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Abstract

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A New Route for the Synthesis of α-β-Disubstituted Furans

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As is known, under the action of electrophilic agents on furan, thiophene, and similar systems, the α-hydrogen atoms are substituted. Even when one meta-orienting substituent is present in the α-position of the ring, the α'-position is usually attacked in the case of furan, whereas in the case of thiophene a mixture of 2,4- and 2,5-disubstituted products may be obtained. As far as we know, for furan only one case has been described (^{1}), regarded as direct alkylation in the β-position—the formation of 4-*iso*-propylfurfural from furfural. In view of this, the synthesis of β-substituted furans by a substitution reaction in the presence of even one free α-position in the ring is practically impossible to carry out. Therefore, 3-monosubstituted and 2,3-disubstituted furans are usually obtained by cyclization of the corresponding compounds of the aliphatic series, or from α, α', β-trisubstituted furans by removal, respectively, of two or one α-substituent.

Recently it has been shown that the introduction of a β-furfuryl residue into certain physiologically active compounds entails a considerable increase in activity (^{2}). In this connection we decided to develop a sufficiently accessible route for the synthesis of 3-mono- or 2,3-disubstituted furans bearing a function in position 3 through which they could be linked with a physiologically active moiety.

The essence of the method proposed by us consists in the preparation, from readily available 2-substituted furans, of bicyclic condensed systems with a "bridge" between the second and third positions of the furan ring, including as one of the links a heteroatom, for example sulfur. This link, which may be separated from the ring by carbon atoms or linked to the α-carbon atom, is eliminated at the following stage by one method or another. Proceeding from the principle indicated, we carried out the synthesis of sylvans acylated in position 3*:

$$\text{2-furfuryl mercaptan} + \text{Hal—CH(R)—COOH} \longrightarrow \text{S-(furfuryl-2)-}\alpha\text{-mercaptocarboxylic acid } (I)$$

$$(I) \longrightarrow (II) \longrightarrow (III) \longrightarrow (IV) \longrightarrow (V)$$

$$\text{Ia, IIa, IIIa, IVa: } R = \text{H}; \qquad \text{Ib, IIb, IIIb, IVb: } R = \text{CH}_3;$$
$$\text{Iv, IIv, IIIv, IVv: } R = \text{C}_2\text{H}_5.$$

As is seen from the scheme, the first stage consists in the condensation of readily available 2-furfuryl mercaptan (3) with an α-halocarboxylic acid; in this process S-(furfuryl-2)-α-mercaptocarboxylic acids (I) are obtained in 75-80% yield, and through the stage of formation of the acid chloride (II) they are cyclized in approximately 80% yield into bicyclic ketones (III). Under the action of Raney nickel on the latter, sulfur is removed as a result of reductive desulfurization (hydrogenolysis), and ketones (IV) are formed (yield 50-60%). It should be noted that in hydrogenolysis one might have expected complications associated with the possibility of partial or complete hydrogenation of the furan ring. However, under the conditions chosen by us, no appreciable amounts of hydrogenated compounds could be detected. This fact is consistent with the observations of Berdick and Adkins, who, by the action of Raney nickel, reduced the exocyclic double bond in furan compounds at the expense of hydrogen adsorbed on it, without disturbing the double bonds of the furan ring (⁀4). It might have been assumed that, under the action of $SnCl_4$ on the acid chlorides (II), closure would occur in the β-position, since precisely in this case an energetically favorable six-membered ring is formed. Indeed, the formation of 2-methylfuran-3-carboxylic acid* (V) as a result of the transformations shown in scheme 1 confirms this assumption. Ketones (III) are analogous to ketones of the benzene and thiophene series—isochromanone-4, first synthesized by Lesser et al. (⁀7, ⁀8), as well as 4,5-dihydro-7H-thieno-[2,3-c]-thiapyranone-4 and other similar compounds obtained by Cagniant et al. (9-11). The last ketone is of interest as a possible starting compound for obtaining 2,3-disubstituted thiophene, since, probably, by selecting an appropriate agent it will be possible to remove the sulfide sulfur without affecting the "thiophene" sulfur.

Work of this kind is being carried out in our laboratory by B. P. Fedorov. The data obtained in the realization of scheme 1 prompted us to use the same principle of eliminating a heteroatom in condensed bicyclic systems for obtaining ortho-alkyl-substituted ketones of the benzene series. In this connection it should be noted that the problem of synthesizing such compounds of the benzene series without the accompanying formation of para- and meta-isomers, in many cases, still remains unresolved. In recent years, owing to the development of gas chromatography, it has been shown that some disubstituted benzenes which earlier could be considered sufficiently pure in fact contained impurities of isomeric compounds.

We subjected isothiochromanone-4 to hydrogenolysis by the action of Raney nickel; methyl-*o*-tolyl ketone was thereby obtained in 55% yield. It may be assumed that it contains no isomeric impurities. In conclusion, it should be noted that ketones (III), in which the methylene group is bonded to the keto group and to a sulfur atom, should be distinguished by high reactivity. It appears possible to use them as starting compounds for further syntheses. The

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* The possibility of tautomerism of ketones III is not provided for in the scheme.

derivatives obtained under the action of Raney nickel may be converted into new 2,3-disubstituted furans.

Preparation of S-(furfuryl-2)-α-mercaptocarboxylic acids (I); cf. (^12). To a solution of 114.1 g (1 mole) of furfuryl mercaptan and the corresponding acid** (1.5 moles) in alcohol (450 ml) was added—

Table 1

	Acids and gross formula	B.p., °C/mm	n_D^{20}	Yield, %	Found, % C	Found, % H	Found, % S	Calculated, % C	Calculated, % H	Calculated, % S
Ia	S-(furfuryl-2)-mercaptoacetic acid, $C_7H_8O_3S$	149–150/4	1.5414	79	48.74 48.75	4.73 4.77	18.37 18.48	48.83	4.68	18.62
Ib	S-(furfuryl-2)-α-mercaptopropionic acid, $C_8H_{10}O_3S$	142/3	1.5269	75	51.68 51.52	5.35 5.65	17.21 16.94	51.60	5.41	17.21
Iv	S-(furfuryl-2)-α-mercaptobutyric acid, $C_9H_{12}O_3S$	153–154/3	1.5227	71	53.98 53.70	6.45 6.03	15.82 15.81	53.98	6.04	16.01

—over the course of 1.5–2 h, 140 g (3.5 moles) of NaOH in 450 ml of alcohol and 250 ml of water. After heating for 5–6 h at 70–80°, the alcohol was distilled off (800 ml), and the residue was washed with ether to remove neutral impurities. The aqueous—

* Ketone (IVa) was oxidized by the hypochlorite method (^5). Ketones (IVb) and (IVv) were oxidized with iodine in the presence of pyridine (^6).
** α-Chloroacetic, α-bromopropionic, α-bromobutyric acid.

Table 2

	Ketones, empirical formula	B.p., °C/mm	M.p., °C	n_D^{20}	Yield, %	Found, % C	Found, % H	Found, % S	Calculated, % C	Calculated, % H	Calculated, % S	Molecular weight found	Molecular weight calculated	Semicarbazones (from alcohol): empirical formula, m.p., °C	Semicarbazones: found N, %	Semicarbazones: calculated N, %
IIIa	4,5-Dihydro-7H-furo(2,3c)thiapyran-4-one, $C_7H_6O_2S$	123–124/7	49.5–50.5 (from aqueous alcohol; from heptane)	—	80	54.65	4.04	20.35	54.53	3.92	20.79	152	154	$C_8H_9N_3O_2S$, 232–233[1]	19.73; 20.01	19.89
IIIb	5-Methyl-4,5-dihydro-7H-furo(2,3c)-thiapyran-4-one, $C_8H_8O_2S$	109–110/3	34.5–35.5 (from heptane)	1.5677	73	56.89; 57.17	4.84; 4.87	18.81; 18.93	57.11	4.79	19.06	161	168	$C_9H_{11}N_3O_2S$, 212–213.5[2]	18.64; 18.45	18.65
IIIc	5-Ethyl-4,5-dihydro-7H-furo(2,3c)-thiapyran-4-one, $C_9H_{10}O_2S$	115.5–116.5/3	—	1.5578	81	59.22; 59.48	5.38; 5.41	17.60; 17.60	59.32	5.53	17.59	179	182	$C_{10}H_{13}N_3O_2S$, 202–203.5[3]	17.45; 17.40	17.56

[1] Oxime m.p. 160–161° (from aqueous alcohol; from heptane and benzene). $C_7H_7NO_2S$. Found %: N 8.08; 8.21. Calculated %: N 8.28.
[2] Oxime m.p. 99–99.5° (from aqueous alcohol). $C_8H_9NO_2S$. Found %: N 7.48; 7.72. Calculated %: N 7.65; 2,4-dinitrophenylhydrazone m.p. 221–222° (from alcohol and ethyl acetate). $C_{14}H_{12}N_4O_5S$. Found %: N 16.39; 16.63. Calculated %: N 16.09.
[3] 2,4-Dinitrophenylhydrazone m.p. 180–181° (from alcohol and ethyl acetate). $C_{15}H_{14}N_4O_5S$. Found %: N 15.51; 15.59. Calculated %: N 15.46.

Table 3

	Ketones and empirical formula	B.p., °C/mm	n_D^{20}	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Semicarbazones (from alcohol): empirical formula, m.p., °C	Semicarbazones: found N, %	Semicarbazones: calculated N, %	Oxidation product of ketones (IV)[4]: m.p., °C	Oxidation product: yield, %
IVa	Methyl (2-methylfuryl-3) ketone, $C_7H_8O_2$[1]	69.5/16	1.4850	52	67.31; 67.35	6.40; 6.58	67.73	6.50	$C_8H_{11}N_3O_2$, 191–192	23.26; 23.60	23.18	102–102.5[4]	66
IVb	Ethyl (2-methylfuryl-3) ketone, $C_8H_{10}O_2$	76.5–77.5/13	1.4831	57	69.08	7.43	69.54	7.30	$C_9H_{13}N_3O_2$, 192.5–193.5	21.40; 21.54	21.53	100–101[4]	44
IVc	Propyl (2-methylfuryl-3) ketone, $C_9H_{12}O_2$	101/22; 91/13	1.4802	53–55	71.17; 70.87	8.04; 7.97	71.02	7.95	$C_{10}H_{15}N_3O_2$, 173.5–174.5	19.76; 19.86	20.08	100.5–101[4]	51

	Ketones and empirical formula	B.p., °C/mm	n_D^{20}	Yield, %	Found, % C	Found, % H	Calculated, % C	Calculated, % H	Semicarbazones (from alcohol): empirical formula, m.p., °C	Semicarbazones found N, %	Semicarbazones: calculated N, %	Oxidation product of ketones (IV)[4]: m.p., °C	Oxidation product: yield, %
IVd	Methyl-o-tolyl ketone[2], $C_9H_{10}O$	91.5–93.5/16	1.5325	55	80.53; 80.48	7.62; 7.49	80.56	7.51	$C_{10}H_{13}N_3O$[3], 200–202.0	22.01; 21.97	21.98	–	–

[1] 2,4-Dinitrophenylhydrazone m.p. 205° (from alcohol and ethyl acetate). $C_{13}H_{12}N_4O_5$. Found %: N 18.76; 18.69. Calculated %: N 18.41.
[2] Literature data (17): b.p. 92–93°/17 mm, b.p. 89–92°/10 mm; n_D^{20} 1.535; n_D^{20} 1.5320.
[3] Literature data (18): m.p. 201–203°.
[4] 2-Methylfuran-3-carboxylic acid. $C_6H_6O_3$. Found %: C 56.92; 57.14; H 4.57; 4.43. Calculated %: C 57.14; H 4.80. Literature data: m.p. 102–103° (19); 101° (20).

the extract, upon cooling, was acidified with HCl to an acid reaction, and the acid that separated was extracted with ether. The ether layer was washed with saturated NaCl solution, dried over $CaCl_2$, and the residue after removal of the ether was distilled twice in vacuo (Table 1).

Preparation of acid chlorides of S-(furfuryl-2)-α-mercaptocarboxylic acids (II); cf. (13). To 0.15 mole of the acid dissolved in 100 ml of abs. benzene was added 44.7 g (0.375 mole) of thionyl chloride in 100 ml of benzene. The solution was heated at 40–50° for 1–1.5 h; the benzene was removed in vacuo with a water-jet pump while heating to 45°, and the residue was distilled in vacuo; considerable resinification occurred. The acid chlorides are colorless, fairly mobile liquids, decomposing very rapidly, and therefore they were not analyzed. Their boiling points and yields, calculated on the starting acid, were: IIa—b.p. 104°/4 mm, yield 64%; II —b.p. 101–102°/5 mm, yield 85%; II —b.p. 107–108°/3 mm, yield 75%.

Cyclization of acid chlorides (II); cf. (14). To $SnCl_4$ (0.18–0.3 mole) in 500 ml of dry benzene, at a temperature of 2-5°, the corresponding acid chloride (0.05-0.09 mole) in 500 ml of dry benzene was added dropwise. The mixture was stirred at room temperature for 1-2 h, after which it was decomposed with water while cooling and stirring. The benzene layer was separated and washed with saturated NaCl solution, $NaHCO_3$ solution, and again with NaCl solution. After removal of the benzene the residue was distilled in vacuo. The ketones obtained (Table 2) darken on storage.

Reductive desulfurization of ketones (III) (15, 16). To 25-60 g of Raney nickel was added a solution of the ketone (0.03-0.08 mole) in a mixture of alcohol (250-600 ml) with acetone (35-100 ml). The mixture was heated for 1.5-2 h at 40-50°* and with stirring until a negative reaction for sulfur with sodium nitroprusside was obtained. The nickel was filtered off and washed 5-6 times with ether. The ether extracts were combined with the alcoholic extract. The solvents were removed, and water was added to the small residue. The aqueous solution was treated twice with ether (100 ml each). The ether layer was dried over $CaCl_2$. The residue after removal of the ether was distilled in vacuo. The ketones obtained are colorless liquids, rapidly darkening in air (Table 3).

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* Ketone (III) (see Table 2) was desulfurized at 26–35° for 3 h.

Note: Figure translations are in progress. See original paper for figures.

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