Tetrahedron 69 (2013) 5112–5118

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

A simple and general approach for the synthesis of highly functionalized 6-oxo-1,6-dihydropyridines

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ARTICLE INFO

Article history:
Received 28 February 2013
Received in revised form 15 April 2013
Accepted 17 April 2013
Available online 22 April 2013

Keywords:
2-Cyanoacetamides
2-Cyanoacrylamides
Ketene dithioacetals
β-Keto esters
Potassium hydrogen carbonate
6-Oxo-1,6-dihydropyridine-3-carboxylates

ABSTRACT

A variety of 5-cyano-4-methylthio-6-oxo-1,6-dihydropyridine-3-carboxylates have been efficiently synthesized in a one-pot reaction from *N*-alkyl and *N*-aryl derivatives of 2-cyano-3,3-bis(methylthio)acrylamides and selected β-keto esters. The reaction proceeds via potassium hydrogen carbonate mediated conjugate addition of a β-keto ester to 2-cyano-3,3-bis(methylthio)acrylamide followed by loss of methyl mercaptan and subsequent intramolecular condensation of amide group with the acyl carbonyl group. The mechanism of the reaction has been established by isolation of the 2-acetyl-4-cyano-5-amino-3-(methylthio)-5-oxopent-3-enoate intermediate and its independent cyclization to the desired 6-oxo-1,6-dihydropyridine.

1. Introduction

6-Oxo-1,6-dihydropyridine (synonymous with 2-oxo-1,2-dihydropyridines and pyridine-2(1*H*)-ones) core structure frequently occurs in pharmaceuticals and biologically active compounds.[1] This highly important heterocyclic system is found in both natural products such as camptothecin, and its analogues,[2] huperzine A,[3] and pharmaceutical products or preclinical lead molecules such as milrinone,[4] perampanel,[5] pirfenidone,[6] piridicillin,[7] ciclopiroxolamine,[8] amrinone,[9] bimakalim,[10] and trametinib.[11] Therefore, development of new methods for pyridine-2(1*H*)-ones synthesis with broad scope and generality is of high importance. Many methods have been reported for the synthesis of this class of compounds.[12] One of the most generally used approaches is the reaction of an appropriate enamino ketone or aldehyde with 2-cyanoacetamide in the presence of a base to give pyridine-2(1*H*)-ones.[4,13] The condensation of 1,3-dicarbonyl compounds with 2-cyanoacetamides is also known to give pyridine-2(1*H*)-ones.[14] There are several reports on the preparation of pyridine-2(1*H*)-ones from ketene dithioacetals.[15] The reaction of α-acetyl-α-carbamoyl ketene dithioacetals with Vilsmeier reagent under domino reaction conditions is also reported for the synthesis of pyridine-2(1*H*)-ones.[16] The reaction of ketene dithioacetals derived from 2-cyanoacetamides with active methylene ketones and β-keto ester is also reported to give pyridine-2(1*H*)-ones.[17] However, this approach has limited scope for the synthesis of *N*-alkyl and *N*-aryl pyridine-2(1*H*)-ones. The *N*-alkyl pyridine-2(1*H*)-ones are generally prepared by N-alkylation of pyridine-2(1*H*)-ones, while the *N*-aryl derivatives are prepared by copper-catalyzed arylation of pyridine-2(1*H*)-ones.[18] A direct method for the preparation of 2-aminopyridine-2(1*H*)-one is reported by the reaction of the corresponding carbamoyl ketene dithioacetal with cyanothioacetamide.[19] A similar approach is also reported for 2-amino *N*-benzyl pyridine-2(1*H*)-ones starting from 3,3-bis(methylthio)-2-cyano-*N*-phenylacrylamide.[20] An approach for the synthesis of 6-oxo-1,6-dihydropyridine was discovered in the course of our experiments designed to prepare an intermediate required for one of our medicinal chemistry projects.

2. Results and discussion

We required ethyl [5-amino-4-(methylcarbamoyl)-1,2-oxazol-3-yl]acetate **4** as starting material for the synthesis of a lead molecule for one of our medicinal chemistry projects (Fig. 1). No such fully functionalized isoxazole has been reported in the literature as revealed by SciFinder and STN database searches. In 2011, we reported the first synthesis of this intermediate using an alternative novel approach.[21] We envisioned that the molecule could be prepared by the retrosynthetic approach given in Fig. 1. Thus, we planned a base-catalyzed Michael addition of ethyl acetoacetate to 2-cyano-*N*-methyl-3,3-bis(methylthio)acrylamide **1a**[22] with

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0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.04.082

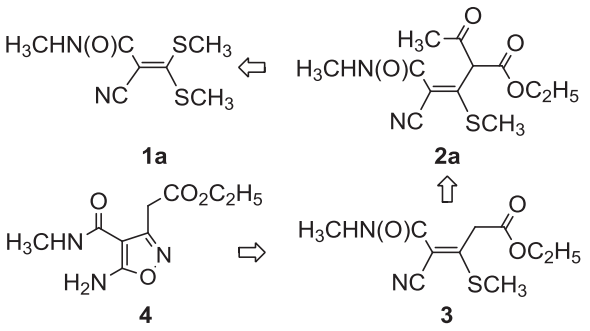


Fig. 1. Retrosynthetic approach for isoxazole **4**.

concomitant elimination of methyl mercaptan to prepare adduct **2a**. Acyl ester of the general formula **2a** was expected to give the deacylated intermediate **3** under appropriate basic reaction conditions. The regioselective addition of hydroxylamine to **2a** under basic reaction conditions was expected to give the desired functionalized isoxazole **4**.

With the retrosynthetic plan in place, we prepared the known ketene dithioacetal **1a** from 2-cyano-*N*-methylacetamide by using a modified approach.[23] The conjugate addition of ethyl acetoacetate **5a** to **1a** using excess (2.5 equiv) of anhydrous potassium carbonate (K_2CO_3) in dry dimethyl sulfoxide (DMSO) at room temperature for 4 h resulted in the formation of two major products along with a small amount of starting material **1a**. The less polar product, characterized as the required adduct **2a**, was isolated in 55% yield as a white solid by column chromatography. The more polar minor product (15%) isolated from the reaction mixture was characterized as pyridone **6a**. Both the products were fully characterized by analytical and spectroscopic data.

The next step in the retrosynthetic scheme is deacetylation of **2a** to the desired β,γ-unsaturated ester **3** using a suitable known procedure. Thus, **2a** was treated with catalytic amounts of sodium ethanolate in ethanol at room temperature for 6 h, but the expected deacetylated product was not detected in the reaction mixture.[24] A more polar product was isolated in small amounts, which was identical in all respects with the pyridone **6a** isolated from the previous experiment. The deacetylation was then attempted as reported using sodium acetate in a mixture of water and ethanol at room temperature.[25] A mixture of starting ester **2a** and pyridone **6a** was detected after 96 h at ambient temperature along with unidentifiable products. Heating the above reaction mixture at 80 °C for 6 h resulted in the conversion of **2a** to **6a**. The desired deacetylated product **3** was not detected in the mixture. Deacetylation was then attempted using excess propylamine in chloroform at ambient temperature for 12 h according to a published procedure, which also did not give the expected deacetylated ester **3**.[26] The reaction remained incomplete and both ester **2a** and pyridone **6a** were detected in the reaction mixture. Finally, deacetylation[27] was attempted using triethylamine in water at 60 °C, which resulted in the conversion of **2a** to pyridone **6a**. These results strongly suggest that the intermediate ethyl 2-acetyl-4-cyano-5-(methylamino)-3-(methylthio)-5-oxopent-3-enoate **2a** exists as its tautomer 5-oxopent-2-enoate **2a′** under the described conditions, which is not amenable to a deacetylation reaction (Fig. 2).

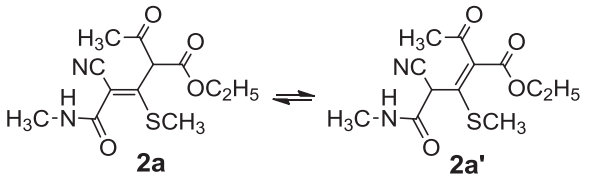
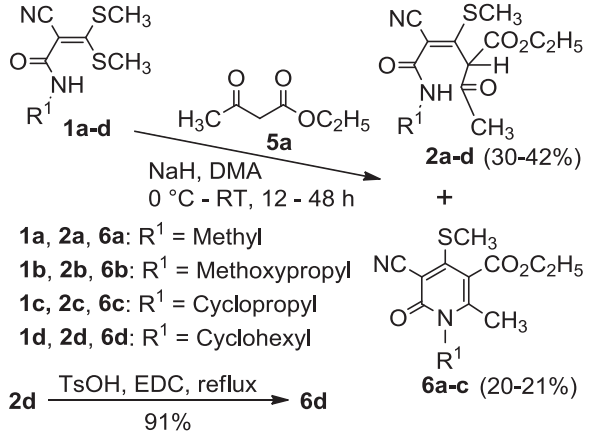


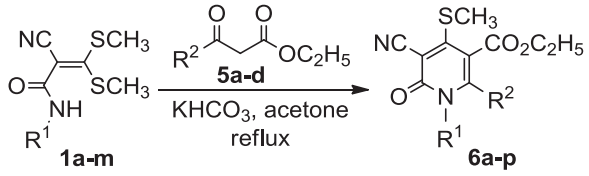
Fig. 2. Tautomeric forms **2a** and **2a′**.

Having failed in our efforts to prepare the intermediate **3** required for the synthesis of desired isoxazole **4** (Fig. 1), we reexamined this reaction with a view to develop a general approach for the synthesis of pyridone esters **6** with an optional substitution at its 2-position. In this paper, we describe an optimized simple, general and highly flexible single-step procedure for the syntheses of *N*-alkyl and *N*-aryl 6-oxo-1,6-dihydropyridine-3-carboxylates **6**.

We decided to study the base-assisted conjugate addition of **5a** to carbamoyl ketene dithioacetals **1a**–**d** in more detail before attempting optimization of a single-step procedure as shown overleaf in Scheme 2. To check the generality of the reaction and to confirm the intermediacy of ester **2** in the formation of pyridone **6**, we selected ketene dithioacetals **1a**–**d** bearing dissimilar substituents on the amide nitrogen. After a few trial experiments, sodium hydride (NaH) in *N*,*N*-dimethylacetamide (DMA) was selected for this optimization study (Scheme 1). Thus, the reaction of ketene dithioacetal **1a** with **5a** in the presence of NaH (1.2 equiv) in dry DMA at 0 °C followed by maintaining the mixture at ambient temperature for 12 h resulted in the formation of a mixture of ester **2a** (42%) and pyridone **6a** (21%) along with small amounts of **1a** (4%). The reaction of **5a** with the methoxypropyl derivative **1b** also showed a similar trend and ester **2b** (32%) and pyridone **6b** (20%) were isolated from the reaction mixture along with small amounts of starting material **1b** (5%). The structures of **2b** and **6b** were fully established by spectral and analytical data. Under identical conditions, the cyclopropyl derivative **1c** also yielded ester **2c** (34%) and pyridone **6c** (20%) along with unreacted starting material **1c** (7%). The cyclohexyl derivative **1d** yielded only the open chain ester **2d** (30%) and the pyridone **6d** was not formed in the reaction mixture even after 48 h at ambient temperature.



Scheme 1. Synthesis of esters **2a**–**d** and pyridones **6a**–**d**.



Scheme 2. $KHCO_3$ mediated synthesis of pyridones **6a**–**p**.

It is interesting to note that all the four reactions remained incomplete even after stirring for 12–48 h at room temperature. Heating the reactions at 80 °C resulted in a reddish brown mixture, probably due to decomposition of unreacted ketene dithioacetal **1**. The sterically more demanding cyclohexyl derivative stopped at the ester stage **2d** and subsequent cyclization to pyridone **6d** seemed unviable. In a separate experiment, the ester **2d** isolated was treated