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The Synthesis of 2-(Chloromethyl)-6-Hydroxy-*2H*-Pyran-3 (6H)-one via Achmatowicz Rearrangement

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Achmatowicz rearrangement was carried out with 2-chloro-1-(furan-2-yl) ethanol, which was synthesized starting from 1-(furan-2-yl) ethanone. It was shown that the oxidation of 2-chloro-1-(furan-2-yl) ethanol with m-CPBA produced 2-(chloromethyl)-6-hydroxy-2H-pyran-3 (6H)-one in good yield (70%).

Key Words: Oxidation, furan, 2-chloro-1-(furan-2-yl) ethanol, m-CPBA, rearrangement, pyranones.

Introduction

Furan, pyran, and dihydropyran types of compounds are currently of interest as alternative, renewable raw materials for the synthesis of fine chemicals.[1−4] Since furan compounds are readily available and can be employed in a wide range of transformations, they are useful for the synthesis of many structurally diverse molecules. However, due to their high reactivity, these oxygen heterocycles are susceptible to side reactions such as cleavage and polymerization. Therefore, considerable care has to be taken in the selection of reagents, catalysts, and reaction conditions in order to obtain desired products in reasonable yields.

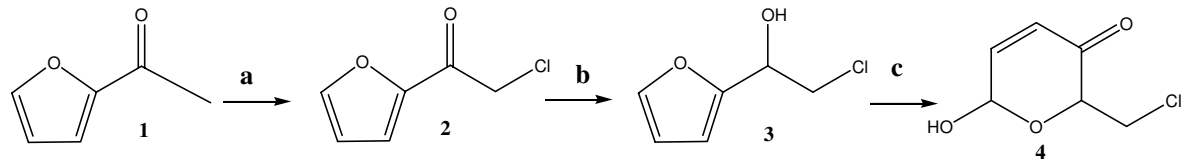
Since the first discovery of the Achmatowicz reaction there have been several attempts to synthesize pyrans.[5−7] In addition to their antimicrobial and anticolilidal activities, 2*H*-pyran-3 (6*H*)-one derivatives are building blocks of many important biological active compounds such as sugar analogues, pheromenones, and anticancer drugs.

As far as we know there is no reaction that can furnish 2-(chloromethyl)-6- hydroxy-2*H*-pyran-3 (6H)-one starting from 1-(furan-2-yl) ethanone. Herein we describe the first synthesis of 2-(chloromethyl)-6-hydroxy-2*H*-pyran-3 (6H)-one. This pyran derivative with multifunctionality is very important for further functionalization.

Results and Discussion

The importance of **4** as a building block for the synthesis of many biologically active compounds led us to explore a method for obtaining it in reasonable yield.

In our previous work, we described the enantioselective synthesis of 2-chloro-1-(furan-2-yl) ethanol[8]. In connection with this work, we aimed to carry out Achmatowicz rearrangement with 2-chloro-1-(furan-2-yl) ethanol. As an initial reaction (Scheme), chlorination of commercially available 1-(2-furyl)ethanone **1** with $(NH_4)_2Ce(NO_3)_6/CH_3COCl$[9] was performed to obtain the chloroketone **2**,[10] in 85% yield after purification by column chromatography. BH_3SMe_2 mediated reduction of **2** afforded **3** in 84% yield after purification. The reaction of **3** with tert-butyl-hydroperoxide in dichloromethane with NBS[11] and with m-chloroperbenzoic acid was performed to synthesize **4**. The best result was obtained from the reaction of **3** with m-chloroperbenzoic acid at 0 °C yielding **4** with 70% yield after purification by column chromatography. The target compound is identified by spectroscopic methods.



Reagents and conditions: a. CH_3COCl, CH_3CN,$(NH_4)_2Ce(NO_3)_6$, RT; **b.** $BH_3.SCH_3$, toluene, RT; **c.** m-CPBA, CH_2Cl_2, 0 °C.

Scheme

Conclusion

In summary, we reported herein the first efficient synthesis of 2-(chloromethyl)-6- hydroxy-2*H*-pyran-3 (6H)-one via the reaction of 2-chloro-1-(furan-2-yl)ethanol with m-CPBA in high yield.

Experimental

Materials and methods

NMR spectra were recorded on a Bruker DPX 400. Chemical shifts d are reported in ppm relative to $CHCl_3$ (^{1}H: δ = 7.27), $CDCl_3$ (^{13}C: δ = 77.0) and CCl_4 (^{13}C: δ = 96.4) as internal standards. Column chromatography was conducted on silica gel 60 (0.040-0.063 mm).

TLC was carried out on aluminum sheets pre-coated with silica gel 60F254 (Merck), and the spots were visualized with UV light (k = 254 nm).

The synthesis of 2-chloro-1-(furan-2-yl) ethanone 2.

Freshly distilled acetyl chloride (36.2 mmol, 2.82 g) was added to 1-(furan-2-yl)ethanone (36.2 mmol, 3.98 g) in acetonitrile (10 mL) under inert atmosphere. Ammonium ceric nitrate (1.78 mmol, 0.97 g) in acetonitrile (10 mL) was added to the mixture dropwise. After the completion of the reaction the organic layer was extracted with saturated $NaHCO_3$, water, and brine, and dried over $MgSO_4$. The crude product was purified by flash chromatography over silica (n-hexane/ethyl acetate, 3:1). The product **2** was obtained as a yellow oil in 85% yield (31 mmol, 4.46 g).

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 4.46 (s, 2H), 6.56 (m, 1H, C-4H furan), 7.22 (d, J= 3.6 Hz, 1H, C-3H, furan), 7.56 (m, 1H, C-5H, furan). ^{13}C-NMR ($CDCl_3$): 44.89, 112.64, 118.54, 147.06, 150.44, 179.69.

The synthesis of 2-chloro-1-(furan-2-yl) ethanol 3.

2-Chloro-1-(furan-2-yl) ethanone (3.312 mmol, 0.477 g) in 10 mL of toluene was added to $BH_3.SMe_2$ (2 M in THF, 3.312 mmol, 0.252 g) in 5 mL of toluene under inert atmosphere. The reaction mixture was stirred for 3 h at room temperature. When the reaction was over, saturated NH_4Cl solution was added and the organic layer was separated. The organic layer was extracted with water and brine and dried over $MgSO_4$. The crude product was purified by flash chromatography over silica (n-hexane/ethyl acetate, 3:1). The product, **3**, was obtained as a pale yellow oil in 84% yield (2.78 mmol, 0.4 g).

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.63 (broad s, 1H, OH), 3.71-3.81 (m, 2H), 4.88 (m, 1H), 6.3 (m, 2H), 7.32 (m, 1H). ^{13}C-NMR ($CDCl_3$): 47.62, 68.05, 107.55, 110.41, 142.55, 152.68.
MS: m/z 146 $(M)^+$, 144, 110, 96, 93, 81, 53.

The synthesis of 2-(chloromethyl)-6- hydroxy-2H-pyran-3 (6H)-one 4.

2-Chloro-1-(furan-2-yl)ethanol (1 mmol, 0.146 g) was added to the solution of m-CPBA (1 mmol, 0.172 g) in CH_2Cl_2 (1 mL) at 0 °C. The mixture was stirred for ca. 3 h at that temperature. After the reaction period, precipitated m-chlorobenzoic acid was filtered and the crude product was purified by flash chromatography over silica (n-hexane/ethyl acetate, 3:1). The product, **4**, was obtained as a colorless liquid in 70% yield (0.7 mmol, 0.114 g).

^{1}H-NMR (400 MHz, $CDCl_3$): δ= 2.09 (s, 1H, OH), 3.76 (dd, J= 12.8 Hz, 6.2 Hz, 1H), 3.85 (dd, J= 12.8 Hz, 2.6 Hz, 1H), 4.74 (dd, J= 6.2 Hz, 2.9 Hz, 1H), 5.67 (d, J= 3.46 Hz), 6.08 (d, J= 10.3 Hz, 1H), 6.83 (dd, J= 10.3 Hz, 3.5 Hz). ^{13}C-NMR ($CDCl_3$): 42.5, 87.8, 89.9, 127.5, 144.4, 196.5.
MS: m/z 163 $(M)^+$, 144, 95, 84.

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