Pergamon

Tetrahedron Letters 41 (2000) 8011–8013

TETRAHEDRON
LETTERS

Michael addition of ethyl acetoacetate to α,β-unsaturated oximes in the presence of $FeCl_3$: a novel synthetic route to substituted nicotinic acid derivatives

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Received 10 July 2000; revised 11 August 2000; accepted 16 August 2000

Abstract

The $FeCl_3$-catalyzed reaction of α,β-unsaturated oximes with ethyl acetoacetate resulted in Michael addition followed by ring closure to produce substituted nicotinic acid derivatives in a very efficient way.
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Keywords: Michael addition; iron(III) chloride hexahydrate; unsaturated oxime; nicotinic acid.

The reaction of β-dicarbonyl compounds with α,β-unsaturated ketones (Michael addition) is a very important and useful synthetic method for carbon–carbon bond formation. In the case of enimines the reaction leads to 1,4-dihydropyridines.[1] The Michael type addition is usually a base-catalyzed process. Recently it was found that iron(III) chloride is an extraordinarily efficient catalyst for the Michael reaction: reaction conditions were very mild and gentle, and the reaction procedure was reasonably easy.[2]

We have studied the reaction of α,β-unsaturated oximes with ethyl acetoacetate and pentane-2,4-dione in the presence of $FeCl_3{\cdot}6H_2O$ and found in certain cases the formation of highly substituted pyridines as the main products.

In contrast to the reported reactions of ethyl acetoacetate and β-diketones with α,β-unsaturated ketones, neither pentane-2,4-dione nor ethyl acetoacetate reacted with enone oximes at ambient temperature in the presence of $FeCl_3{\cdot}6H_2O$. However, at higher temperature (about 150°C) a number of oximes of unsaturated acyclic ketones **1a**–**1e** as well as monocyclic and bicyclic oximes (**1d** and **1e**, respectively) were easily transformed to the nicotinic acid ethyl esters **2a**–**2e** in the reaction with ethyl acetoacetate (Scheme 1).[3]

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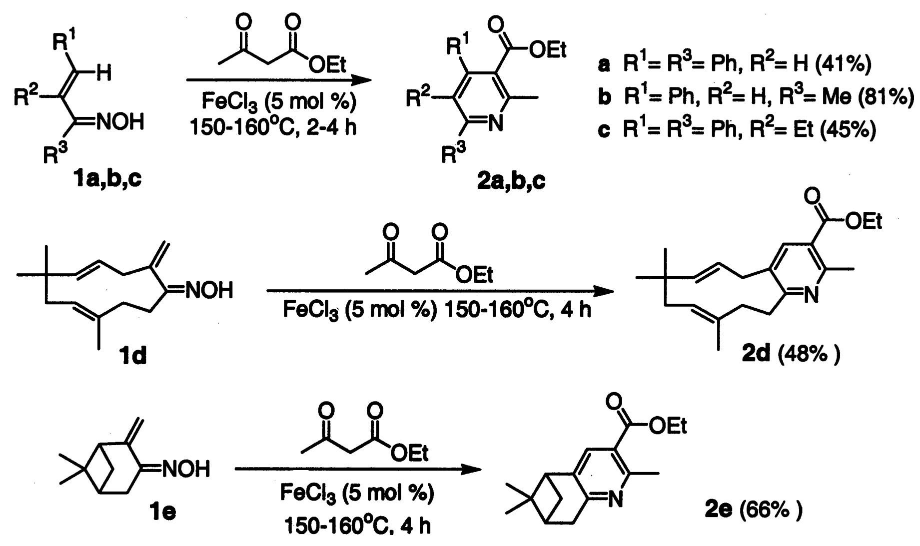
PII: S0040-4039(00)01391-5

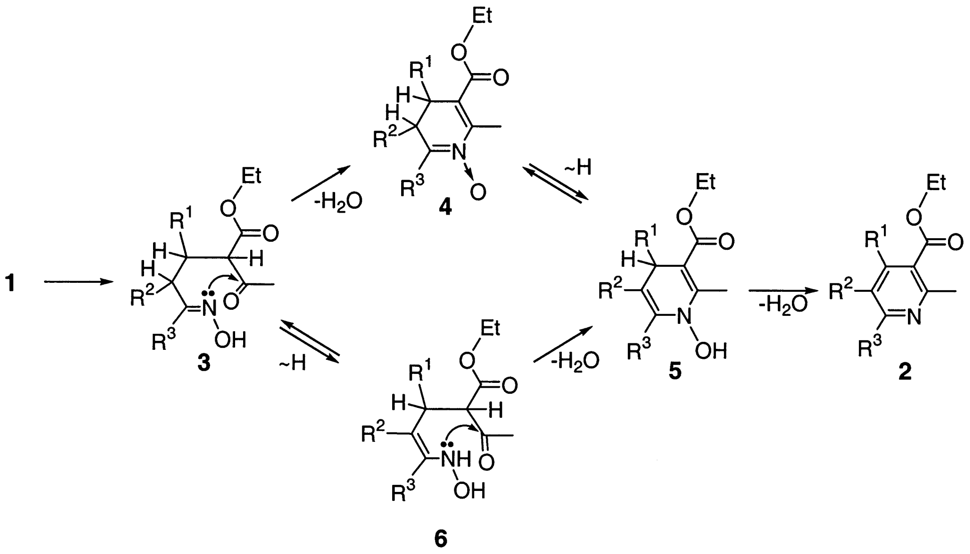


Scheme 1.

In the case of oxime **1e**, derived from pinocarvone, we investigated the catalytic activity of different transition metal chlorides, e.g. $NiCl_2 \cdot 6H_2O$, $CuCl_2 \cdot 2H_2O$, and $CoCl_2 \cdot 6H_2O$. Although all the chlorides showed catalytic activity and resulted in complete conversion of the starting oxime, only $FeCl_3 \cdot 6H_2O$ provided a high yield of the pyridine **2e**.

Substituted pyridines can be prepared from conjugated oximes under Vilsmeier conditions.[4] In this case the first stage of the multi-step process requires a Beckman rearrangement of the starting oxime followed by ring closure, resulting in a substituted pyridine with the rearranged (as compared with the starting oxime) carbon frame. In the case of oximes derived from cyclic α,β-unsaturated ketones such a reaction is impossible. Addition of ethyl acetoacetate to oximes of cyclic α,β-unsaturated ketones does not require the rearrangement stage and proceeds as an addition ring closure sequence. The mechanism of the pyridine formation is not yet clear, although a possible scheme might be formulated as follows (Scheme 2). Primary Michael addition of ethyl acetoacetate to the enone oxime **1** gives the adduct **3**, which undergoes a ring closure accompanied by dehydration and subsequent migration of a proton to form the *N*-hydroxy derivative **5**. Alternatively, the cyclic *N*-hydroxy derivative **5** could arise from intramolecular cyclization of *N*-hydroxy enamine **6**. Elimination of an extra water molecule from compound **5** provides the formation of the substituted pyridine **2**.

The strength of this protocol for the synthesis of pyridines is its simplicity. The generality and usefulness of this new pyridine synthesis is underlined by the use of complex oximes **1d**,**e**. The method allows the synthesis of tetra- and pentasubstituted pyridines. Thus, equimolar amounts of ethyl acetoacetate and 5 mol% of $FeCl_3 \cdot 6H_2O$ were added to enone oximes **1a**–**1e**, and the reaction mixture was heated under vigorous stirring to 150–160°C and kept at this temperature for 2–4 h. Unreacted acetoacetate was distilled off at reduced pressure. The residue was taken up in *tert*-butyl methyl ether and the resulting mixture was extracted with 1 M HCl. The combined acidic aqueous extracts were adjusted to pH 9 by means of aqueous ammonia and extracted with CH_2Cl_2. The organic extract was dried and concentrated at reduced pressure to afford the crude product, which was then purified by chromatography on a silica gel column to give pyridines **2a**–**e** as viscous oils.



Scheme 2.

The synthetic route described can be considered as an alternative method to the well-known pyridine synthesis from an amine or hydroxylamine and 1,5-diketones, which are usually obtained by a Michael addition of 1,3-dicarbonyl compounds to enones.[5]

Acknowledgements

The authors thank the Russian Foundation for Basic Research (Grants 98-03-32910), the International Association for the promotion of cooperation with scientists from the New Independent States of the former Soviet Union (INTAS, Grant # 97-0217) and the Siberian Division of RAS (Grant for young scientists 2000) for the financial support of this work.

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