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Synthetic Methods

Overall “Pseudocationic” Trifluoromethylation of Dihydropyridines with Triflic Anhydride**

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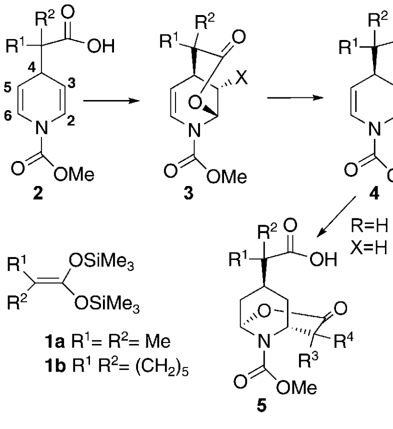
Dihydropyridines of type **2** substituted at the C4-position by a carboxylic acid are valuable intermediates for the synthesis of new heterocyclic compounds, including tetrahydropyridine-fused δ-lactones **3**, polysubstituted tetrahydropyridines **4**, and piperidine-fused δ-lactones **5** (Scheme 1).[1]

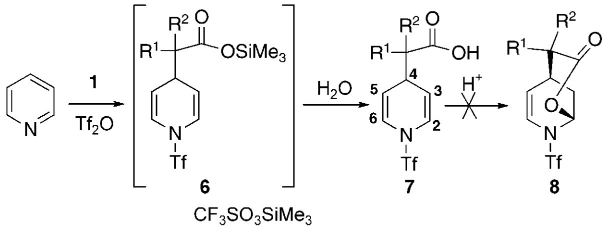


Scheme 1. Transformations of dihydropyridines.

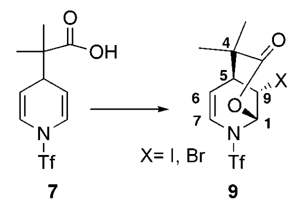
The starting materials for all those transformations were differently substituted pyridines, which underwent stepwise nucleophilic addition reactions with ketene acetals **1** upon activation by methyl chloroformate. The ring-closure reaction, leading from **2** to **3**, is stereospecific: only the *trans*-diaxial-oriented functionalized lactones are formed. These transformations are part of a special class of reactions of dihydropyridines: nonbiomimetic oxidations, which do not lead, as one would expect, to pyridinium salts.[2] Indeed, the electrophiles preferentially react with one of the double bonds of the ene-carbamates **2** than with the proton at C4.

The activation of the pyridinium nucleus towards carbon nucleophiles is not limited to alkyl chloroformates or acid chlorides, since several research groups have also used triflic anhydride for that purpose; in addition to the higher stability of the intermediate pyridinium salts and the general higher yields of the addition products, the absence of rotamers at room temperature is also beneficial.[3] For the purpose of comparing the two activation procedures, with methyl chloroformate or triflic anhydride, we synthesized a series of dihydropyridines subsituted by a triflyl group on the nitrogen atom. This led us to the discovery of a new, unexpected transformation of these dihydropyridines.

Thus, the reaction of pyridine with ketene acetals **1a**,**b** (1 equiv) and then with triflic anhydride (1 equiv) at −30 °C led, as expected, after warming the mixture to room temperature and stirring for 17 h, to the same type of acid-substituted dihydropyridines **7a**,**b** in high yield (97 %, Scheme 2). Although the reaction of these dihydropyridines with either silica gel or an anhydrous solution of HCl in diethyl ether did not lead to the expected lactones **8a**,**b**, they did react with I_2 and $CuBr_2$ to give, as for **2**, the corresponding halolactones **9** (Scheme 3).[1,4]



Scheme 2. Preparation of **7**.



Scheme 3. Formation of lactone **9**.

However, further studies allowed us to discover a new transformation of these dihydropyridines. Indeed, it appeared that the yield of the dihydropyridines **7a**,**b** was dependent both on the reaction conditions (order of addition, time of reaction) and on the amount of triflic anhydride used with respect to the starting pyridine: no such an influence was observed when methyl chloroformate was used as the activating agent. The use of an excess of triflic anhydride, however, led to the yield of the dihydropyridines decreasing as a function of time. Surprisingly, according to TLC analysis,

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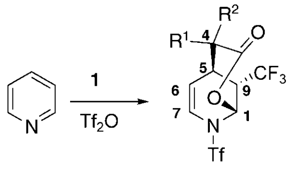
new, less-polar products, suspected initially to be the unknown **8a**,**b**, were formed. After two days at room temperature, the reaction mixture obtained starting from two equivalents of triflic anhydride, was hydrolyzed, extracted, and the crude product purified by column chromatography on silica gel (Scheme 4). Elution with dichloromethane led to new crystalline compounds (28 %, m.p. 91 °C for **10a**; 48 %, m.p. 117 °C for **10b**). Their structures were assigned by NMR spectroscopy and secured for **10b** by an X-ray crystallographic analysis.[5]



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Scheme 4. Unexpected transformation of pyridine.

The ^{13}C and ^{1}H NMR spectra of **10a** were very insightful: the ^{1}H NMR spectrum depicted, besides a signal corresponding to the two methyl groups, signals for five different protons, as in the spectra of the related halolactones. The ^{13}C NMR spectrum showed a signal at $\delta = 172.19$ ppm, which was compatible with the presence of a δ-lactone, as in **9**, an observation corroborated by the presence of a signal at $\delta = 78.49$ ppm for an NCO carbon atom. More intriguing, however, was the signals for two CF_3 groups: instead of the one expected signal, two quartets were observed at $\delta = 123.75$ ppm ($J = 280$ Hz) and $\delta = 119.21$ ppm ($J = 322$ Hz), and a signal for a carbon atom was observed as a quartet at $\delta = 37.49$ ppm ($J = 30$ Hz). The presence of these two CF_3 groups could also be confirmed by the ^{19}F NMR spectrum, which showed a sharp singlet at $\delta = -69.7$ ppm and two broad singlets at $\delta = -76.7$ and -75.8 ppm.[6] An HMQC sequence confirmed the presence of a hydrogen atom (δ 3.39 ppm) on the carbon atom corresponding to the signal at δ 37.49 ppm. The shape of this signal, a quartet of quintuplets ($J_{HF} = 8$ Hz, $J_{H\text{-}H} = 1.3$ Hz, Figure 1 B), was indeed also typical for that of a hydrogen atom geminate to a CF_3 group. Together with the elemental analysis, these data were in full agreement with a structure such as **10a**, with one CF_3 group attached at C9.

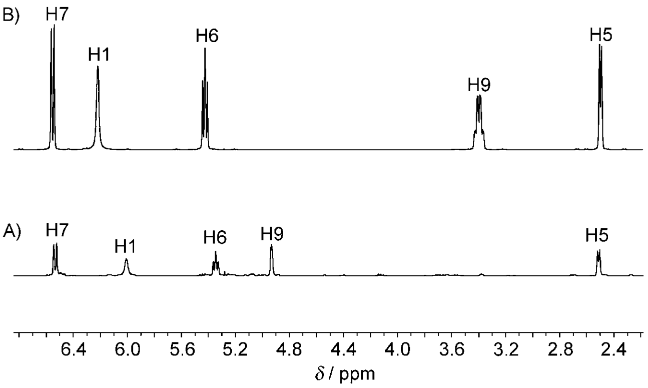


Figure 1. Partial ^{1}H NMR spectra of: A) **9a** (X = Br) and B) **10a**.

Crystals suitable for an X-ray analysis were grown from a mixture of hexanes and dichloromethane. It confirmed the molecular structure of **10b** (Figure 2), the initial dihydropyridine **7b** having undergone a lactonization reaction akin to those described in Scheme 3, but involving CF_3. As in the previous functionalized lactones, the introduced group is *trans* to the lactone bridge.[1]

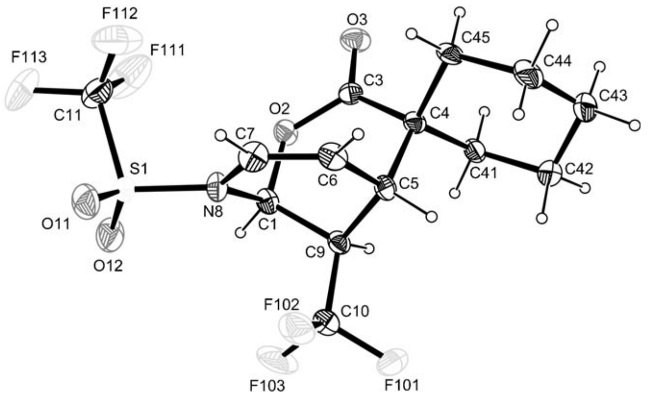
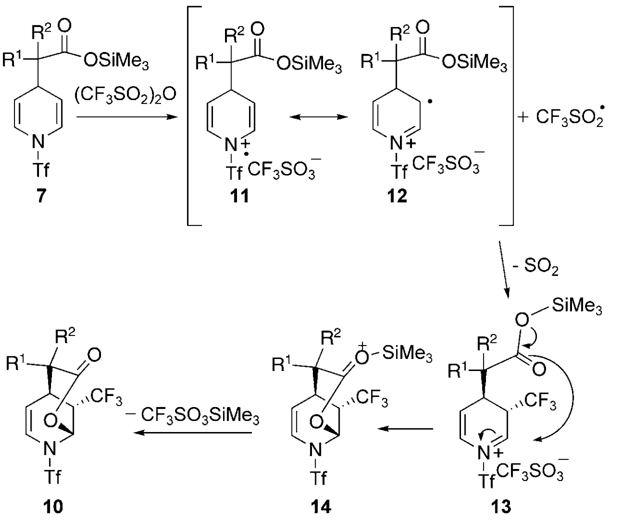


Figure 2. X-ray structure of **10b**.

To improve the yield of these new lactones, we slightly modified the experimental procedure: one equivalent of triflic anhydride, and one equivalent of the ketene acetal **1a** were added sequentially to a solution of pyridine at −30 °C. The reaction mixture was then allowed to warm slowly to room temperature. After 17 h, an aliquot was taken and analyzed by ^{1}H NMR spectroscopy: the spectrum confirmed the presence of the dihydropyridine **7a**, with only a trace amount of **10a**. The reaction mixture was then again cooled to −30 °C and a second equivalent of triflic anhydride added. After the mixture had stood for 17 h at room temperature, the NMR spectrum confirmed the complete disappearance of the dihydropyridine and the presence, besides the pyridinium salt, of the lactone **10a**. Extraction with dichloromethane and washing of the organic layer with aqueous sodium hydroxide gave the pure lactone **10a** (28 %). The question is, therefore, how the introduced CF_3 group is formed starting from triflic anhydride. The reagents present in solution, at the end of the expected reaction are the trimethylsilyl ester **6a** and trimethylsilyltriflate ($CF_3SO_3SiMe_3$). Since only trace amounts of the lactones **10a**,**b** are formed in the presence of one equivalent of triflic anhydride (< 5 %), and moreover since an excess of that reagent increases the yield of these lactones significantly, then the origin of the CF_3 is probably the second equivalent of triflic anhydride.

Two points have to be considered. First, dihydropyridines **7a**,**b** are part of a general family of reducing agents, which can give, depending on the oxidizing agent, either pyridinium salts (biological oxidation) or the double bond functionalized tetrahydropyridines (nonbiomimetic oxidation).[7] Second, it has been established by Stang and co-workers that triflic anhydride could indeed act as an oxidizing agent, especially towards thiourea and activated ketones, to give isolable dimeric cationic species.[8,9] One of the possible mechanisms suggested by these authors might be especially meaningful as far as the present transformation is concerned: the transfer of an electron from thiourea to triflic anhydride might lead to one equivalent of triflate ($CF_3SO_3^-$) and one equivalent of the triflyl radical $CF_3SO_2^{\bullet}$. This latter species would readily fall apart to give SO_2 and $CF_3^{\bullet}$ (Scheme 5). A similar transfer of an electron from dihydropyridine to triflic anhydride might thus lead to a pyridinium radical **11**↔**12** and $CF_3^{\bullet}$. These pyridinium radicals could possibly expel SO_2 to give the adduct **13**, which after an intramolecular nucleophilic addition of the trimethylsilyl ester to the iminium group followed by a $CF_3SO_3^-$-induced cleavage of the activated O–$SiMe_3$ bond in **14** would give lactone **10**. Such a route indeed relies on one of the generally accepted mechanisms of dihydropyridine-induced reductions, namely by electron transfer.[10] It also relies on the trifluoromethanesulfinate-induced trifluoromethylation of enol esters, via electrophilic $CF_3^{\bullet}$ radicals described by Langlois and co-workers.[11] It is nevertheless clear that at this point other mechanisms cannot be excluded.[12,13] The transformations described herein, although taking place on a specific substrate and in modest yields, are interesting since the introduction of a CF_3 group in to an organic molecule is an important challenge.[14] Further work to try to improve the yield of the lactones **10**, to get a deeper insight into the reaction described herein, and to adapt it to related transformations is in progress. Moreover, attempts will be made to use different sources of CF_3 to carry out similar transformations of these dihydropyridines.



Scheme 5. Proposed mechanism.

Experimental Section

10a: white solid, m.p. 91 °C (28 % yield). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.55$ (d, $J = 8.5$ Hz, 1H, H7), 6.21 (brs, 1H, H1), 5.42 (ddd, $J = 8.5, 6, 1.3$ Hz, 1H, H6), 3.39 (qqt, $J = 8, 1.3$ Hz, 1H, H9), 2.49 (d, $J = 6$ Hz, 1H, H5), 1.42 (s, 3H, CH_3), 1.41 ppm (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.19$ (CO), 123.75 (q, $J = 280$ Hz, C9-CF_3), 121.37 (C7), 119.21 (q, $J = 322$ Hz, SO_2CF_3), 108.51 (C6), 78.49 (d, $J = 6.8$ Hz, C1), 44.61 (C4), 37.49 (q, $J = 30$ Hz, C9), 34.21 (C5), 26.76 (CH_3), 25.38 ppm (CH_3); ^{19}F NMR (376 MHz, $CDCl_3$): $\delta = -76.7$ and -75.8 (brs, SO_2CF_3), -69.7 ppm (s, C9-CF_3).

10b: white solid, m.p. 117 °C (48 %). ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.57$ (d, $J = 8.5$ Hz, 1H, H7), 6.17 (brs, 1H, H1), 5.38 (ddd, $J = 8.5, 6, 1.3$ Hz, 1H, H6), 3.32 (qqt, $J = 8, 1.3$ Hz, 1H, H9), 2.92 (d, $J = 6$ Hz, 1H, H5), 2.05–1.30 ppm (m, 10H, cyclohexyl); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 171.94$ (CO), 123.92 (q, $J = 278$ Hz, C9-CF_3), 121.78 (C7), 119.22 (q, $J = 320$ Hz, SO_2CF_3), 107.90 (C6), 77.66 (d, $J = 6.8$ Hz, C1), 48.29 (C4), 37.00 (q, $J = 30$ Hz, C9), 33.23 (CH_2), 32.42 (CH_2), 28.15 (C5), 25.02 (CH_2), 20.92 (CH_2), 20.52 ppm (CH_2). Elemental analysis calcd for $C_{14}H_{15}F_6NO_4S$: C 41.28, H 3.71, N 3.44; found: C 41.31, H 3.89, N 3.42.

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