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New and Convenient Syntheses of Anhydro-2-alkyl-3-iminothiazolo-[3,2-*a*]pyridinium Hydroxide Derivatives

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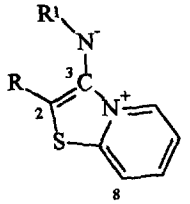
Abstract: The 2-alkyl derivatives of anhydro-3-trifluoroacetyliminothiazolo[3,2-*a*]pyridinium hydroxide were synthesized in quantitative yield by treatment of either 2-(pyridine-2-thiyl)-carboxamides or the corresponding nitriles with trifluoroacetic anhydride in dichloromethane. © 1997 Elsevier Science Ltd.

Mesoionic compounds are theoretically interesting owing to their unique electronic and structural features.[1] Studies on these compounds have resulted in practical syntheses of numerous substituted monocyclic and ring-annulated heterocycles. Mesoionic systems containing an exocyclic imino group are stable when the imino nitrogen atom is substituted with an unsaturated electron-delocalizing group such as an acyl or a nitroso group. The anhydro-3-iminothiazolo[3,2-*a*]pyridinium hydroxide system, generalized as formula **1**, can be modified at the exocyclic imino group by attaching, amongst others, nitroso, nitro, and carbamoyl groups as in the sydnone system.[2] It can also undergo nucleophilic displacement (after acylation) with amines.[3] The mesoionic imine systems have generated considerable attention because they display a variety of interesting pharmacological properties. For example, berninamycinic acid, a hydrolysis product of the antibiotics Berninamycin A[4] and Sulfomycin I[5], contains a pyridothiazolopyridinium chromophore. A simple 8-methyl-2-phenyl-thiazolo[3,2-*a*]pyridinium salt is reported to have hypoglycemic activity.[6]

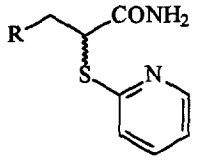
Although many studies on the preparation of thiazolo[3,2-*a*]pyridinium compounds,[7] including the 3-oxide derivatives,[8] have been done, very few syntheses of anhydro-3-iminothiazolo[3,2-*a*]pyridinium hydroxide derivatives have been reported. To our knowledge, the only synthesis of the latter involves a reaction between 2-mercaptopyridine and an α-halo nitrile followed by treatment with an acyl chloride.[9,10] The feasibility of this method depends largely on the availability of the α-halo nitriles and, consequently, the 2-substituted derivatives of **1** are less explored. In the present paper we report a convenient synthesis of 2-alkyl anhydro-3-

acyliminothiazolo[3,2-*a*]pyridinium hydroxide derivatives by a dehydration-cyclization sequence utilizing 2-(pyridine-2-thiyl)-carboxamides. Furthermore, the synthesis of the title compounds through 2-(pyridine-2-thiyl)-nitriles, prepared by the radical chemistry of Barton esters, is also described.

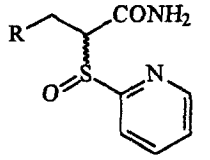
In the preceding paper, we demonstrated that crystalline 2-(pyridine-2-thiyl)-carboxamides **2a-e** are easily attainable through Barton ester radical chemistry. Thus, the 2-(pyridine-2-sulfinyl)-carboxamides **3a,b** were obtained in excellent yields by oxidation of **2a,b** with mCPBA in dichloromethane. When compounds **3a,b** were treated with trifluoroacetic anhydride (TFAA) in dichloromethane at 0°C, the only products obtained were the corresponding 2-(pyridine-2-sulfinyl)-nitriles **4a** (IR: 2238 cm^{-1}) and **4b** (IR: 2233 cm^{-1}), respectively. The Pummerer rearrangement was not observed. The structure of **4a** was confirmed by an independent synthesis through oxidation of 3-cyclohexyl-2-(pyridine-2-thiyl)-propanitrile **5** (IR: 2236 cm^{-1}) with mCPBA in dichloromethane. Compound **5** was synthesized by a radical reaction between the cyclohexanecarboxylic acid Barton ester and acrylonitrile.[11]



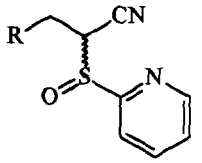
1



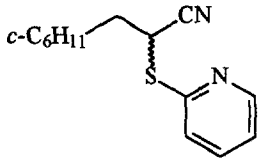
2a-e



3a,b



4a,b



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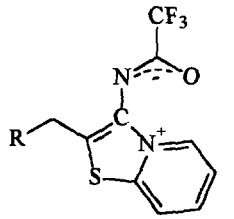


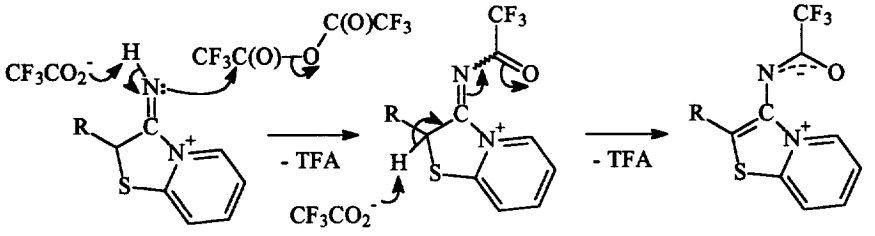
6a-e

2a-6e: R = **a**: *c*-C_6H_{11}; **b**: $(CH_3)_2CH$; **c**: $Ph(CH_2)_2$; **d**: $(CH_3)_3C$; **e**: 1-adamantyl.

When **2a** was treated with three equivalents of TFAA in dichloromethane at 0°C, the starting material disappeared in five minutes and a more polar product was formed. The mesoionic structure **6a** was deduced for the yellow crystalline product based on the unusual down-field signals of the pyridine ring in the ^{1}H-NMR spectrum and the existence of a trifluoroacetyl group in the ^{13}C-NMR spectrum.[12] To our knowledge, this is the first example of **1** with a trifluoroacetyl group on the 3-imino nitrogen. Treatment of **2e** with TFAA for 3.5

hours at 0°C to room temperature afforded **6e** (m.p. 207-208°C) in 99% isolated yield. Treatment of **2b-d** with TFAA also furnished the corresponding mesoionic compounds **6b-d** quantitatively by ^{1}H-NMR. The IR (~1600 cm^{-1}) and ^{13}C-NMR (~160 ppm) values for the trifluoroacetyl carbonyl group suggest the delocalization of the negative charge over the imino nitrogen and the carbonyl group.

Mechanistically, it is conceivable that the dehydration of the amide group by TFAA could give the protonated nitrile. The latter then cyclizes to form the key intermediate: an imino-pyridinium salt. The acylation of the imino group followed by deprotonation eventually furnishes the mesoionic structure. The pyridine ring in the starting material is believed to facilitate the dehydration of amide. This was proved by treatment of 3-(adamant-1-yl)-propionamide (preceding paper) with 3.6 equivalents of TFAA in dichloromethane to give the corresponding nitrile (IR: 2246 cm^{-1}) and the starting material in only 2:1 ratio by ^{1}H-NMR after two hours.



As expected, treatment of the nitrile **5** with TFAA in dichloromethane afforded the mesoionic compound **6a** in a similar fashion in 96% yield after five hours. The observation that the reaction of the nitrile **5** is slower than that of **2a** suggests that the protonated nitrile is an essential intermediate in the dehydration-cyclization sequence. The acceleration of the nitrile reaction by a catalytic amount of TFA in a control experiment supports this speculation.

In conclusion, the Barton ester-mediated addition of carbon-centered radicals to either acrylamide or acrylonitrile and subsequent intramolecular cyclization of the intermediate adducts with TFAA provides a convenient route to mesoionic compounds.

Typical Procedure: To a solution of **2a** (264 mg, 1 mmol) in dry dichloromethane (10 ml) was added 0.42 ml of TFAA (630 mg, 3 mmol) at 0°C under an argon atmosphere. After the reaction mixture had stirred for 15 minutes, TLC indicated complete consumption of the starting material and the reaction mixture was evaporated to dryness. The residue was dissolved in $NaHCO_3$ solution and extracted thrice with dichloromethane. The organic extracts were combined and dried over magnesium sulfate. Removal of the solvent afforded pure **6a** as yellow crystals (325 mg, 95% yield).[12]

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12. **6a**: $C_{16}H_{17}F_3N_2OS$ requires C 56.12, H 5.01, N 8.18, S 9.36; found C 56.03, H 4.98, N 8.12, S 9.29. m.p. 137-138°C (Et_2O-CH_2Cl_2); IR (KBr): 2909, 2838, 1600 (C=O), 1556, 1271, 1157, 1112 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 200 MHz): 0.90-1.82 (m, 11H), 2.91 (d, J = 6.7 Hz, 2H), 7.65 (m, 1H), 7.93 (m, 1H), 8.13 (m, 1H), 8.99 (m, 1H); ^{13}C-NMR ($CDCl_3$, 75 MHz): 25.9, 26.0, 32.9, 34.9, 38.7, 118.2 (q, J = 428.6 Hz, CF_3), 119.4, 120.2, 121.0, 121.9, 131.8, 132.8, 142.9, 148.4, 160.3 (q, J = 49.6 Hz, C=O).

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