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An expedient approach to tetrahydrofuro[3,2-*b*]pyridine-2(3*H*)-ones via activation of pyridine *N*-oxide by triflic anhydride

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ABSTRACT

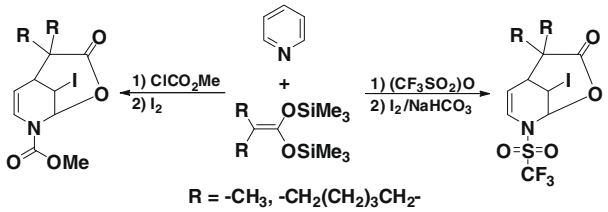
The double addition of *bis*(trimethylsilyl) ketene acetals [R_1, R_2 = CH_3, $-(CH_2)_5-$] to pyridine *N*-oxide promoted by triflic anhydride under mild conditions generates *N*-[(trifluoromethane)sulfonyl-1,2-dihydropyridine-2,4-dicarboxylic acids **2a**–**b**. Subsequent reaction of these acids upon iodolactonization conditions affords tetrahydrofuro[3,2-*b*]pyridine-2(3*H*)-ones **3a**–**b** containing an *exo*-insaturation on the products as a result of an unexpected decarboxylation.

1. Introduction

The functionalization of nitrogen heterocycles is a powerful tool for the synthesis of natural products and bioactive substances. In this context, dihydropyridines[1] show interesting features that make them attractive due to the high number of available derivatives. Thus, DHPs can be easily obtained from pyridines and their derivatives, which after activation react with a large variety of nucleophiles.[2] The activation of the pyridinium nucleus toward carbon nucleophiles can be achieved by alkyl chloroformates,[3] acid chlorides[4], or triflic anhydride,[5,6] among others.

Following this approach, we and other research groups have described the one-pot synthesis of functionalized δ-lactones via a double nucleophilic addition of *bis*-(TMS)ketene acetals to activated pyridines using methyl chloroformate as an activating agent and the appropriated halogen to induce the formation of corresponding halolactones (Scheme 1).[7] A similar activation of the pyridine directed to the synthesis of lactones can be achieved if triflic anhydride is used as an activating agent, but in this case better yields and more stable 1,4-dihydropyridines were obtained. As in the previous case, in iodolactonization conditions, the corresponding γ-lactones provided excellent yields.[8] We have recently described how a double nucleophilic addition reaction of ketene acetals, which leads to lactones, can be extended to other diazines such as pyrazine, quinoxaline, and pyrimidine, and the course of the reaction in some cases depend on the nature of the nitrogen-activating agent.[9]

Despite the use and application of these activating methods, several research groups have also focused their attention on *N*-oxide activation.[10] The advantage of the former is the easy elimination of the activating agent and control on the regiochemistry of nucleophilic addition. In this respect, pyridine *N*-oxide has received wide attention as a synthetic intermediate, oxidant,[11] catalyst, and ligand.[12] In addition, some of the related compounds also have important biological or pharmaceutical activities.[13] Pyridine *N*-oxides have been used as an important tool to functionalize the pyridine ring including nitration, halogenation, and cyanation. For example, considerable efforts have recently been reported in the conversion of the *N*-oxides into (a) 2-aminopyridine with Ts_2O-*t*$BuNH_2$ followed by in situ deprotection with



Scheme 1.

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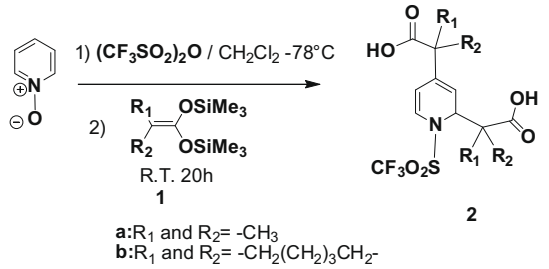
TFA,[14] (b) 2-aminopyridine amides with imidoyl chlorides,[15] (c) tetrazolopyridines with sulfonyl or phosphoryl azides[16] and imidazolopyridines with sulfuryl diimidazole,[17] (d) 2-alkyl, alkynyl, and arylpyridines with Grignard reagents,[18] and (e) 3-(2-hydroxyaryl)pyridines via arynes.[19] It is noteworthy that pyridine *N*-oxides also served as an ideal choice to direct C–H functionalization of the pyridine ring.[20]



Scheme 2.

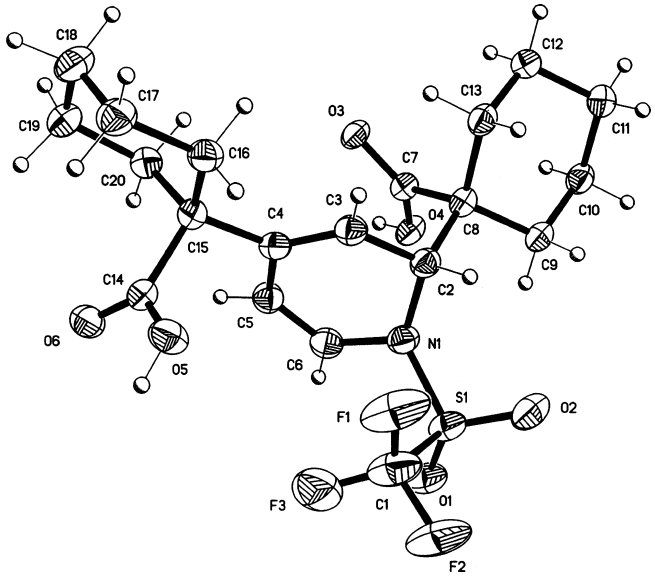


Figure 1. ORTEP view of **2b**.

With the aim of promoting a double nucleophilic addition of (TMS)ketene acetals over pyridine, we describe a new one-pot method that involves two simultaneous activation procedures, *N*-oxide activation in the presence of triflic anhydride. This strategy gave 1,2-dihydropyridines 2,4-disubstituted, which after an iodolactonization procedure affords tetrahydrofuro[3,2-*b*]pyridine-2(3*H*)-ones containing an *exo*-insaturation on the products as a result of an unexpected decarboxylation.

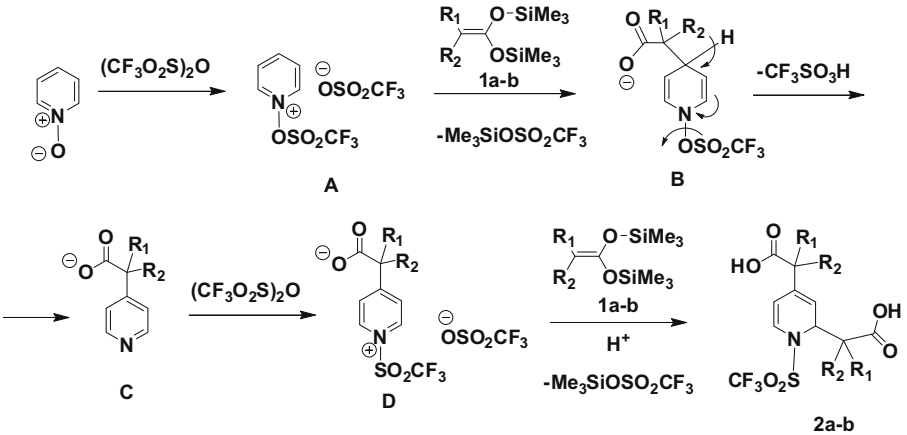
2. Results and discussion

Triflic anhydride was added by a syringe to a solution of pyridine *N*-oxide in dry CH_2Cl_2 at −78 °C, followed by 2.5 equiv of *bis*-(trimethylsilyl)ketene acetal **1a**, which led to the formation of a white solid (Scheme 2). After the work-up the 1,2-dihydropyridine 2,4-disubstituted **2a** was obtained as a solid (mp 162–164 °C) with 54.4% yield.

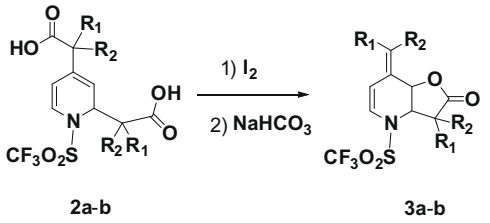
The ^{1}H NMR data are in agreement with the molecular structure of **2a** and confirmed the addition of two equivalents of **1a** over the 2,4-position of the pyridine ring, giving signals at 1.1, 1.17, 1.23, and 1.28 ppm as singlets for four methyl groups. We also observed at 5.8 and 6.44 ppm two doublets assigned to H5 and H6, with J = 7.2 Hz and a double signal at 5.57 ppm (J = 6.06 Hz) for H3, which coupled with the signal shifted at 4.87 ppm assigned to H2. Additionally, only one signal was observed at 5.04 ppm for two carboxylic acids. The ^{13}C NMR spectrum also exhibited signals at 62.1, 117.6, 123.7, 115.7, and 62.1 ppm assigned to carbon 2–6 of the dihydropyridine ring, respectively. At 178.3 and 178.8 two signals were shifted for the carboxylic groups.

Product **2b** (mp 179–180 °C) was obtained using the same procedure in 76.1% yield, and shows the nucleophilic addition of two equivalents of the (TMS)ketene acetal **1b** at the 2,4-position of pyridine *N*-oxide. In contrast with the results obtained by Medley,[21] the compounds **2a** and **2b** do not show rearomatization in the final products, leading to *N*-[(trifluoromethane)sulphonyl]-1,2-dihydropyridine-2,4-carboxylic acids. The structure of **2b** was fully established through an X-ray diffraction analysis (Fig. 1).[22]

In accordance with the experimental results, a possible mechanism for the formation of **2a–b** can be suggested (Scheme 3). First, the pyridine *N*-oxide reacts with triflic anhydride in a similar way to phosphine oxides[23] that lead to intermediate **A**, then (TMS)ketene acetal is additioned at 4-position, leading to **B**. Then a rearomatization of the system through the loss of OTf occurs, leading to **C**. A subsequent activation of this new pyridine promoted by a second equivalent of triflic anydride favors the nucleophilic addition of a second molecule of (TMS)ketene acetal, to give the



Scheme 3.



Scheme 4.

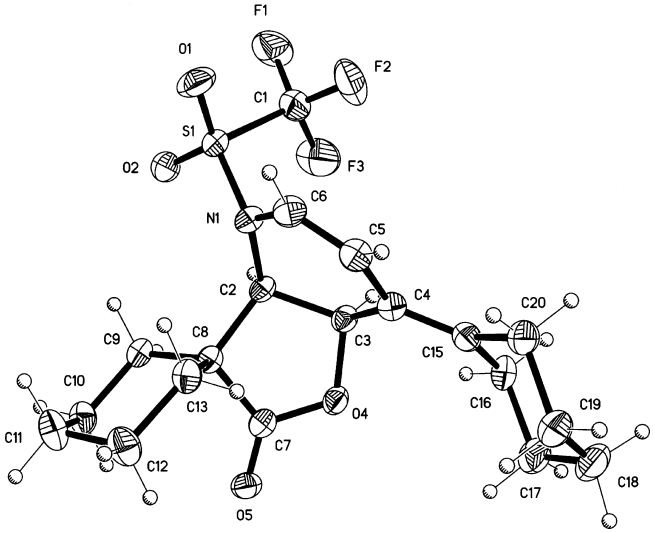
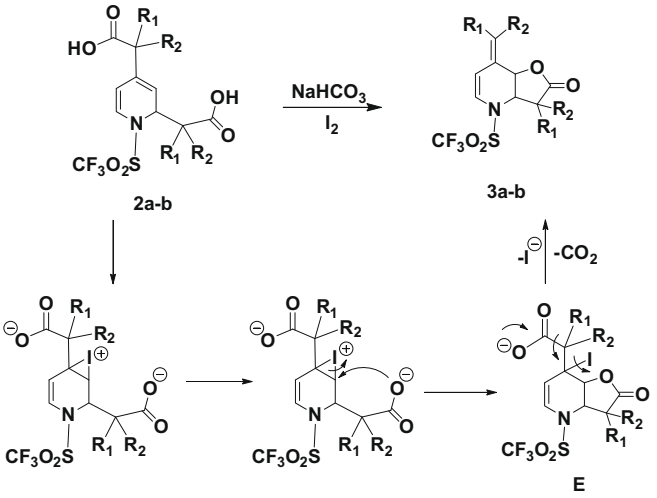


Figure 2. ORTEP view of **3b**.

corresponding *N*-[(trifluoromethane)sulphonyl]-1,2-dihydropyridine-2,4-carboxylic acids. The formation of intermediate **A** is crucial in explaining the obtention of an 1,2-dihydropyridine as the end product, which indicates a high 4-regioselectivity in the addition of C-nucleophiles as (TMS)ketene acetals over pyridines *N*-oxide.[21]

We have studied the transformation of the 2,4-dicarboxylic acids **2a–b** into iodolactones following the strategy of a halolactonization protocol. Thus, when compounds **2a** and **2b** were reacted in the condition described in Scheme 4, the bicyclic lactones [4.3.0] **3a** (mp 132 °C, yield: 43.9%) and **3b** (mp 126–128 °C, yield: 63.1%) were obtained, but surprisingly these do not contain iodine in their structure and the presence of an *exo*-cyclic double bond as a result of a decarboxylation at room temperature was observed. These results are quite different from lactones previously obtained by us under similar conditions.[9,10]

According to its ^{1}H NMR, spectrum, **3a** contains four simple signals shifted at 1.19, 1.39, 1.89, and 2.02 ppm assigned to methyls, two coupled methine groups H2 and H3 (δ = 4.64 and 6.36, J = 8.79 Hz) consistent with a *cis*-fused lactone system. Additionally, the double bond hydrogens in the tetrahydropyridine ring are localized at 6.13 and 6.36 ppm. The ^{13}C spectrum confirmed the presence of an *exo*-cyclic double bond by signals at 118.4 and 118.9 ppm; the olefinic carbons of the tetrahydropyridine ring (C5 and C6) at 113.8 and 141.0 ppm; the carbonyl group of the lactone at 176.4 ppm, and lastly, the trifluoromethyl group at 119.6 (J = 321 Hz). Similar spectroscopic data were obtained for the analogous **3b**. Crystals suitable for X-ray analysis were grown from **3b** and allowed an unambiguous assessment of their structure (Fig. 2).[24]



Scheme 5.

The transformation of **2** into **3** could involve the formation of an iodonium intermediate that favors the intramolecular ring-closing reaction leading to iodolactone **E**, which undergoes decarboxylation promoted by the basic medium and the loss of the iodide ion. This assumption is supported by an experiment performed in the absence of iodine, which gave negative results (Scheme 5).

To summarize, we have developed a new means of obtaining *N*-[(trifluoromethane)sulfonyl-1,2-dihydropyridine-2,4-dicarboxylic acids **2a–b**, under mild conditions, using as a strategy the formation of a new activating group that promotes the nucleophilic addition of (TMS)ketene acetal on 4-position as an initial step. Using halolactonization protocol, compounds **2a–b** provide tetrahydrofuro[3,2-*b*]pyridine-2(3*H*)-ones **3a–b,** containing an *exo*-insaturation, as a result of an unexpected decarboxylation. Further studies will widen the scope of this methodology.

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Supplementary data

Supplementary data (spectroscopic characterization of products **2a**, **2b**, **3a** and **3b** and general methods) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.030.

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