

CATALYTIC REDUCTIVE DEBROMINATION — A NEW METHOD FOR THE
PREPARATION OF DEUTERO-SUBSTITUTED THIOPHENES AND FURANS

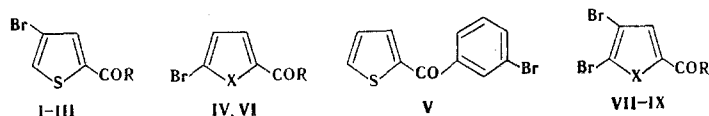
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The principles of the reductive dehalogenation of a number of mono- and dibromo-substituted functional derivatives of thiophene and furan in the presence of a palladium complex applied to silica gel modified with γ -aminopropyl groups were investigated. A one-step method for the preparation of mono- and dideutero-substituted carbonyl compounds of the furan and thiophene series was developed.

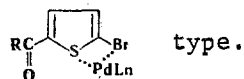
We have recently shown that dehalogenation of mono- and dihalogen derivatives of benzene [1] and thiophene [2] proceeds selectively under mild conditions (20°C, P_2H_2 , 1 atm, alcohol) under the influence of a palladium complex applied to silica gel modified with γ -aminopropyl groups. It seemed of interest to make a further study of the catalytic dehalogenation of halogen derivatives of heterocyclic compounds in order to ascertain the effect of the structure of these compounds on the rate of the process and to establish the possibility of the development of a method for the preparation of the corresponding deuterated compounds on the basis of this reaction. It is known that the preparation of deuterium-containing functional compounds of the thiophene and furan series, particularly those that contain deuterium in the β positions of the ring, is fraught with considerable difficulties. In particular, the preparation of deuterium-substituted carbonyl compounds is a multistep process that includes protection of the carbonyl group by conversion to an acetal or ketal group, introduction of a deuterium atom by means of direct metallation or lithium-halogen exchange, and, finally, removal of the protective grouping [3, 4]. The synthesis is even more complicated in the case of deuterium-substituted acids and esters, for which oxidation of the corresponding deuterated aldehydes and subsequent esterification are used [5].

In the present research we studied the principles of dehalogenation of a number of bromo-substituted thiophenes, furans, and benzenes in the presence of an immobilized complex palladium catalyst and on the basis of this reaction developed a one-step method for the synthesis of the corresponding deuterated products.



I R=CH₃; II R=H; III R=C₆H₅; IV, VII X=S, R=H; VI, IX X=O, R=OCH₃; VIII X=S, R=C₆H₅

The results of debromination of monobromo-substituted derivatives I-VI are presented in Table 1. As one can see, the rate of splitting out of bromine from 4-bromo-substituted thiophenes I-III depends on the character of the substituent in the 2 position. On passing from 4-bromo-2-acetylthiophene (I) to 4-bromo-2-formylthiophene (II) and 4-bromo-2-benzoylthiophene (III) the initial rate of debromination increases by factors of four and nine, respectively. The dehalogenation of 5-bromo-2-formylthiophene (IV) takes place more slowly by a factor of three than the dehalogenation of the isomeric 4-bromo-substituted compound (II). This is possibly explained by simultaneous coordination of the metal with the bromine and sulfur atoms to give a relatively stable (and, consequently, less reactive) complex of the



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TABLE 1. Catalytic Debromination of Monobromo-Substituted Compounds of the Thiophene, Furan, and Benzene Series (with CaO as the HBr acceptor)

Starting compound	Reaction conditions		Initial rate of splitting out of bromine, moles/liter·min per mole of Pd
	temp., °C	solvent	
I	20	C ₂ H ₅ OH	33
I	70	C ₂ H ₅ OH	53
II	20	C ₂ H ₅ OH—C ₆ H ₆	130
III	20	C ₂ H ₅ OH—C ₆ H ₆	300
III	70	C ₂ H ₅ OH—C ₆ H ₆	400
IV	20	C ₂ H ₅ OH	40
IV	70	C ₂ H ₅ OH	68
V	70	C ₂ H ₅ OH—C ₆ H ₆	100
VI*	20	C ₂ H ₅ OH—C ₆ H ₆	315

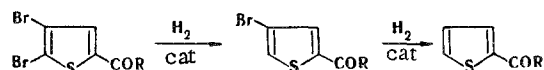
*Sodium bicarbonate was used as the HBr acceptor.

For steric reasons, 4-bromo-substituted thiophenes are not capable of such coordination, which also may explain their high rate of dehalogenation. The effect of the coordinating capacity of the substrate on the course of the reaction is clearly seen in the case of the dehalogenation of a mixture of equimolar amounts of the 4- and 5-bromides (I, IV), which react individually at close rates (Table 1). Dependences of the degree of conversion of the reagents on the time (Fig. 1) show that I initially reacts extremely slowly and that the reaction is accelerated sharply only after almost all (~95%) of bromide IV has reacted.

The same effect of coordination displacement is also illustrated by the results of experiments on the dehalogenation of a binary mixture of bromobenzene with chlorobenzene (Fig. 2). It is apparent from the kinetic curves that only hydrogenolysis of the C—Br bond in bromobenzene takes place initially, and splitting out of chlorine from chlorobenzene begins only after conversion of bromobenzene reaches 90-95%. It should be noted that in this case the rate of dehalogenation of bromobenzene is higher by a factor of only four than the rate of dehalogenation of chlorobenzene (210 and 55 moles/liter·min per mole of Pd, respectively).

The rate of debromination depends substantially on the nature of the aromatic ring. Splitting out of bromine from the 3 position of the benzene ring of *m*-bromophenyl-2-thienyl ketone (V) takes place more slowly by a factor of four than in the case of the isomeric substituted bromothiophene (III). It must be emphasized that in the dehalogenation of methyl 5-bromofuran-2-carboxylate (VI) the rate of the process considerably exceeds the rate for the investigated bromo-substituted thiophenes (Table 1): at 20°C splitting out of bromine is complete in ~20 min. This is possibly associated with the weaker coordinating capacity of the ring heteroatom and the smaller degree of aromatic character of furan as compared with thiophene.

Interesting results were obtained in the dehalogenation of dibromo-substituted thiophenes and furans (Table 2). The overall rates of splitting out of bromine from 4,5-dibromo derivatives of thiophene and furan are somewhat lower than for the monobromo derivatives (Table 1). The ratios of the rates of splitting out of the first and second bromine atoms in the 4,5-dibromo-2-formylthiophene (VII), 2-benzoylthiophene (VIII), and methyl 4,5-dibromofuran-2-carboxylate (IX) are 9-10, 4-5, and 2.5, respectively. Data from GLC and PMR spectroscopy show that bromine is primarily split out from the 5 position:



As in the case of 2,5-dichlorothiophene derivatives [2], the greatest selectivity of the process with respect to the monobromide is observed when zinc metal is used as the HBr acceptor (Fig. 3). It should also be noted that, as in the case of the monobromides, splitting out of halogen from the dibromofuran compound (IX) takes place considerably more rapidly than from dibromothiophenes (Table 2).

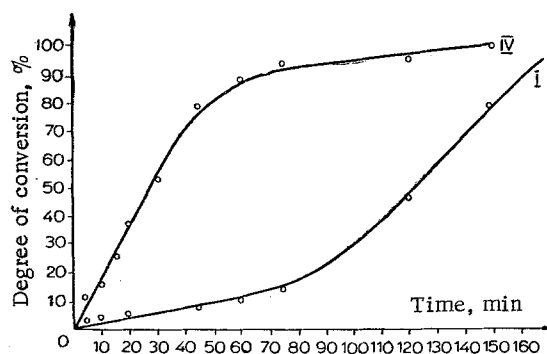


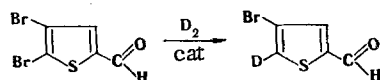
Fig. 1. Catalytic debromination of a mixture of 4-bromo-2-acetylthiophene (I) with 5-bromo-2-formylthiophene (IV) for I:IV = 1:1 (10^{-3} mole each) at 70°C and $P_{\text{H}_2} = 1$ atm in the presence of 0.1 g of CaO and 10 ml of $\text{C}_2\text{H}_5\text{OH}$.

TABLE 2. Reductive Debromination of Dibromo-Substituted Compounds of the Thiophene and Furan Series (70°C)

Starting compound	Reaction conditions		Initial rate of formation, moles/liter · min per mole of Pd		Maximum amount of the monobromo-substituted compound, %
	acceptor	solvent	monobromo compound	bromine-free product	
VII	CaO	$\text{C}_2\text{H}_5\text{OH}$	33	3	74
VII	Zn	$\text{C}_2\text{H}_5\text{OH}$	53	5	78
VII	CaO	$\text{C}_2\text{H}_5\text{OH}-\text{C}_6\text{H}_6$	40	5	70
VIII	CaO	$\text{C}_2\text{H}_5\text{OH}-\text{C}_6\text{H}_6$	66	17	67
VIII	Zn	$\text{C}_2\text{H}_5\text{OH}-\text{C}_6\text{H}_6$	73	16	80
IX*	NaHCO_3	$\text{CH}_3\text{OH}-\text{C}_6\text{H}_6$	130	50	32

*At 20°C .

The principles of reductive debromination described above have made it possible, by replacing hydrogen by deuterium, to use this reaction to obtain mono- and dideutero-substituted carbonyl compounds of the thiophene and furan series. The experimental conditions and the results are presented in Table 3, from which it is apparent that the preparation of deutero derivatives of thiophene can be carried out in both deuterated methanol and in ordinary alcohols. The structures of the deutero derivatives obtained are confirmed by data from the PMR spectra. In the deuteration of VII the reaction was stopped after the absorption of 1 mole of D_2 , and the 4-monodeutero derivative was obtained in 80% yield (according to GLC data).



It should be noted that virtually no replacement of the proton of the aldehyde group by deuterium is observed under the indicated conditions according to the PMR data.

Thus we have investigated the dependence of the rate of reductive debromination of bromo derivatives of the thiophene, furan, and benzene series on their structure and have proposed a new method for the preparation of ring-deuterated functional derivatives of thiophene and furan.

EXPERIMENTAL

Analysis was carried out by GLC at $120-220^{\circ}\text{C}$ with an LKhM-8MD chromatograph with a flame-ionization detector, a $1\text{ m} \times 3\text{ mm}$ stainless steel column, 10% SE-301 on Chromosorb W, and nitrogen as the carrier gas. The PMR spectra of solutions of the dehydrobrominated and dedeutero-brominated products in CCl_4 , CD_3OD , or $(\text{CD}_3)_2\text{CO}$ were recorded with a Varian DA-60-Jh radio-spectrometer (60 MHz) with tetramethylsilane as the internal standard.

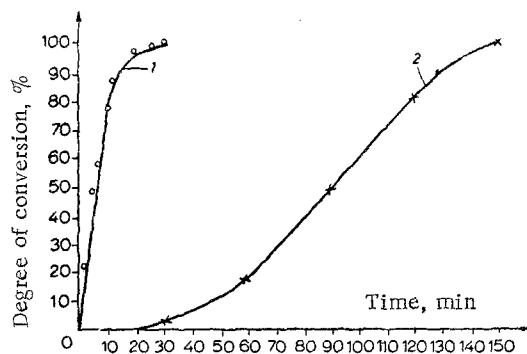


Fig. 2

Fig. 2. Catalytic dehalogenation of a mixture of C_6H_5Br (1) with C_6H_5Cl (2) under the following conditions: (1):(2) = 1.1 (10^{-3} mole each), $20^\circ C$, $P_{H_2} = 1$ atm, 0.1 g of CaO, and 10 ml of C_2H_5OH .

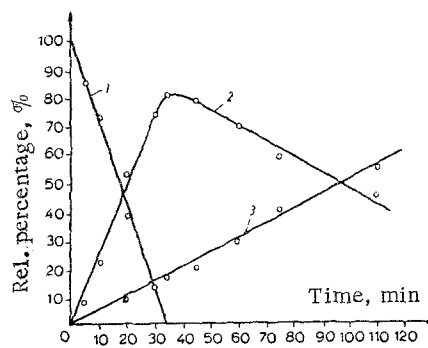


Fig. 3

Fig. 3. Catalytic debromination of 4,5-dibromo-2-benzoylthiophene (VIII): 1) starting compound; 2) 4-bromo-2-benzoylthiophene; 3) 2-benzoylthiophene.

TABLE 3. Preparation of Mono- and Dideutero-Substituted Carbonyl Compounds of the Thiophene and Furan Series

Starting compound (g)	Amount of catalyst, g	Temp., $^\circ C$	Deuteration conditions			Deuterated products
			solvent (ml)	HBr acceptor (g)	reaction time, min	
III (1,1)	0,3	50	CH_3OH (15)	CaO (0,3)	480	
VII (0,26)	0,1	50	CD_3OD ; (7)	Zn; (0,1)	55	
VII (0,26)	0,1	50	CD_3OD ; (7)	CaO; (0,1)	155	
I (0,26)	0,1	20	C_2H_5OH ; (20)	CaO; (0,1)	190	
IX (0,3)	0,1	20	CH_3OH ; (20)	$NaHCO_3$; (0,5)	30	

Method of Reductive Debromination. The metal complex of palladium applied to silica gel modified by γ -aminopropyl groups and previously reduced with sodium borohydride was prepared as in [1]. The starting bromides were prepared by known methods: I and II [6]; III, V, and VIII [7]; IV [8]; VI and IX [9]. Compound VII was obtained under the conditions described in [10] for the synthesis of II, except that 2 moles of Br_2 were used. According to GLC data, the products were 93-98% pure. The experiments were carried out at $20-70^\circ C$ and atmospheric hydrogen pressure [1]. A 0.1-g ($3 \cdot 10^{-5}$ mole/Pd) sample of the catalyst, $1 \cdot 10^{-2}$ g of $NaBH_4$, $1 \cdot 10^{-3}$ mole of the substrate, $(1.5-3) \cdot 10^{-3}$ mole of the HBr acceptor, and 10 ml of the solvent were used in the experiments. Methanol, ethanol, and mixtures of these alcohols with benzene in an alcohol-benzene volume ratio of 9:1 were used as the solvents.

Preparation of Deuterated Products. A reaction vessel of the "duck" type was charged with 0.1-0.3 g [(3-9)•10⁻³ mole/Pd] of the catalyst, (1-3)•10⁻³ g of NaBH₄, and (2-8)•10⁻³ mole of the HBr acceptor, argon was blown through the vessel, 3-15 ml of the solvent (methanol, ethanol, or D₄-methanol with a purity of >98%) was added by syringe through the resin condensate, and the stirrer was switched on. After 15-20 min (after decomposition of the NaBH₄), D₂ (98-99% pure) was blown into the reactor, the mixture was heated to the necessary temperature, and a solution of (1-4)•10⁻³ mole of the substrate in 2-5 ml of the solvent was added. The composition of the products was studied by GLC and PMR spectroscopy. The degree of deuteration reached 95-97% and was determined by means of integral curves from the H⁴ signals for 4-deutero-2-acetylthiophene (7.07 ppm in CCl₄), 4-deutero-2-formylthiophene [7.15 ppm in (CD₃)₂CO], 4,5-dideutero-2-formylthiophene (6.95 ppm in CD₃OD), and methyl 4,5-dideuterofuran-2-carboxylate (7.00 ppm in CD₃OD).

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[3,3]-SIGMATROPIC REARRANGEMENT OF CHLORO-SUBSTITUTED ALLYL

THIENYL SULFIDES

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The kinetics of the rearrangement of allyl 5-chloro-2-thienyl sulfide and β-chloroallyl 2-thienyl sulfide to, respectively, 5-chloro-3-allyl-2-thiophenethiol and 3-(β-chloroallyl)-2-thiophenethiol were investigated. It is shown that an acceptor substituent in the allyl group decreases the reactivity of the sulfide significantly, whereas an acceptor in the heterocyclic ring does not have an appreciable effect on it.

A study of the [3,3]-sigmatropic rearrangement of allyl thienyl sulfides has shown [1] that a six-membered transition state with partial charge separation is most likely for it. In contrast to sulfides of the benzene series, stable allylthiophenethiols are the products of rearrangement of allyl thienyl sulfides.

We have studied the rearrangement of allyl 5-chloro-2-thienyl sulfide (Ia) and β-chloroallyl-2-thienyl sulfide (Ib):

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