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CATALYTIC REDUCTIVE DEHALOGENATION OF THIOPHENE DERIVATIVES

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UDC 547.733.732:542.944.797

A method for the preparation of 3-substituted derivatives of thiophene by reductive dehalogenation of 2,5-dihalo-substituted thiophenes in the presence of a palladium complex is proposed. The dehalogenation reaction is a stepwise process. The presence of an acyl group in the 3 position increases the rate of the process.

β-Substituted thiophenes are intermediates in the synthesis of physiologically active substances. According to the prevailing opinion [1], β-substituted thiophenes are more active than α-substituted thiophenes vis-à-vis equal or lower toxicities. However, the accessibility of β-substituted thiophenes that have free α positions is limited, since their direct preparation from thiophene is impossible in view of the fact that the reactivities of both α positions of the thiophene ring exceed the reactivities of the β positions by approximately three orders of magnitude with respect to electrophilic substitution [2].

One of the methods for the preparation of thiophenes that are functionally substituted in the β position is the use of α,α'-dihalo derivatives for the introduction of a substituent with subsequent elimination of the halogens. Various dehalogenation methods are used for this purpose. The noncatalytic methods include removal of the halogens by the action of copper in propionic acid (this method is suitable only for the elimination of halogen atoms that are activated by the presence of a nitro or carbonyl group) [3, 4]. Other noncatalytic methods include dehalogenation by means of copper in quinoline [5], the action of sodium telluride in methanol [6], etc. Catalytic dehalogenation is realized by hydrogenation in the presence of palladium [7]. This method, in addition to certain advantages, has certain disadvantages: Large amounts of the catalyst must be used, products of partial hydrogenation of the ring are formed, and the selectivity is low. Even when halogen is removed from the side chains of thiophene derivatives, the yields of products range from 30 to 40% [8].

The good results obtained in the dehalogenation of chlorobenzenes and substituted chlorobenzenes in the presence of a chloride complex of palladium applied to silica gel containing γ-aminopropyl groups [9] compelled us to investigate the suitability of this catalyst for the preparation of β-substituted thiophenes from α,α'-dihalo-β-substituted thiophenes. In model experiments it was established that chlorine is split out from 2,5-dichlorothiophene (I) under mild conditions (20°C, 1 atm abs. H_2, NaOH) to give 2-chlorothiophene (II) and thiophene (III) in the presence of a palladium chloride complex applied to modified silica gel. Hydrogenolysis of the C—Cl bond proceeds selectively without hydrogenation of the thiophene ring. The process takes place via a consecutive scheme:

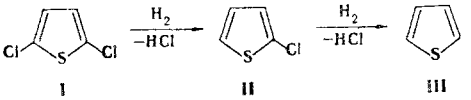
N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 171-175, February, 1982. Original article submitted May 18, 1981.

 0009-3122/82/1802-0130$07.50

TABLE 1. Catalytic Reductive Dehalogenation of 2,5-Dihalothiophenes

Starting compound	Temp., °C	Acceptor	Rate of formation, moles/liter·min per mole of Pd		Maximum percentage of the monohalide
			monohalide	thiophene (acetylthiophene)	
I	20	CaO	22	0,4	62
I	50	CaO	66	2,3	75
I	50	ZnO	58	3,0	62
I	50	$CaCO_3$	64	2,0	75
I	50		57	2,8	60
IV	50	CaO	20	5,0	45
V	20	CaO	67	2,8	82
V	50	CaO	193	13,0	78
V	50	ZnO	186	7,3	75
V	50	$CaCO_3$	200	10,0	75
V	50	Zn	183	7,7	92
V*	70	CaO	90	2,0	80

*The solvent was Methyl Cellosolve.



I II III

The initial rate of elimination of the first chlorine atom is 18 moles/liter·min per mole of Pd, while the rate of elimination of the second chlorine atom is 0.8 mole/liter·min per mole of Pd.

When the temperature is increased to 50°C, the initial reaction rate increases; however, the activity of the catalyst decreases sharply in the process. The framework of the support is evidently disrupted under the influence of NaOH. This leads to decomposition of the complex catalyst and reduction of the palladium to the metal form. In subsequent experiments we therefore used CaO, ZnO, $CaCO_3$, and Zn, the presence of which in the reaction mixture does not give rise to destruction of the support of the metal complex, to tie up the resulting HCl. It is apparent from the data presented in Table 1 that, as in the case of NaOH, hydrogenolysis of the C—Cl bonds in I is a stepwise process in the presence of other HCl acceptors: The first chlorine atom is split out 20 to 25 times faster than the second. When the temperature is raised from 20°C to 50°C, the reaction rate increases by a factor of approximately three; the nature of the acceptor does not have a substantial effect.

A comparison of the kinetic curves (Fig. 1) shows that starting dichlorothiophene I underwent complete reaction after 100-120 min at 50°C. Although splitting out of a second chlorine atom does occur at the start of the reaction, it takes place extremely slowly. As a result of this, the relative percentage of II reaches 60-75%. This sort of selectivity with respect to the splitting out of the first chlorine atom cannot be explained by the effect of only a statistical factor. It may be assumed that this phenomenon is due to coordination displacement of II by dichlorothiophene (I).

It was of interest to ascertain the behavior of 2,5-dibromothiophene (IV) under similar conditions. We found that replacement of the first bromine atom by hydrogen is complete in 20-25 min (Fig. 2). The curves presented in Fig. 2 are typical for a consecutive process. The rate of accumulation of bromothiophene in the catalyzate is only approximately four times higher than the rate of accumulation of thiophene (III). This evidently explains the lower selectivity with respect to the formation of monobromothiophene than in the case of dehalogenation of I and II.

To ascertain the effect of an electron-acceptor substituent on the ease of elimination of a halogen atom in the thiophene ring we investigated the transformation of 2,5-dichloro-3-acetylthiophene (V). It is apparent from Table 1 that the rate of splitting out both the first and second halogen atoms increased by a factor of approximately three as compared with the rate of dehalogenation of dichlorothiophene (I). The resulting mixture of monochloro derivatives contains 96% 2-chloro-4-acetylthiophene (VI) and 4% isomer VII according to data from gas-liquid chromatography (GLC) and the PMR spectra. Compound VI was obtained as the principal product in the reduction of V with copper in propionic acid [4]. Starting dichloro

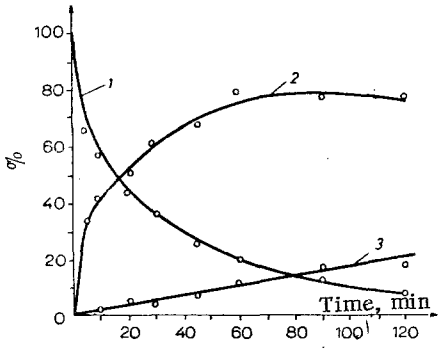


Fig. 1

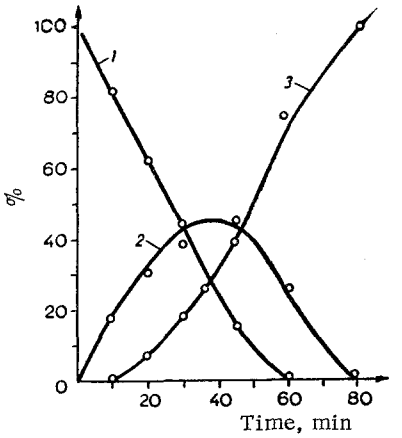


Fig. 2

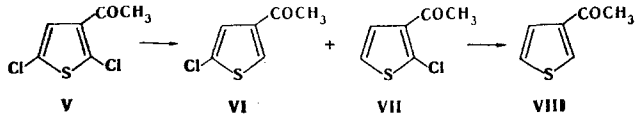
Fig. 1. Catalytic dechlorination of 2,5-dichlorothiophene (50°C, CaO, ethanol): 1) 2,5-dichlorothiophene; 2) 2-chlorothiophene; 3) thiophene.

Fig. 2. Catalytic debromination of 2,5-dibromothiophene (50°C, CaO, ethanol): 1) 2,5-dibromothiophene; 2) bromothiophene; 3) thiophene.

ketone V undergoes complete conversion in 55-65 min when CaO, ZnO, or $CaCO_3$ is used as the HCl acceptor, whereas conversion is complete after 20-25 min in the presence of Zn (Fig. 3); the amount of monochloro ketone VI in the reaction mixture reaches 75-80%, as compared with 92% when Zn is added (Table 1). In the case of complete dehalogenation of acetylthiophene V (70°C, CaO, 180-200 min) 3-acetylthiophene (VIII) was obtained in virtually quantitative yield. According to GLC data, its purity was greater than 98%. The reaction can be carried out at a higher temperature using other hydroxy-containing solvents, particularly Methyl Cellosolve.

Thus the data obtained show that splitting out of a chlorine atom from dichloroacetylthiophene (V) also proceeds successively through an intermediate step involving the formation of monohaloacetylthiophenes.

The accelerating effect of the acyl group is in agreement with the previously proposed [9] mechanism of hydrogenolysis of an aromatic C—Cl bond in the presence of an applied palladium complex. According to this mechanism, the ease of splitting out of halogen, which proceeds through a step involving the formation of a metal aryl σ complex, is due to the degree of polarization of the C—Cl bond. It should be especially noted that hydrogenation of the ring and reduction of the carbonyl group do not occur in the dehalogenation of dihalogen derivatives of thiophene.



In view of the accessibility of 2,5-dichlorothiophene (I), the method developed in this research opens up new possibilities for the synthesis of β-functionally substituted thiophenes.

EXPERIMENTAL

2,5-Dichloro-3-acetylthiophene (V). A 60-g (0.45 mole) sample of anhydrous $AlCl_3$ was added gradually at 15°C to a solution of 60 g (0.31 mole) of 2,5-dichlorothiophene (I) and 60 g (0.76 mole) of acetyl chloride in 500 ml of chloroform, and the reaction mixture was stirred at ~20°C for 5 h. It was then poured over ice, and the organic layer was separated. The aqueous layer was extracted with chloroform, and the organic layers were combined and washed with dilute hydrochloric acid, aqueous sodium carbonate solution, and water, and dried over $MgSO_4$. The solvent was removed by distillation, and the residue was distilled in vacuum to give 40.3 g (52%) of 2,5-dichloro-3-acetylthiophene with bp 120-122°C (6 mm) and mp 39-40°C (mp 39°C [10]).

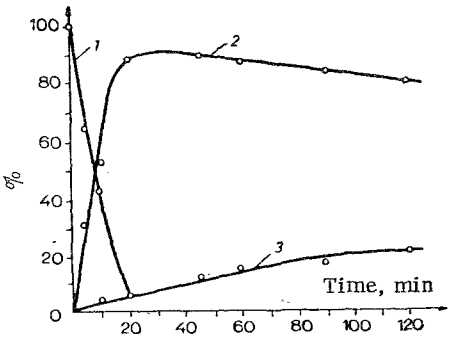


Fig. 3. Catalytic dechlorination of 2,5-dichloro-3-acetylthiophene (50°C, Zn, ethanol): 1) 2,5-dichloro-3-acetylthiophene; 2) 2-chloro-4-acetylthiophene; 3) acetylthiophene.

The preparation of the chloride complex of palladium on the support, its activation, and the method used to conduct the catalytic experiments were described in [11]. The starting 2,5-dichlorothiophene, 2,5-dibromothiophene, and 2,5-dichloro-3-acetylthiophene had purities of 95-98% according to the GLC data. The reaction was carried out at 20-70°C and 1 atm abs. H_2. A 0.1-0.3-g [$(3-9)\cdot10^{-5}$ mole of Pd] sample of the catalyst, $1\cdot10^{-2}$ g ($2.5\cdot10^{-4}$ mole) of $NaBH_4$, $(2-3)\cdot10^{-3}$ mole of the hydrogen halide acceptor, $1\cdot10^{-3}$ mole of the substrate, and 10 ml of ethanol were used in the experiments. The products were analyzed by GLC with an LKhM-8MD chromatograph with a flame-ionization detector; the carrier gas was nitrogen, the column was made of stainless steel (1 m × 3 mm), and the liquid phase was SE-301 (10%) on Chromosorb W.

Isolation of 3-Acetylthiophene (VIII). The reaction mixtures from several experiments involving the dehalogenation of 2,5-dichloro-3-acetylthiophene were filtered, the solvent was removed by vacuum distillation, and the residue was distilled *in vacuo*. The fraction with bp 90-95°C (7 mm) crystallized to give a product with mp 59-60°C (from petroleum ether) (mp 57°C [12]). PMR spectrum (in CCl_4): 7.85 (1H, q, 2-H), 7.45 (1H, q, 4-H), 7.15 (1H, q, 5-H), and 2.36 ppm (3H, s, CH_3O). Found: C 56.9; H 4.5; S 25.3%. C_6H_6OS. Calculated: C 57.1; H 4.8; S 25.4%.

2-Chloro-4-acetylthiophene (VI). PMR spectrum (in CCl_4): two doublets at 7.5-8.5 ppm with spin–spin splitting constant J_{H-H} = 1.5 Hz, which indicates coupling of the protons in the 5 and 3 positions of the thiophene ring, i.e., the presence of a chlorine atom in the 2 position.

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