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Regioselective Heterocyclization of 3-(Cyclohex-2′-enyl)-4-hydroxy-6-methylpyran-2-one

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Summary. Regioselective heterocyclization of 3-(cyclohex-2′-enyl)-4-hydroxy-6-methyl pyran-2-one with various reagents afforded different heterocycles. With *N*-iodosuccinimide in acetonitrile at 0–5°C it gave 6-methyl-9′-iodo-2′-oxabicyclo[3.3.1]nonano[3,2-*c*]pyran-2-one, with $C_5H_5NHBr_3$ or $C_6H_{12}N_4HBr_3$ in $CHCl_3$ at 0–5°C it furnished 6-methyl-9′-bromo-2′-oxabicyclo[3.3.1]nonano[3,2-*c*]pyran-2-one. Cold concentrated H_2SO_4 lead to 6-methyl-2′-oxabicyclo[3.3.1]nonano[3,2-*c*]pyran-2-one, whereas $PdCl_2(PhCN)_2$ in C_6H_6 at 80°C afforded 9-methyl benzofuro[3,2-*c*]pyran-2-one.

Keywords. Pyridine hydrotribromide; *N*-Iodosuccinimide; Palladium chloride bisbenzonitrile; Heterocycles; Cyclization.

Introduction

4-Hydroxy-6-methylpyran-2-one (**1**) is a natural product of polyketide origin [1]. Many natural products containing the fundamental skeleton of 4-hydroxy- or 4-methoxy-6-methyl-2-pyrone have been isolated, some of them carrying biogenetically plausible groups at C-3 or C-5 or both. Elasnin, isolated from *Streptomyces*, is a specific inhibitor of human leucocyte elastase [2]. As a logical extension, many pyrones structurally related to elasnin have been synthesized, and their biological activity has been tested [3]. In continuation of our work on the synthesis of bioactive heterocycles [4] by application of [3,3]-sigmatropic rearrangements [5] we became interested in the synthesis of heterocycles derived from **1** [6, 7]. Presently, we report our results on the regioselective cyclization of 3-(cyclohex-2′-enyl)-4-hydroxy-6-methylpyran-2-one (**4**) with a variety of reagents.

Results and Discussion

The starting material for this investigation (**4**) was obtained by thermal [3,3]-sigmatropic rearrangement of 4-(cyclohex-2′-enyloxy)-6-methylpyran-2-one (**3**) in refluxing xylene as an extension of our study of *Claisen* rearrangements. **3** in turn was prepared by the reaction of **1** with 3-bromocyclohexene (**2**) in refluxing acetone in

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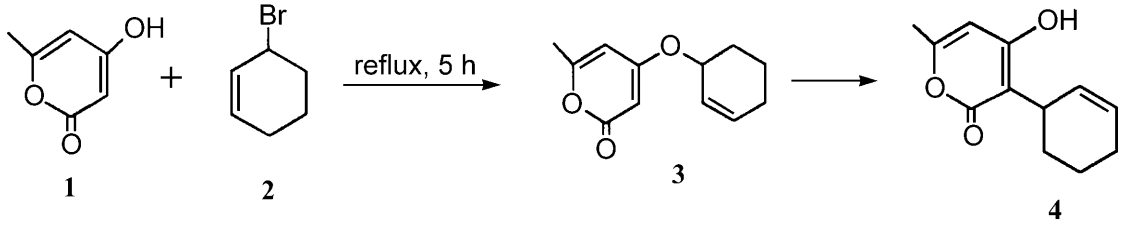


1 2 3 4

Scheme 1

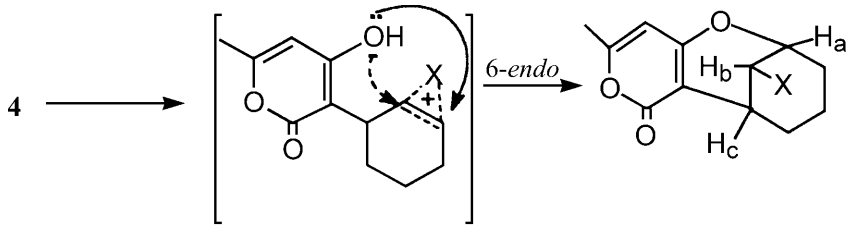
the presence of anhydrous potassium carbonate (Scheme 1). *Manas et al.* have reported [8] the preparation of **4** from **1** and cyclohex-2-enyl acetate in the presence of Pd(*acac*)$_2$ and Ph_3P exploiting thermodynamically controlled conditions.

Compound **3** was characterized from by elemental analysis and spectroscopic data; compound **4** had an identical ^{1}H NMR spectroscopic pattern and melting point to those of the compound prepared by *Manas et al.* [8].

The present investigation involves heterocyclization of **4** to the construction of the pyran or furan ring in the resulting heterocycles. To achieve this goal, four different approaches were considered: (*i*) reaction of **4** with *N*-iodosuccinimide, (*ii*) reaction of **4** with pyridine hydrotribromide and hexamine hydrotribromide, (*iii*) acid-catalyzed cyclization of **4**, and (*iv*) $PdCl_2(PhCN)_2$ mediated intramolecular oxidative cyclization of **4**.

4 was treated with *N*-iodosuccinimide in acetonitrile at 0–5°C for 1 h to furnish **6a** in 80% yield (Scheme 2). **6a** was characterized by elemental analysis and spectroscopic data. The ^{1}H NMR spectrum of **6** showed three protons (3.43–3.50 ppm, H_c; 4.25–4.33 ppm, H_a; 5.05–5.10 ppm, H_b). H_a appeared as an eight-line multiplet (ddd, $J = 10$, 6.9, and 4.5 Hz), H_b as a triplet which upon expansion revealed a doublet of doublets with J values of 6.9 and 6.7 Hz, and H_c as a doublet of triplets with J values of 6.8 and 6.7 Hz. The proton assignments were deduced from a COSY spectrum and proton decoupling experiments. A *Dreiding* model of **6a** could be constructed by 1,3-fusion of the pyran ring in the half-chair conformation with the cyclohexane ring in the chair conformation (distorted) as shown in Fig. 1. However, the coupling constant of 10 Hz found for H_a cannot be explained if **6a** attains this conformation. An alternative model can be constructed by 1,3-fusion of the pyran ring in the half-chair form with the cyclohexane ring in the boat (distorted) form (Fig. 2) which is in accordance with the above coupling information. It may be noted that bicyclo[3.3.1]nonane is known to prevail in the chair-boat conformation [9]. The bicyclic nature of **6a** is reflected in its reluctance to undergo any change in refluxing diphenyl ether containing palladium on charcoal as well as in refluxing xylene in the presence of *DDQ*. Treatment of **4** with pyridinium hydrotribromide [10] in chloroform at 0–5°C for 1 h afforded **6b** which was characterized by its elemental analysis and spectroscopic data. It was assigned the structure shown in Scheme 2 by reasoning similar to that followed for **6a**. The use of hexamine hydrotribromide [11] instead of pyridinium hydrotribromide gave the same result.

Acid catalysis has been used to generate pyran and furan rings from 2-allyl enols [12, 13]. Treatment of **4** with cold concentrated sulfuric acid gave the bicyclic compound **6c** in 66% yield (Scheme 2). Its ^{1}H NMR spectrum displayed two broad singlets at 3.26 and 4.84 ppm due to the ring juncture protons; the residual

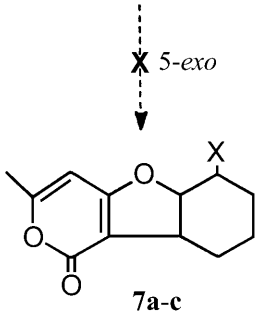


5a-c

a: $X = I$
b: $X = Br$
c: $X = H$

6a-c

a: $X = I$
b: $X = Br$
c: $X = H$



7a-c

a: $X = I$
b: $X = Br$
c: $X = H$

Scheme 2

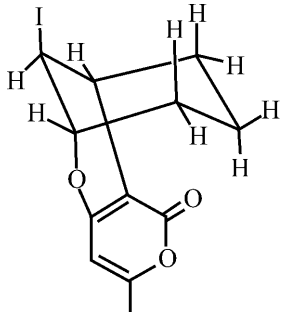


Fig. 1. Chair conformation of **6a**

six protons of the cyclohexane ring appeared at 1.40–1.47 (1H), 1.59–1.65 (3H), 2.11–2.13 (1H), and 1.84 (3H) ppm as three multiplets and one broad singlet, respectively. Compound **6c** resisted dehydrogenation in refluxing diphenyl ether containing palladium on charcoal or in refluxing xylene containing *DDQ*.

Palladium chloride bisbenzonitrile ($PdCl_2(PhCN)_2$) and palladium chloride bisacetonitrile ($PdCl_2(MeCN)_2$) have been successfully employed in the synthesis of benzofurans [14] and indoles [15] from the sodium salts of 2-allyl phenols and 2-allylanilines. Recently, our group has reported a facile synthesis of a linearly

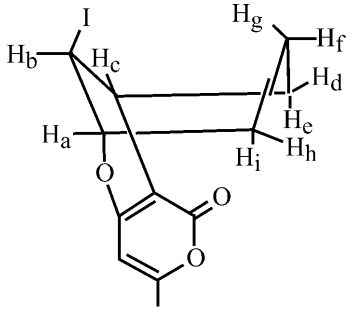
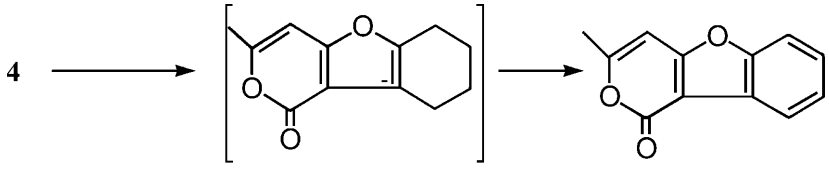


Fig. 2. Boat conformation of **6a**



8 **9**

Scheme 3

fused pyrimidine-annealated heterocycle from 6-(cyclohex-2′-enyl)-5-hydroxy-1,3-dimethyluracil by treatment with the above reagent [16]. These results prompted us to treat a suspension of **4** in thiophene-free dry benzene with $PdCl_2(PhCN)_2$ at room temperature in the presence of $NaOCH_3$, followed by refluxing the reaction mixture for 6 h. The isolated product (**9**) may result from dehydrogenation of the incipient intermediate **8** (not isolated) by the initially deposited palladium (Scheme 3).

Recently there has been interest in the intramolecular epoxidation of suitably substituted alkenes in the context of the synthesis of various furo [17] and pyrano [18] compounds. The cyclization of **4** was therefore also attempted with *m*-chloroperoxybenzoic acid in dry thiophene-free benzene; however, no tractable products were obtained.

In conclusion, **4** was regioselectively cyclized under different conditions to achieve different polyheterocycles in appreciable yields. Only in one case a furo derivative was obtained by a 5-*exo* cyclization; in the other cases, bicyclic pyran derivatives were produced by 6-*endo* cyclization.

Experimental

Melting points were measured on a H_2SO_4 bath and are uncorrected. UV spectra (EtOH) were recorded on a Hitachi 200–20 spectrophotometer. IR spectra were run on KBr disks on a Perkin-Elmer 1330 apparatus. ^1H NMR spectra were determined for solutions in $CDCl_3$ with *TMS* as internal standard on Bruker AC-250 (300 MHz) and Bruker DRX-500 (500 MHz) NMR spectrometers. Elemental analyses in accordance with the calculated values. Mass spectra were carried out by RSIC (CDRI) Lucknow on a JEOL D-300 (El) instrument. Silica gel (60–120 mesh, Spectrochem, India) was used for chromatographic separation. Petroleum ether refers to the fraction boiling between 60 and 80°C.

4-(Cyclohex-2′-enyloxy)-6-methyl-2-one (**3**; $C_{12}H_{14}O_3$)

A mixture of 1.26 g 4-hydroxy-6-methylpyran-2-one (10 mmol), 1.6 g 3-bromocycloxene (10 mmol), and 3 g anhydrous K_2CO_3 was refluxed in 100 cm^3 dry acetone for 5 h. The reaction mixture was cooled and filtered. The solvent was distilled off, and the residual mass was chromatographed over silica gel. Elution of the column with benzene:ethyl acetate = 9:1 gave compound **3** as a transparent sticky liquid.

Yield: 1.1 g (55%); ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.43–2.28 (m, 6H), 2.21 (s, 3H, C-6-CH_3), 4.74–4.78 (m, 1H, C_1-H), 5.47 (s, 1H, C_3-H), 5.76 (s, 1H, C_5-H), 5.81–6.26 (m, 2H, C_2-H, C_3-H) ppm; IR (KBr): ν = 1700, 1540, 1480, 1230 cm^{-1}; UV/Vis (EtOH): λ_{max} = 216, 277 nm; MS: m/z = 206 (M^+).

3-(Cyclohex-2′-enyl)-4-hydroxy-6-methylpyran-2-one (**4**)

A solution of 1 g (5 mmol) **3** in 3 cm^3 xylene was refluxed for 17 h. A solid was obtained after cooling the reaction mixture; this was separated by filtration and purified by recrystallization from an acetone/petroleum ether mixture (yield: 65%). The obtained compound was shown to be **4** by comparison of its physical data with those of an authentic sample [8].

6-Methyl-9′-iodo-2′-oxabicyclo[3.3.1]nonano[3,2-c]pyran-2-one (**6a**; $C_{12}H_{13}IO_3$)

A solution of 0.2 g (1 mmol) **4** in 50 cm^3 dry CH_3CN was stirred at 0–5°C with 0.23 g (1 mmol) solid *N*-iodosuccinimide for 1 h. The solvent was distilled off, and the residual mass was dissolved in 50 cm^3 $CHCl_3$. The organic phase was washed with 20 cm^3 saturated Na_2SO_3 solution, twice with 20 cm^3 H_2O, and dried (Na_2SO_4). Removal of $CHCl_3$ gave a gummy residue which was purified by column chromatography over silica gel. Elution of the column with benzene:ethyl acetate = 9:1 gave raw **6a** which was recrystallized from a $CHCl_3$/petroleum ether mixture.

Yield: 0.25 g (80%); white solid; m.p.: 129–130°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 1.45–1.69 (m, H_g, H_i), 1.92–2.06 (m, H_d, H_e, H_f), 2.10–2.20 (m, H_h), 2.26 (s, 3H, C_6-CH_3), 3.43–3.50 (dt, J = 6.8 and 6.7 Hz, H_c), 4.25–4.33 (ddd, J = 10, 6.9, and 4.5 Hz, H_a), 5.05–5.10 (dd, J = 6.9 and 6.7 Hz, H_b), 5.97 (s, 1H) ppm; IR (KBr): ν = 1100, 1200, 1240, 1400, 1560, 1690 cm^{-1}; UV/Vis (EtOH): λ_{max} = 211, 297 nm; MS: m/z = 332 (M^+).

6-Methyl-9′-bromo-2′-oxabicyclo[3.3.1]nonano[3,2-c]pyran-2-one (**6b**; $C_{12}H_{13}BrO_3$)

A solution of 0.2 g (1 mmol) **4** in 100 cm^3 $CHCl_3$ was stirred with 0.32 g (1 mmol) solid pyridinium hydrotribromide [19] or 0.38 g (1 mmol) hexamine hydrotribromide [20] at 0–5°C for 1 h or 40 min, respectively. The $CHCl_3$ solution was washed twice with 10 cm^3 5% Na_2CO_3 solution, twice with 25 cm^3 H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ left a gummy residue which was purified by column chromatography over silica gel. Compound **9** was obtained when the column was eluted with benzene:ethyl-acetate = 4:1. The material was then recrystallized from a $CHCl_3$/petroleum ether mixture.

Yield: 0.2 g (72%); white solid; m.p.: 88–89°C; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.53–1.60 (m, H_g), 1.70–1.75 (m, H_i), 1.87–1.94 (m, H_e), 1.99–2.03 (q, J = 6.5 Hz, H_d, H_f), 2.14–2.20 (m, H_h), 2.25 (s, 3H, C_6-CH_3), 3.60–3.64 (dt, J = 6.6 and 6.4 Hz, H_c), 4.26–4.30 (ddd, J = 10, 6.7, and 4.5 Hz, H_a), 4.96–4.99 (dd, J = 6.7 and 6.4 Hz, H_b), 5.96 (s, 1H) ppm; IR (KBr): ν = 1110, 1270, 1430, 1580, 1670 cm^{-1}; UV/Vis (EtOH): λ_{max} = 211, 281 nm; MS: m/z = 284, 286 (M^+).

6-Methyl-2′-oxabicyclo[3.3.1]nonano[3,2-c]pyran-2-one (**6c**; $C_{12}H_{14}O_3$)

Compound **4** (0.1 g, 0.5 mmol) was added in portions to 2 cm^3 concentrated H_2SO_4 at 0–5°C, and the mixture was stirred for 2 h at this temperature. The solution was then poured into crushed ice and

extracted with $CHCl_3$. The $CHCl_3$ layer was washed with $3\times10\,cm^3$ 5% Na_2CO_3 solution, then with $3\times20\,cm^3$ H_2O, and dried (Na_2SO_4). Evaporation of $CHCl_3$ gave a gummy residue which was purified by column chromatography over silica gel. Elution with benzene:ethyl acetate = 3:1 gave **6c** which was recrystallized from a $CHCl_3$/petroleum ether mixture.

Yield: 0.066 g (66%); white solid; m.p.: 104–105°C; ^{1}H NMR ($CDCl_3$, δ, 500 MHz): 1.40–1.47 (m, 1H), 1.59–1.65 (m, 3H), 1.84 (br s, 3H), 2.11–2.13 (m, 1H), 2.23 (s, 3H, C_6-CH_3), 3.26 (br s, 1H), 4.84 (br s, 1H), 5.98 (s, 1H) ppm; IR (KBr): $\nu = 1140$, 1230, 1570, 1670 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 210$, 260 nm; MS: $m/z = 206$ (M^+).

9-Methyl-benzofuro[3,2-c]pyran-2-one (**9**; $C_{12}H_8O_3$)

A suspension of 0.2 g (1 mmol) **4** in $50\,cm^3$ dry thiophene-free benzene was treated with 0.38 g (1 mmol) $PdCl_2(PhCN)_2$ in presence of 0.055 g (1 mmol) $NaOCH_3$ at room temperature. The mixture was then refluxed for 6 h. Benzene was distilled off, and the residual mass was extracted with $50\,cm^3$ acetone. Evaporation of acetone left a white solid which was purified by column chromatography over silica gel using benzene:ethyl acetate = 3:1 as eluent.

Yield: 0.11 g (58%); white solid; m.p.: 226–228°C; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 2.27 (s, 3H, C_9-CH_3), 5.99 (s, 1H, C_8-H), 7.36–7.50 (m, 4H) ppm; IR (KBr): $\nu = 1180$, 1350, 1400, 1580, 1650 cm^{-1}; UV/Vis (EtOH): $\lambda_{max} = 211$, 299 nm; MS: $m/z = 200$ (M^+).

Attempted aromatization of **6a–c**

0.068 g (0.2 mmol) **6a**, 0.062 g (0.3 mmol) **6b**, or 0.060 g (0.2 mmol) **6c** were refluxed with 0.020 g Pd–C in $2\,cm^3$ diphenyl ether or with 0.020 g *DDQ* in $5\,cm^3$ xylene for 2 h. The isolated products were shown to be identical with the starting compounds in each case.

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