4) as these catalysts, aldehyde and solvent were used in our previous work on the mechanism of trimethylsilyl cyanide addition to aldehydes.[15] Tetrabutylammonium thiocyanate **3** was the most effective catalyst for the addition of trimethylsilyl cyanide to benzaldehyde, so this catalyst was studied first. However, when 0.5 mol % of **3** was employed with $[\mathbf{5}]_0$=0.45 M and $[\mathbf{1}]_0$=0.49 M, no reaction occurred after 2.5 h at 0 °C or even after 18 h at room temperature. Even when the catalyst loading was increased to 5 mol %, only 8% conversion of benzaldehyde into cyanohydrin ethyl carbonate **6** was observed after a reaction time of 2.5 h at 0 °C. Thus it was apparent that tetrabutylammonium thiocyanate was not an effective catalyst for the addition of ethyl cyanoformates to benzaldehyde.



3: Bu_4NSCN; **4:** Bu_4NCN; **7:** Et_2NMe; **8:** $^iPr_2NEt$; **9:** Me_2NEt

Scheme 4. Reaction used for kinetic studies.

This result is consistent with either mechanism shown in Schemes 2 and 3 since although thiocyanate is a very good nucleophile, it is a very soft nucleophile and so will not readily react with a hard electrophile such as a carbonyl group as required by the mechanism shown in Scheme 2. In addition, thiocyanic acid (HSCN) has a pK_a (in water) of −1.1,[23] so thiocyanate is a very weak base and would not deprotonate hydrogen cyanide (pK_a 9.0 in water[24]) as required by the mechanism shown in Scheme 3.

It was also not possible to monitor reactions catalysed by tetrabutylammonium cyanide **4**. Reactions carried out with 5 mol % or 1 mol % of catalyst **4** proceeded very rapidly and were complete in less than 1 min when $[\mathbf{5}]_0$=0.45 M and $[\mathbf{1}]_0$=0.49 M. In contrast, reactions carried out with 0.75 mol % or 0.5 mol % of catalyst **4** were very slow and did not give reliable kinetic data. It was noticed that a solution of tetrabutylammonium cyanide in dichloromethane was not stable, changing from a colourless to brown colour over a period of 24 h. This may explain why the reactions with less than 1 mol % of catalyst **4** gave poor kinetic data. It is not surprising that higher concentrations of tetrabutylammonium cyanide gave extremely fast kinetics as the mechanisms shown in both Schemes 2 and 3 rely upon the in situ formation of cyanide to attack the aldehyde and catalyst **4** provides a higher concentration of this nucleophile.

In contrast to the systems catalysed by tetrabutylammonium salts, reactions catalysed by triethylamine **2** were kinetically well-behaved and could be analysed by UV spectrophotometry, monitoring the disappearance of the benzaldehyde carbonyl absorption at 246 nm. A reaction carried out at 0 °C with $[\mathbf{5}]_0$=0.45 M, $[\mathbf{1}]_0$=0.49 M and using 5 mol % of triethylamine went to completion in 2.5 h. It was observed that reactions catalysed by triethylamine had an induction period of about 20 min as shown in Fig. 1. Once this induction period was over, the reaction showed a good fit to first order kinetics (Fig. 2).

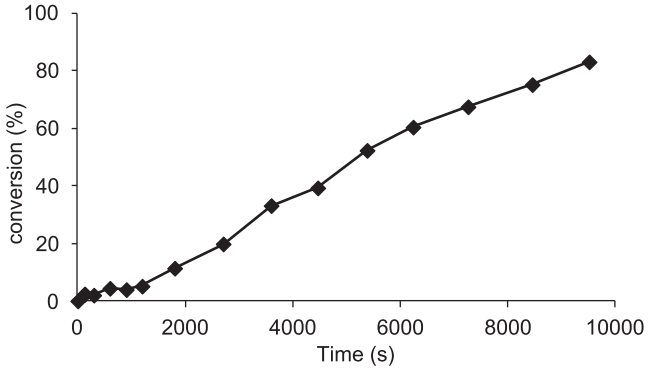


Fig. 1. Reaction profile versus time plot for the conversion of benzaldehyde and ethyl cyanoformate into **6** catalysed by Et_3N.

To determine the order with respect to substrates **1** and **5**, reactions were carried out at three concentrations of each substrate whilst keeping all other reactant concentrations constant. The results shown in Figs. 3 and 4 clearly show that the reaction rate does not depend on benzaldehyde concentration (Fig. 3), but does increase as the initial concentration of ethyl cyanoformate increases (Fig. 4). Thus, the reaction follows a rate equation of the form: rate=k_{obs}[EtOCOCN].