IONIC HYDROGENATION OF 4-HYDROXYCOUMARIN DERIVATIVES

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Abstract

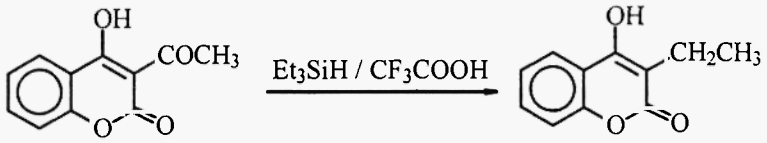
Ionic hydrogenation of 3-acetyl-4-hydroxycoumarin **1** and 3-aryl-1-(4-hydroxy-3-coumarinyl)-2-propen-1-ones **2**-**5** in CF_3COOH/ $HSiEt_3$ and BF_3:H_2O/ $HSiEt_3$ reducing systems is described.

Carbonyl compounds are known to undergo facile deoxygenation under ionic hydrogenation conditions, which involve addition of H^+ from a protic acid and H^- from a hydride ion source (1, 2). The most commonly ionic hydrogenation (I. H.) pair used for this purpose was developed by Kursanov and coworkers over three decades ago and utilized CF_3COOH as the acid and $HSiEt_3$ as the hydride donor (3). This reduction system is relatively stable under typical carbonyl hydrogenation conditions. However, for hydrogenation which occurs more slowly, the decomposition of $HSiEt_3$ by CF_3COOH might become a predominant reaction. Hence, several alternative I. H. pairs have been developed for this purpose (2, 4), boron trifluoride monohydrate – triethylsilane (5) being one of them. The latter ionic hydrogenation pair is able to hydrogenate a broader scope of organic molecules as evidenced by hydrogenation of aromatic compounds, thiophene derivatives, *etc.* (6, 7)

As a part of our interest in ionic hydrogenation of complex heterocyclic molecules (6, 7), in this paper we report on the novel application of CF_3COOH/ $HSiEt_3$ and BF_3:H_2O/ $HSiEt_3$ reducing systems in the reductive deoxygenation of 3-acetyl-4-hydroxycoumarin **1** and 3-aryl-1-(4-hydroxy-3-coumarinyl)-2-propen-1-ones **2** - **5**.

The ionic hydrogenations of the molecules **2** - **5** is of special interest due to the presence of conjugated C=C and C=O bonds. I. H. of such compounds could proceed by either 1,2- or 1,4-addition of hydrogen giving rise to the formation of propanone or propenol derivatives, respectively. The direction of hydrogenation depends strongly on the nature of substituents at the C1 and C3 atoms as well as on molar ratio of the substrate and the I. H. components. For instance, I. H. of a variety of chalcones in the CF_3COOH/ $HSiEt_3$ reducing system (1, 2, 8) resulted in exclusive hydrogenation of the C=C bond upon treatment with equimolar quantities of the I. H. components, whereas in the presence of an excess of the acid and $HSiEt_3$, these compounds yielded

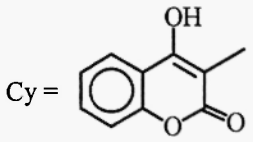
the aryl substituted propanes as single products (8). This, as shown below, differs considerably from the selectivity observed in our study.



1 **1S**

$$CyCOCH{=}CHAr \xrightarrow{[H^{\cdot}]\,/\,[H^{-}]} CyCH_2CH{=}CHAr + CyCH_2CH_2CH_2Ar$$

2, Ar = C_6H_5	**2U**, Ar = C_6H_5	**2S**, Ar = C_6H_5
3, Ar = *p*-$MeOC_6H_4$	—	**3S**, Ar = *p*-$MeOC_6H_4$
4, Ar = *p*-ClC_6H_4	**4U**, Ar = *p*-ClC_6H_4	**4S**, Ar = *p*-ClC_6H_4
5, Ar = *p*-$NO_2C_6H_4$	**5U**, Ar = *p*-$NO_2C_6H_4$	—



Scheme

For the first screening, we chose the reaction of **1** with the CF_3COOH/ $HSiEt_3$ reducing system. Stirring a mixture of **1** in an excess of the I. H. components (9) at room temperature for 6 h provided 3-ethyl-4-hydroxycomarin **1S** in 30% yield after quenching reaction with aqueous sodium carbonate, subsequent extraction with diethyl ether and evaporation of the solvent. The prolongation of the reaction time to 48 h, resulted in a slight yield improvement only (35%). However, when the reaction was carried out at 50 °C, the quantitative conversion of coumarin **1** into ethylbenzene was achieved within 18 hours (Table).

By applying the same reaction conditions to **2** - **5**, the conversion of the starting compound into a deoxygenated product was also attained, but it was substantially slower than that in the case of **1** (Table). Another interesting feature concerns the selectivity of the reduction process. Namely, by the reduction of chalcone analogues **2**, **4** and **5**, double bond within the cynnamoyl group remains intact, whereas the reduction of compound **3** results in the reduction of carbonyl group and the double bond. Preferential formation of the

unsaturated product during the reduction of **2**, **4** and **5** indicates that the reaction of these compounds most likely proceeds through the formation of α,β-unsaturated alcohol as an intermediate product, which is subsequently reduced *via* formation of the corresponding allylic carbocation. Assuming the same mechanism for 1. H. of **3**, we conclude that the primarily formed α,β-unsaturated product **3U** undergoes further hydrogenation through an intermediation of the corresponding benzyl cation, the formation of which is facilitated owing to a strong electron donating ability of methoxy group in the *para*-position of aromatic ring in cinnamoyl part of the molecule (10).

Table. Reduction of Compounds **1** - **5** with CF_3COOH/ $HSiEt_3$ (I) and $BF_3{:}H_2O$/ $HSiEt_3$ (II).[a]Molar ratio of substrate : acid : Et_3SiH = 1 : 15 : 10

Starting compd.	Hydrogenation product[c]	Reducing system	Time/temp./conv.[b] h/ °C/ %
1	**1S**	I	6/ r.t./ 30
1	**1S**	I	18/ 50
2	**2U**	I	6/ 50/ 70
2	**2U**	I	80/ 50
2	**2U**	II	6/ r.t./ 90
2	**2S**	II	60/ r.t.
3	**3S**	I	240/ 50
3	**3S**	II	60/ r.t.
4	**4U**	I	240/ 50
4	**4U**(75%)+**4S** (25%)[d]	II	60/ r.t.
5	**5U**	I	240/ 50

[(a)]In each of the cases, quantitative conversion of starting base into hydrogenated product, except where indicated[(b)], was achieved. Yields were determined by ^{1}H NMR spectroscopy from the crude product mixture; [(c)]Satisfactory spectral (IR and NMR) data were obtained for all compounds; [(d)]Composition of the product mixture as determined by ^{1}H NMR and g. c. spectrometry.

We next examined the reduction of chalcone analogoues **2** - **5** in $BF_3{:}H_2O$/ $HSiEt_3$. In each of the cases, the complete conversion of starting propenones into hydrogenated product was achieved in a period of time significantly shorter than in the former reaction (Table). Moreover, the reaction proceeds at room temperature,

the procedure is easy to perform and no special handling technique is required. It should be also noted that the BF_3:H_2O/ $HSiEt_3$ reducing system facilitates the reduction of both C=O and C=C groups within the cinamoyl fragment. However, the extent of reduction could be controlled by reaction time. For instance, after 6 hours when the reduction of **2** was stopped, a deoxygenated product was isolated only, whereas the prolongation of the reaction time to 60 h resulted in the formation of a fully reduced product. This strongly suggests that I. H. of the considered chalcone analogues in BF_3:H_2O/ $HSiEt_3$ follows the same mechanism as in CF_3COOH/ $HSiEt_3$.

Finally, it should be mentioned that in none of the reducing agents the hydrogenation of a coumarin ring was observed. This was further corroborated by some attempts to reduce the parent 4-hydroxycoumarin, which also turned out to be unsuccessful.

To conclude, we have found that 3-acetyl-4-hydroxycoumarin, which is easy to access synthetically, undergoes facile deoxygenation under ionic hydrogenation conditions. We have also shown that the same method could be used for obtaining the 3-arylalkyl- and 3-arylalkenyl-4-hydroxycoumarin derivatives if started from the corresponding derivatives. Finally, the present work demonstrates that efficacy and selectivity of the reduction could be controlled by the ionic hydrogenation pair used.

Starting compounds were prepared and purified according to the procedures described earlier (11). Boron trifluoride monohydrate was obtained by bubbling BF_3 into ice-cooled water (5). Et_3SiH was reagent 99% grade and used with no further purification. The purity of the starting compounds and identification of products was accomplished by ^1H and ^{13}C NMR (Varian-Gemini, Model 300, solvent $CDCl_3$, acetone-d_6 or DMSO-d_6, internal reference tetramethylsilane) and IR spectrometry (Perkin Elmer, Model 297). The hydrogenation experiments were performed by using 15 M excess of the acid and 10 M excess of Et_3SiH. The ionic hydrogenation experiments were performed according to the procedures outlined below.

Ionic hydrogenation of 1 in CF_3COOH/ $HSiEt_3$

Triethylsilane (1.6 ml) was added dropwise to a flask containing 1 mmol of **1** (206 mg) and 1.2 ml of trifluoracetic acid cooled to 0 °C. After completing the addition, the mixture was stirred at 50 °C for 18 h, then concentrated *in vacuo*, the residue dissolved in CH_2Cl_2 and washed with a saturated solution of sodium carbonate (twice) and water (twice). After drying with magnesium sulfate, the solvent was evaporated in rotatory evaporator to leave ca. 200 mg of the crude product which according to ^1H NMR analysis contained ca. 90% of **1S**. Purification of the crude product was accomplished by column chromatography on silica gel using dichloromethane as eluent. The mp and IR data of **1S** were identical with those reported (12); ^1H NMR ($CDCl_3$) δ 1.12 (t, 3H), 2.53-2.78 (q, 2H), 7.21-7.98 (m, 4H).

Reductions of **2** - **5** were performed following the same procedure. In each case the ratio of the hydrogenated/starting compound (Table) was worked out from an unseparated reaction mixture by employing ^1H NMR spectroscopy. The selected spectroscopic data of the so obtained hydrogenation products are as

follows: **2U**: IR (KBr, cm^{-1}) 2940, 1710, 1630, 1610. ^1H NMR ($CDCl_3$) δ 2.63-2.77 (q, 2 H), 5.18 (d, 1 H), 5.28 (d, 1 H), 7.32-7.84 (m, 9 H). ^{13}C NMR (CD_3COCD_3) δ 28.73, 79.38, 101.53, 115.89, 116.41, 122.41, 123.93, 126.15, 126.20, 126.25, 128.39, 128.40, 128.45, 131.47, 131.62, 140.44, 152.66, 159.31, 161.80. **3S** (Anal. calcd. for $C_{19}H_{18}O_4$: C 73.53; H 5.85; Found: C 73.64; H 6.00 %): ^1H NMR ($CDCl_3$) δ 1.82-1.90 (t, 2 H), 2.54-2.76 (m, 4 H), 6.95 - 7.72 (m, 8 H). ^{13}C NMR (DMSO-d_6) δ 23.82, 30.40, 34.59, 48.87, 105.36, 113.83, 116.26, 116.65, 123.36, 123.93, 129.35, 131.61, 134.31, 152.20, 157.68, 160.21, 163.37. **4U**: IR (KBr, cm^{-1}) 2940, 1710, 1640. ^1H NMR ($CDCl_3$) δ 2.64-2.78 (q, 2 H), 5. 18 (d, 1 H), 5.26 (d, 1 H), 7.24 - 7.83 (m, 8 H). **5U**: 2.67 - 2.81 (m, 2 H), 5.21 (d, 1 H), 5.33 (d, 1 H), 7.21 - 8.36 (m, 8 H). Compounds **2U** and **5U** were described previously (13).

Typical Procedure for Ionic Hydrogenation in BF_3-H_2O

The starting compound (1.0 mmol) dissolved in 3 ml of CH_2Cl_2 was added dropwise to a flask containing BF_3-H_2O (15 mmol) at 0 °C. After completing the addition, the mixture was stirred for 10 - 15 min, allowed to warm up to room temperature, and then triethylsilane (10 mmol) was added. The reaction mixture was stirred at room temperature for the time indicated in the Table, neutralized by cold saturated aqueous Na_2CO_3 solution and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were washed with water (2 x 15 ml), dried ($MgSO_4$) and evaporated in a rotatory evaporator to leave the crude product which was analyzed by NMR spectroscopy. In some cases an additional purification of the crude product was accomplished by column chromatography on silica gel using pentane or CH_2Cl_2 as an eluent.

All so obtained hydrogenation products have been fully characterized by ^1H NMR and IR spectra. The spectroscopic data of **2U**, **3S** and **4U** (conversion yields are indicated in Table) are given above. The relevant data for **2S** (14) are as follows: IR (KBr, cm^{-1}) 3150, 3150, 2950, 1680, 1620.^1H NMR ($CDCl_3$) δ 1.89 - 2.10 (m, 2 H), 2.53 - 2.82 (m, 4 H), 7.11 - 7.87 (m, 9 H).

Acknowledgement

This work was supported by the Ministry of Science and Technology of the Republic of Croatia through the projects Nos. 00980801 and 058102.

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(9) All ionic hydrogenation experiments in the present study were performed in the presence of large excess of the acidic and hydride donor components, thus allowing hydrogenation of both unsaturated groups within the cynnamoyl fragment in **2** - **5**.

(10) It should be, however, noted that an alternative mechanism which involves 1,4-addition of hydrogen and subsequent I. H. of the so-formed saturated ketone could also account for the exclusive formation of **3S**.

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Received on October 18, 1999