ISSN 1070-4280, Russian Journal of Organic Chemistry, 2018, Vol. 54, No. 7, pp. 1031–1034. © Pleiades Publishing, Ltd., 2018.
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Substituted Butanolides and Butenolides: XVII.* Substituted 3-(Furan-2-ylmethylidene)furan-2(3*H*)-ones and 3-(Furan-2-ylmethylidene)dihydrofuran-2(3*H*)-ones

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Received December 29, 2017

Abstract—A number of furan-2-ylmethylidene-substituted lactones were synthesized by condensation of 5-alkylfuran-2(3*H*)-ones and 4-alkyldihydrofuran-2(3*H*)-ones with 5-substituted furan-2-carbaldehydes. The reactivity of furan-2(3*H*)-ones was higher than that of furan-2(5*H*)-ones due to formation of intermediate conjugated anion. The condensation of 4-alkyldihydrofuran-2(3*H*)-ones with furan-2-carbaldehydes required more severe conditions than the condensation with furan-2(3*H*)-ones. The substituent in the furan ring affects the reaction time and yield.

DOI: 10.1134/S1070428018070102

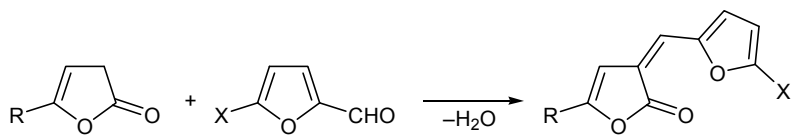
While developing concepts of the condensation of furan-2-ones and dihydrofuran-2-ones with carbonyl compounds, we studied reactions of 5-alkylfuran-2(3*H*)-ones and 4-alkyldihydrofuran-2(3*H*)-ones with 5-substituted furan-2-carbaldehydes with the goal of finding out peculiar features of the condensation of lactones differing from furan-2(5*H*)-one by the position or presence of C=C double bond in the lactone ring. We obtained new ylidene-substituted lactones that are promising as potential biologically active compounds and intermediate products for organic synthesis. We previously reported the synthesis of 5-[aryl-(hetaryl)methylidene]furan-2(5*H*)-ones on the basis of unsub-stituted furan-2(5*H*)-one [2, 3].

The reactions of a number of aromatic aldehydes and furancarbaldehydes with alkyl- and arylfuran-2-ones were carried out in benzene on heating in the presence of sodium acetate or triethanolamine as catalyst [4]. Among furancarbaldehydes, furfural and its 5-iodo and 5-nitro derivatives were used.

In order to exclude the use of toxic benzene, simplify the reaction conditions, and obtain new 5-alkyl-3-(furan-2-ylmethylidene)furan-2(3*H*)-ones, 5-alkylfuran-2(3*H*)-ones **1** and **2** were brought into condensation with substituted furan-2-carbaldehydes **3a**–**3h** in ethanol at room temperature in the presence of piperidine as catalyst (Scheme 1). In all cases, the initial lactone was taken in excess, the ratio furan-2(3*H*)-one–aldehyde–catalyst being 1 : 0.5 : 0.25.

The reaction time and yield did not depend on the nature of alkyl substituent in the lactone ring but depended on the substituent in the furan ring of **3**. The reactions of **1** and **2** with 5-arylfurancarbaldehydes required a longer time than with furfural and its 5-alkyl

Scheme 1.



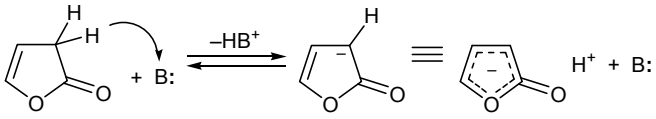
1, **2** **3a**–**3h** **4a**–**4d**, **5a**–**5d**

1, R = Me; **2**, R = Bu; **3**, X = H (**a**), Me (**b**), Cl (**c**), Br (**d**), Ph (**e**), 4-MeC_6H_4 (**f**), 4-BrC_6H_4 (**g**), 4-$O_2NC_6H_5$ (**h**); **4**, R = Me, X = H (**a**), Me (**b**), Cl (**c**), Br (**d**); **5**, R = Bu, X = Ph (**a**), 4-MeC_6H_4 (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**).

* For communication XVI, see [1].

and 5-halo derivatives. Electron-donating substituents in both furan and benzene rings accelerated the reaction and increased the yield of the condensation products. Electron-withdrawing nitro group in aldehyde **3h** appreciably inhibited the reaction, and the yield of **5d** was lower than the yields of **5a** and **5b**. Analogous substituent effects were observed in the reactions of furan- and 5-arylfuran-2-carbaldehydes with furan-2(5*H*)-ones [2]. However, in the latter case the yields of ylidene derivatives having no aryl substituent in the 5-position were considerably lower than in the reactions with furan-2(3*H*)-ones. The higher reactivity of furan-2(3*H*)-ones can be rationalized by higher acidity of the 2-H proton therein due to direct electron-withdrawing effect of the neighboring C=C double bond and oxo group which is a stronger electron acceptor than the carbonyl oxygen atom in furan-2(5*H*)-one. As a result, conjugation-stabilized anion **A** is generated from furan-2(3*H*)-ones more readily than from furan-2(5*H*)-one (Scheme 2). Intermediate formation of conjugated anion is followed from the unusual path of the reaction of furan-2(5*H*)-one with cyclic tertiary enamines [5].

Scheme 2.



A

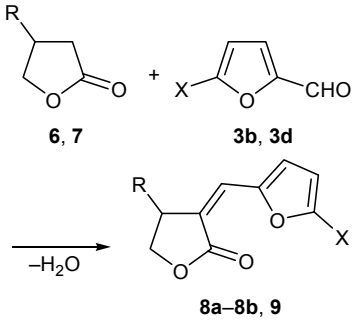
The anion acts as nucleophile toward the carbonyl group of furancarbaldehydes. The adduct thus formed loses water molecule to produce 3-(furan-2-ylmethylidene)furan-2(3*H*)-ones **4a**–**4d** and **5a**–**5d**, which is energetically favorable due to formation of a conjugation system comprising the entire molecule.

Taking the aforesaid into account, it became possible to explain why neither furan-2(5*H*)-ones nor furan-2(3*H*)-ones reacted with aliphatic and alicyclic aldehydes under the conditions of facile condensation with furancarbaldehydes.

An indirect support of the proposed mechanism is provided by comparison of the above discussed reactions of furan-2(5*H*)-ones and furan-2(3*H*)-ones with the condensation of 4-substituted tetrahydrofuran-2-ones with furancarbaldehydes (Scheme 3).

Anion **A** could not be generated in the reaction with dihydrofuran-2(3*H*)-ones, and the conjugation system of 3-(furan-2-ylmethylidene)dihydrofuran-2(3*H*)-ones **8a**, **8b**, and **9** does not include the lactone ring. Therefore, the condensation of furancarbaldehydes **3b** and

Scheme 3.



6, **7** **3b**, **3d**

8a–8b, **9**

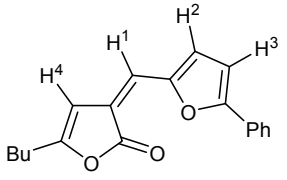
6, R = *cyclo*-C_6H_{11}; **7**, R = $PhCH_2$; **8**, R = *cyclo*-C_6H_{11}, X = Me (**a**), Br (**b**); **9**, R = $PhCH_2$, X = Me.

3d with alkyldihydrofuran-2(3*H*)-ones **6** and **7** required more severe conditions and longer reaction time. The reaction occurred on heating to 70°C in the presence of a strong base (sodium ethoxide).

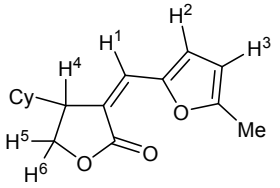
All the synthesized compounds are yellow or orange crystalline solids, readily soluble in chloroform, benzene, toluene, acetone, and boiling ethanol, poorly soluble in diethyl ether, and insoluble in water. Their electronic absorption spectra displayed the main maximum at λ 330–450 nm and lower maxima at λ 240–290 nm. The UV absorption maxima of butanolides **8** and **9** with a saturated lactone ring were observed at shorter wavelengths ($\Delta\lambda_{max} \leq 50$ nm) than those of analogous ylidenefuran-2(3*H*)-ones **4** and **5**. The reason is that the double bond in the lactone ring of **4** and **5** is included in the common conjugation system. This is consistent with the fact that in the UV spectra of aryl-3-(furan-2-ylmethylidene)furan-2(5H)-ones [2], in which the conjugation system is more even than in isomeric (furan-2-ylmethylidene)furan-2(3*H*)-ones, longwave shift of the absorption maximum was observed.

The IR spectra of compounds **4**, **5**, **8**, and **9** showed an absorption band at 1740–1780 cm^{-1}, which is typical of C=O stretching vibrations of lactones. This band was not split as in the spectra of ylidenefuran-2(5*H*)-ones, in which the carbonyl group is conjugated with the C=C double bond. The $\nu_{C=O}$ frequency of saturated lactones **8** and **9** is lower than that of compounds **4** and **5** having an endocyclic double bond conjugated with the carbonyl group. In addition, absorption bands at 1630–1665 (νC=C), 1215–1230, 1100–1125, and 1160–1190 cm^{-1} (νC–O–C, νC–O, lactone) were present in the IR spectra of **4**, **5**, **8**, and **9**, as well as bands belonging to vibrations of C–O–C groups and C–H bonds of the furan and benzene rings (3100–3140, 1010–1025, 1030–1080, 750–760 cm^{-1}). The structure of compounds **4**, **5**, **8**, and **9** was also con-

firmed by ^{1}H NMR spectra; as examples, the spectra of **5a** and **8a** are considered below.



5a



8a

Protons on the double-bonded carbon atom in unsaturated lactones resonate in a fairly narrow range, δ 6.6–7.4 ppm. The 1-H signal (as most deshielded) is located in a weaker field, signals from protons in the furan and benzene rings appear in their usual positions. The butyl substituent in the lactone ring of **5a** gave signals in the region δ 0.90–3.65 ppm (a complex multiplet). The 1-H proton of **8** and **9** resonated almost in the same region as the corresponding proton of **4** and **5**. The 4-H proton is coupled with 5-H and 6-H, and its signal is shifted significantly upfield relative to the 4-H signal of unsaturated lactones. The 5-H and 6-H signals of **8** and **9** constitute the *AB* part of *ABX* spin system (where *X* is 4-H) typical of 3-substituted butanolides. Protons of the methyl group in the furan ring appear at δ 2.35 ppm.

The condensation products of substituted butenolides and butanolides with furancarbaldehydes contain highly reactive lactone and furan rings and are promising as intermediate products for synthetic organic chemistry and potentially biologically active compounds.

EXPERIMENTAL

The UV spectra were measured on a Specord UV-Vis spectrophotometer from solutions in ethanol with a concentration of 10^{-5} M. The IR spectra were recorded on a Specord UR-20 spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were taken on Bruker WM-250 and AC-300 spectrometers at 250 and 300 MHz, respectively, using $CDCl_3$ as solvent and tetramethylsilane as internal standard.

5-Butylfuran-2(3*H*)-one [6], 4-cyclohexyl- and 4-benzyldihydrofuran-2(3*H*)-ones [7], and 5-arylfuran-2-carbaldehydes [8] were synthesized according to known procedures.

Condensation of 5-alkylfuran-2(3*H*)-ones 1 and 2 and 4-substituted dihydrofuran-2(3*H*)-ones 6 and 7 with furancarbaldehydes (*general procedure*). *a*. Piperidine, 0.0025 mol, was added to a solution of 0.01 mol of 5-alkylfuran-2(3*H*)-one **1** or **2** in 25 mL of ethanol, and 0.005 mol of furancarbaldehyde **3** was then added with stirring. The mixture was stirred for 1 h at room temperature and was then kept in a refrigerator for crystallization. The precipitate was filtered off, the mother liquor was evaporated by half, and the residue was kept in a refrigerator to obtain an additional amount of the product. The product was recrystallized from ethanol.

b. A solution of 0.01 mol of dihydrofuran-2(3*H*)-one **6** or **7** and 0.005 mol of furancarbaldehyde **3** in 10 mL of ethanol was cooled in an ice bath, and 2 mL (0.007 mol) of a 25% solution of sodium ethoxide in ethanol was added dropwise. Ethanol, 20 mL, was then added, and the mixture was stirred for 1.5 h at room temperature and for 2 h at 50–60°C until the initial aldehyde disappeared. The mixture was treated with 10% sulfuric acid to neutral reaction, stirred for 1 h, and evaporated by 50–70%. The residue was kept in a refrigerator, and the precipitate was filtered off and recrystallized from ethanol.

3-[(Furan-2-yl)methylidene]-5-methylfuran-2(3*H*)-one (4a). Yield 75%, yellow crystals, mp 76–77°C (from EtOH). UV spectrum (EtOH): λ_{max} 368 nm (logε 4.28). IR spectrum, ν, cm^{-1}: 3100 (C–H), 1765 (C=O), 1630 (C=C), 1225, 1160, 1125 (C–O–C), 1030, 1020, 750. Found, %: C 68.53; H 4.63. $C_{10}H_8O_3$. Calculated, %: C 68.18; H 4.55.

5-Methyl-3-[(5-methylfuran-2-yl)methylidene]-furan-2(3*H*)-one (4b). Yield 85%, yellow crystals, mp 108–109°C (from EtOH). UV spectrum (EtOH): λ_{max} 383 nm (logε 4.30). IR spectrum, ν, cm^{-1}: 3110 (C–H), 1760 (C=O), 1640 (C=C), 1220, 1160, 1120 (C–O–C), 1040, 1020, 760. Found, %: C 69.51; H 5.32. $C_{11}H_{10}O_3$. Calculated, %: C 69.47; H 5.26.

3-[(5-Chlorofuran-2-yl)methylidene]-5-methylfuran-2(3*H*)-one (4c). Yield 60%, yellow crystals, mp 107–108°C (from EtOH). UV spectrum (EtOH): λ_{max} 376 nm (logε 4.30). IR spectrum, ν cm^{-1}: 3110 (C–H), 1780 (C=O), 1650 (C=C), 1220, 1160, 1120 (C–O–C), 1065, 1010, 755. Found, %: C 56.94; H 3.37; Cl 16.89. $C_{10}H_7ClO_3$. Calculated, %: C 57.01; H 3.32; Cl 16.86.

3-[(5-Bromofuran-2-yl)methylidene]-5-methylfuran-2(3*H*)-one (4d). Yield 62%, yellow crystals, mp 111–112°C (from EtOH). UV spectrum (EtOH): λ_{max} 380 nm (logε 4.32). IR spectrum, ν, cm^{-1}: 3120 (C–H), 1780 (C=O), 1650 (C=C), 1210, 1160, 1120 (C–O–C), 1070, 1010, 760. Found, %: C 47.00; H 2.78; Br 31.43. $C_{10}H_7BrO_3$. Calculated, %: C 47.06; H 2.74; Br 31.37.

5-Butyl-3-[(5-phenylfuran-2-yl)methylidene]-furan-2(3*H*)-one (5a). Yield 70%, yellow crystals, mp 91–92°C (from EtOH). UV spectrum (EtOH): λ_{max} 330 nm (logε 4.00). IR spectrum, ν, cm^{-1}: 3100 (C–H), 1760 (C=O), 1645 (C=C), 1220, 1160, 1120 (C–O–C), 1055, 1025, 750. ^{1}H NMR spectrum, δ, ppm: 1.20–3.25 m (9H, Bu), 6.61 s (1H, 4-H), 6.98 s (1H, 1-H), 6.99 d (1H, 3-H), 7.05 d (1H, 2-H), 7.32–7.85 m (5H, H_{arom}). Found, %: C 77.15; H 6.18. $C_{19}H_{18}O_3$. Calculated, %: C 77.55; H 6.12.

5-Butyl-3-{[5-(4-methylphenyl)furan-2-yl]-methylidene}furan-2(3*H*)-one (5b). Yield 80%, yellow crystals, mp 104–105°C (from EtOH). UV spectrum (EtOH): λ_{max} 380 nm (logε 4.40). IR spectrum, ν, cm^{-1}: 3120, 3100 (C–H), 1760 (C=O), 1650 (C=C), 1230, 1165, 1120 (C–O–C), 1080, 1030, 760. ^{1}H NMR spectrum, δ, ppm: 1.00–3.55 m (9H, Bu), 2.5 m (3H, CH_3), 6.61 s (1H, 4-H), 6.96 s (1H, 1-H), 7.05 d (1H, 3-H), 7.09 d (1H, 2-H), 7.28 d (2H, H_{arom}), 7.69 d (2H, H_{arom}). Found, %: C 77.25; H 6.55. $C_{20}H_{20}O_3$. Calculated, %: C 77.32; H 6.39.

3-{[5-(4-Bromophenyl)furan-2-yl]methylidene}-5-butylfuran-2(3*H*)-one (5c). Yield 73%, yellow crystals, mp 210–211°C (from EtOH). UV spectrum (EtOH): λ_{max} 385 nm (logε 4.45). IR spectrum, ν, cm^{-1}: 3100 (C–H), 1770 (C=O), 1650 (C=C), 1220, 1165, 1110 (C–O–C), 1035, 1010, 760. ^{1}H NMR spectrum, δ, ppm: 0.90–3.60 m (9H, Bu), 6.61 s (1H, 4-H), 6.69 s (1H, 1-H), 7.09 d (1H, 3-H), 7.16 d (1H, 2-H), 7.62 d (2H, H_{arom}), 7.77 d (2H, H_{arom}). Found, %: C 61.18; H 4.52; Br 21.52. $C_{19}H_{17}BrO_3$. Calculated, %: C 68.13; H 4.56; Br 21.45.

5-Butyl-3-{[5-(4-nitrophenyl)furan-2-yl]methylidene}furan-2(3*H*)-one (5d). Yield 65%, orange crystals, mp 220–222°C (from EtOH). UV spectrum (EtOH): λ_{max} 450 nm (logε 4.10). IR spectrum, ν, cm^{-1}: 3130 (C–H), 1775 (C=O), 1655 (C=C), 1220, 1160, 1110 (C–O–C), 1035, 1020, 760. ^{1}H NMR spectrum, δ, ppm: 1.20–3.65 m (9H, Bu), 6.63 s (1H, 4-H), 7.35 s (1H, 1-H), 7.00 d (1H, 3-H), 7.11 d (1H, 2-H), 8.02 d (2H, H_{arom}), 8.29 d (2H, H_{arom}). Found, %: C 67.20; H 5.09; N 4.17. $C_{19}H_{17}NO_3$. Calculated, %: C 67.26; H 5.01; N 4.13.

4-Cyclohexyl-3-[(5-methylfuran-2-yl)methylidene]dihydrofuran-2(3*H*)-one (8a). Yield 82%, yellow crystals, mp 150–151°C (from EtOH). UV spectrum (EtOH): λ_{max} 330 nm (logε 4.37). IR spectrum, ν, cm^{-1}: 3125 (C–H), 1750 (C=O), 1650 (C=C), 1220, 1180, 1120 (C–O–C), 1050, 1010. ^{1}H NMR spectrum, δ, ppm: 1.20–1.90 m (10H, CH_2 in C_6H_{11}), 2.32 s (3H, CH_3), 2.52 s (1H, CH in C_6H_{11}), 3.49 s (1H, 4-H), 3.96 m (1H, 6-H), 4.08 m (1H, 5-H), 6.00 d (1H, 3-H), 6.40 d (1H, 2-H), 6.87 d (1H, 1-H). Found, %: C 73.88; H 7.63. $C_{16}H_{20}O_3$. Calculated, %: C 73.85; H 7.69.

3-[(5-Bromofuran-2-yl)methylidene]-4-cyclohexyldihydrofuran-2(3*H*)-one (8b). Yield 50%, yellow crystals, mp 137–138°C (from EtOH). UV spectrum (EtOH): λ_{max} 332 nm (logε 4.36). IR spectrum, ν, cm^{-1}: 3125 (C–H), 1750 (C=O), 1665 (C=C), 1215, 1170, 1100 (C–O–C), 1060, 1025, 1050 (C–O–C). ^{1}H NMR spectrum, δ, ppm: 1.10–2.40 m (10H, CH_2 in C_6H_{11}), 2.50 s (1H, CH in C_6H_{11}), 3.70 s (1H, 4-H), 4.21 m (1H, 6-H), 4.60 m (1H, 5-H), 6.50 d (1H, 3-H), 6.70 d (1H, 2-H), 7.33 d (1H, 1-H). Found, %: C 55.32; H 5.25; Br 24.67. $C_{15}H_{17}BrO_3$. Calculated, %: C 55.38; H 4.23; Br 24.61.

4-Benzyl-3-[(5-methylfuran-2-yl)methylidene]-dihydrofuran-2(3*H*)-one (9). Yield 80%, yellow crystals, mp 116–118°C (from EtOH). UV spectrum (EtOH): λ_{max} 330 nm (logε 4.40). IR spectrum, ν, cm^{-1}: 3140 (C–H), 1740 (C=O), 1665 (C=C), 1215, 1190, 1155 (C–O–C), 1055, 1025, 1010. ^{1}H NMR spectrum, δ, ppm: 2.40 s (3H, CH_3), 2.80 s (1H, 4-H), 3.11 m (2H, C**H**$_2$Ph), 4.10 m (1H, 6-H), 4.20 m (1H, 5-H), 6.25 d (1H, 3-H), 6.83 d (1H, 2-H), 7.18 d (1H, 1-H), 7.13 m (5H, Ph). Found, %: C 76.21; H 5.95. $C_{17}H_{16}O_3$. Calculated, %: C 76.12; H 5.97.

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