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IONIC HYDROGENATION OF THIOPHENES

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Abstract—A new method of synthesising thiophane compounds by hydrogenation of the corresponding thiophenes with a mixture of triethylsilane and trifluoroacetic acid is described. A number of thiophanes, such as 2-, 3-alkyl-, arylthiophanes, 2,5-dimethylthiophane, thiophanes functionally substituted in the side chain and thiaindanes have been obtained by this method.

The known procedures for the synthesis of thiophane compounds are usually complicated, and give low yields of the final products.[1,2] Tetrahydrofuran derivatives are most often employed as the starting compounds: they are converted to the thiophanes directly by reaction with hydrogen sulfide in the presence of a catalyst (usually alumina) by Yur'ev's method,[3] or via the 1,4-substituted derivatives generated upon cleavage of tetrahydrofurans. Such derivatives could be dihalogen substituted,[4] dioles,[5] halo alcohols[6] or their respective esters.[7] The tetrahydrofuran compounds are obtained by hydrogenation of the furan series.

Few catalysts can be used for the reduction of thiophenes to tetrahydro derivatives because of poisoning by thiophenes. Raney nickel (in large quantities) causes desulfurisation of the thiophenes giving the aliphatic and cycloaliphatic derivatives.[8]

Palladium on carbon or barium sulfate[9] can be employed at low temperatures and pressures but the quantity of these catalysts should be nearly equal to or even exceed that of the compound being hydrogenated. Cobalt carbonyl[10] is inconvenient because of the drastic conditions required. Use of renium heptasulfide[11] also requires forcing conditions (250–500°, 100–300 atm) and is expensive. In the case of nickel, molybdenum and tungsten sulfides[12] low yields are obtained.

In this paper we report a new method for converting thiophenes to thiophanes which involves the consecutive addition of a proton and a hydride-ion to the multiple bond.

A mixture of trifluoroacetic acid and alkyl-(aryl)silanes was used as the hydrogenating pair.[13,14] This pair has been employed previously in the hydrogenation of many classes of organic and organometallic compounds resulting in high selectivity in all cases. Olefin hydrogenation is successful only when there is in the case of branching at the ethylene carbon or when the double bond is conjugated with a phenyl or cyclopropane ring. This selectivity may be explained by the mechanism in Scheme 1.

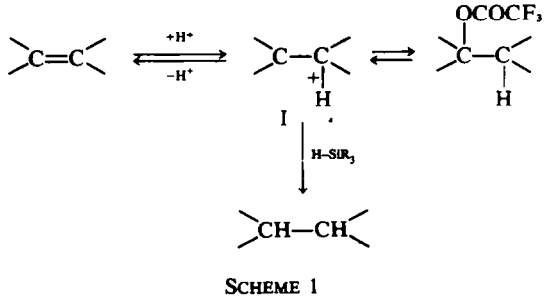
An equilibrium between the olefin, carbonium ion 1 and the trifluoroacetate of the respective alcohol occurs rapidly in the presence of trifluoroacetic acid. Silane reacts irreversibly with the carbonium ion giving the hydrogenation product. Thus it is necessary to create a concentration of the carbonium ions sufficient for reaction with the hydride ions donor: a condition which was shown experimentally to be satisfied by a tertiary carbonium ion and secondary ones stabilized by conjugation with phenyl or cyclopropane rings as well as with the lone electron pair of oxygen and sulfur.[15]

Ionic hydrogenation of ketones depends on the ketone structure: alkyl ketones are transformed to alcohols while aryl ketones afford the respective hydrocarbons.[16]

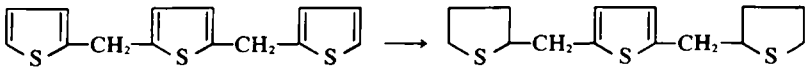
This method of hydrogenation also has the advantage that, in the course of the reaction some functional groups (such as carboxylic, ester, nitro and nitrylic groups etc) are not attacked as in other methods.

The results of ionic hydrogenation of thiophenes[17] are listed in Table 1. The 2-alkyl- and 2,5-dialkylthiophenes give the corresponding thiophanes in good yields. 3-Alkyl-thiophene is hydrogenated at a much slower rate. 3-Phenylthiophene, 2,3-, 2,4- and 3,4-diphenylthiophenes easily form the corresponding phenylthiophanes while 2,5-diphenylthiophene, 2,3,4-tri- and tetraphenylthiophene do not undergo hydrogenation.[18]

The fact that 2,5-diphenylthiophene could not be hydrogenated may be a result of steric hindrance upon protonation. We tried to hydrogenate 2,5-di(t-butyl)thiophene and found that ionic hydrogenation occured giving a mixture of products with a low overall yield. Only the outer thiophene rings in 2,5-di(thenyl-2)-thiophene[19] (2) underwent hydrogenation to give 3; the middle ring could not be reduced even at a ratio of thiophene: silane: acid of 1:8:25 and a reaction time of 80 hr.



SCHEME 1

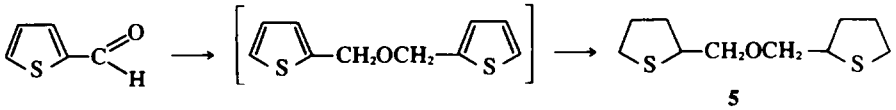


2 3

Thiophane derivatives with functional substituents in the rings such as 2-carboxylic ester groups and halogens could not be prepared by this method. The presence of electron releasing groups in the 2-position, e.g. alkylmercapto group, activated the hydrogenation but formation of alkylmercaptothiophane was followed by replacement of the alkylmercapto group by hydrogen giving rise to thiophane.

Table 1. Hydrogenation of thiophenes at 50°

Starting thiophene	Ratio thiophene: Et_3SiH: CF_3COOH	Reaction time (h)	Chromatography column/ condit.	Hydrogenation products	Yield (%)
2-Me(Et)thiophene	1:2:7	20	I/1	2-Me(Et)-thiophane	80
2,5-Di-Me-thiophene	1:2:7	20	I/1	2,5-di-Me-thiophane	80
3-Me-thiophene	1:2:9	80	I/1	3-Me-thiophane	60
Thiophene	1:2:10	80	I/1	thiophane, dihydrothiophene	15, 30
3-Ph-thiophene	1:3:13 (in benzene)	20	II/3	3-Ph-thiophane	70
2,5-Di-Ph-thiophene	1:5:20 (in $CHCl_3$)	50	II/3	—	—
3,4-Di-Ph-thiophene	1:5:20 (in $CHCl_3$)	50	II/3	3,4-di-Ph-thiophane	70
2,3,4,5-tetra-Ph-thiophene	1:6:27 (in $CHCl_3$)	50	II/3	—	—
1,6-Di-(thienyl-2)-hexane	1:4:8	30	—	1,6-di-(tetra-hydrothienyl-2)-hexane	70
5-Me-2-thiophene-carboxylic acid	1:3:8	65		—	—
5-Cl-2-Et-thiophene	1:3:8	100	I/1	—	—
2,5-Di-Cl-thiophene	1:2:9	50	I/1	—	—
4-Br-2-Me-thiophene	1:2:9	50	—	—	—
t-Bu(i-Bu)-(thienyl-2)sulphide	1:3:10	20	I/1 and 2	thiophane	70
Di-(thienyl-2)-disulphide	1:3:10	20	I/1 and 2	thiophane, thiophene	50, 20
t-Bu(i-Am)-(thenyl-2)sulphide	1:3:10	20	I/1 and 2	2-Me-thiophane	50
t-Bu-3(thienyl-3)-sulphide	1:3:10	200	I/1 and 2	t-Bu-(tetrahyd-rothienyl-3)-sulphide	30
2-Thiophenealdehyde	1:4:8	30	II/3	di-(tetrahydro-thenyl-2)ether (**5**)	65
2-Benzoylthiophene	1:5:9	30	II/3	2-benzylthiophane	75
2-Acetylthiophene	1:5:10	50	I/1	2-ethylthiophane	55
δ-(Thienyl-2)-valeric acid (**9**)	1:2:7	30	—	δ-(tetrahydro-thienyl-2)valeric acid (**10**)	65
Methyl ε-(thienyl-2)caproate (**11**)	1:2:9	30	II/3	Methyl ε-(tetrahydro-thienyl-2)caproate (**12**)	65
2,5-Di-t-Bu-thiophene	1:3:8	100	I/2	2,5-di-t-Bu-thiophane	15
2,5-Di-(thenyl-2)-thiophene (**2**)	1:7:13	50	I/2	2,5-di-(tetra-hydrothenyl-2)-thiophene (**3**)	60
Behzo[b]thiophene	1:3:9	125	I/2	2,3-dihydrobenzo[b] thiophene	55
2-Me-benzo[b]thiophene	1:1.7	20	I/2	2-Me-2,3-dihydro-benzo[b]thiophene	80
3-Me-benzo[b]-thiophene	1:1:7	20	I/2	3-Me-2,3-dihydro-benzo[b]thiophene	90



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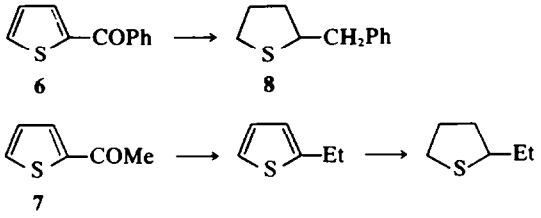
As is shown by the data in Table 1 different results, depending on the halogen position, were obtained when the thiophene group contained both an alkyl group in position 2 and a halogen.

Analogous to benzaldehyde, which afforded dibenzyl ether[20] under conditions of ionic hydrogenation, 2-thiophenaldehide gave rise to the ether (4), the thiophene rings of which underwent further hydrogenation leading to the corresponding ether (5)

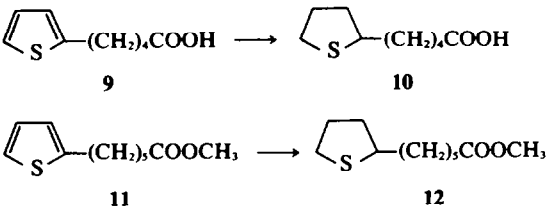
Phenyl-2-thienylketone (6) and methyl-2-thienylketone (7) were hydrogenated to 2-benzylthiophane (8; 75%) and 2-ethylthiophane (55%) respectively. It should be noted that hydrogenation of methyl-2-thienylketone first gave some quantity of 2-ethylthiophene which then disappeared. The first step in the reaction probably is reduction of the CO to CH_2 followed by reduction of the thiophene ring to the thiophane. This is analogous to the reduction of arylketones.[18]



6 8

7

Thiophenes with functional substituents in the side chain underwent reduction in a manner similar to alkylthiophenes. Thus (2-thienyl)valeric acid (9) gave thiophanevaleric acid (10, 65%) (a structural fragment of biothine and lipoic acid). Methyl ϵ-(2-thienyl)-caprate (11) gave methyl tiophanecaprate (12). Several experiments have been carried out in order to elucidate the mechanism of thiophene hydrogenation. The study of electrophilic substitution in the thiophene series, in particular the kinetics of hydrogen isotopic exchange[21,22] has demonstrated an activation of the free α-position of the thiophene ring by alkyl substituent. Even when both α-positions are occupied by alkyl substituents, only the α-position is protonated.[23] In view of this we propose the following scheme for ionic hydrogenation of 2,5-dimethylthiophene (13)



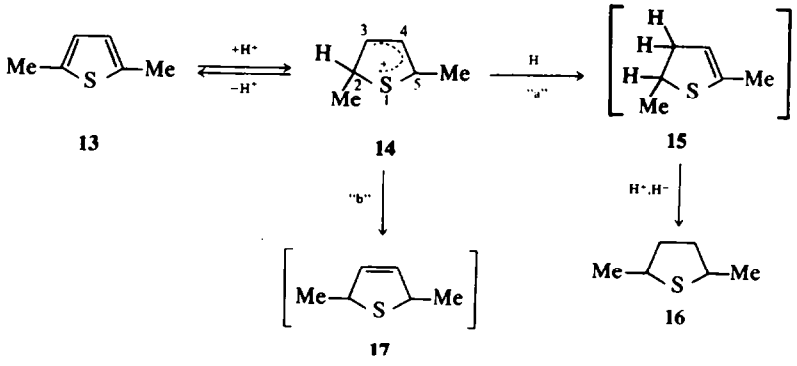
9 10

11 12

The first step is addition of a proton from trifluoroacetic acid to position 2 of the thiophene ring, giving cation (14). Two routes are then possible. Hydride-ion addition from silane to position 3 (route "a") affording 2,5-dimethyl-2,3-dihydro-thiophene (15). In view of previous results, this compound should undergo fast hydrogenation to 2,5-dimethylthiophane (16). Route "b", (the hydride-ion addition to position 5), probably does not take place since the expected product, 2,5-dimethyl-2,5-dihydrothiophene (17) is not observed.

To further check this mechanism we hydrogenated 2,5-dimethylthiophene with trifluoroacetic acid and deuterotriethylsilane. If the scheme holds the deuterium should be distributed equally in position 3 and 5 of the thiophane ring, with 50% protium and 50% deuterium in the α-positions.

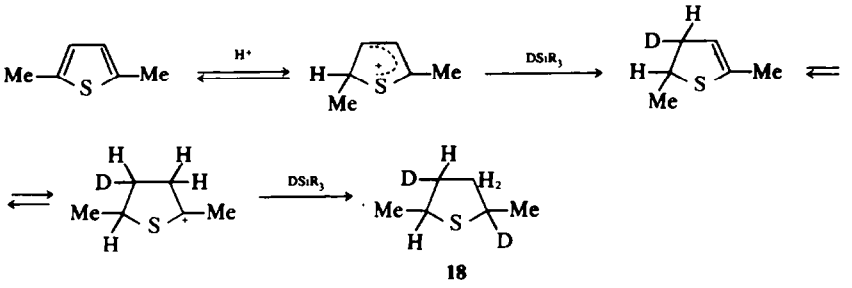
The position of deuterium in 2,5-dimethylthiophane was determined by means of the PMR spectroscopy. In the PMR spectrum of 2,5-dimethylthiophane free of deuterium (compound 16) the Me groups appear as two overlapping doublets corresponding to *cis*- and *trans*-2,5-dimethylthiophanes (Fig 1). When both α-hydrogens are substituted by deuterium, the Me group doublets of *cis*-



13 14 15

17 16

SCHEME 2.



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SCHEME 3.

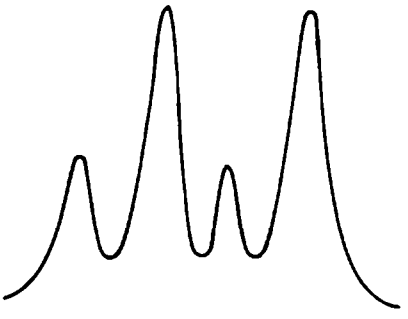


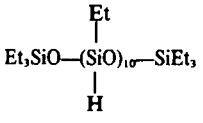
Fig 1. PMR spectra of CH_3-groups in mixture of *cis*- and *trans*-2,5-dimethylthiophane.

and *trans*-2,5-dimethylthiophane (Fig 2a) should be triplets with the same chemical shifts (Fig 2b). With a mixture of protium and deuterium at the α-positions (compound **18**) the spectrum should be a composite of spectra 2a and 2b (Fig 2c).

It was found that the PMR spectrum (Fig 3) of 2,5-dimethylthiophane, prepared with Et_3SiD, corresponded with the theoretical spectrum of **18** (2c) demonstrating approximately equal quantities of D and H at the α-positions of the thiophane ring. The data obtained are in good agreement with the scheme suggested (Scheme 3).

Ionic hydrogenation of the thiophene ring has also been extended to benzthiophenes[24] (Table 1). Unsubstituted benzthiophene was reduced to dihydrobenzthiophene. The reaction however is very slow. Hydrogenation of benzthiophenes with alkyl substituents is faster: 2-methyl- and 3-methyl-benzthiophenes gave the respective dihydrobenzthiophenes in 75 and 85% yields after 3 hr.

It has been shown[14] that trialkyl- and diphenylsilanes can also be used as the hydride donors in ionic hydrogenation. We found that in some cases silanes could even be replaced by a polymeric hydrophobing silicon liquid HSL-94[25] which is inexpensive and commercially available



Thus with a reagent ratio of thiophene : HSL-94 : acid =

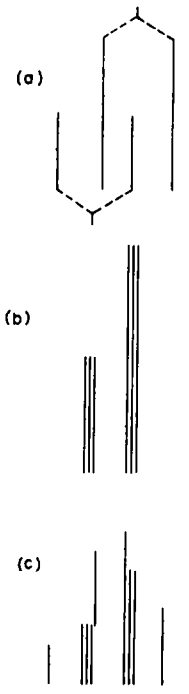


Fig 2. (a) Theoretical PMR spectra of Me-groups in mixture of *cis*- and *trans*-2,5-dimethylthiophane. (b) Theoretical PMR spectra of Me-groups in mixture of *cis*- and *trans*-2,5-dimethylthiophane-2d,5d. (c) Theoretical PMR spectra of Me-groups in mixture of *cis*- and *trans*-2,5-dimethylthiophane-2d.

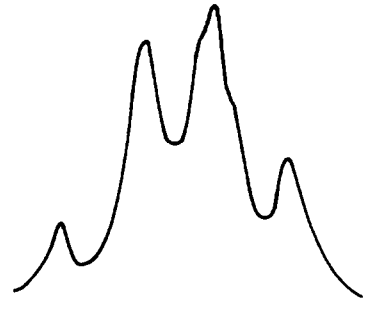


Fig 3. PMR spectra of Me-groups in mixture of *cis*- and *trans*-2,5-dimethylthiophane-2d.

Table 2. Physical properties and elemental analyses of new thiophanes

Compound		B.P. (°C)	mm Hg	n_D^{23}	Calculated % C	H	S	Found % C	H	S
1,6-Di-(tetrahydro-thienyl-2)hexane	$C_{14}H_{26}S_2$	153–156	7×10^{-2}	1·5332	65·05	10·13	24·80	64·97	9·81	24·22
Di-(tetrahydrothenyl-2) ether (5)	$C_{10}H_{18}OS_2$	150–152	8	1·4721	54·54	8·31	24·79	54·88	8·03	25·11
Methyl ε-(tetrahydro-thienyl-2)caproate (12)	$C_9H_{20}O_2S$	170–172	17	1·4842	61·07	9·32	14·82	60·89	9·46	14·90
2,5-Di-(tetrahydro-thenyl-2)thiophene (3)	$C_{14}H_{20}S_3$	235–236	6	1·5931	59·10	7·09	33·80	58·97	7·16	33·33

1:0, 5:16 in $CHCl_3$ solution at 50° and 55 hr, hydrogenation of 2,5-dimethylthiophene gave 2,5-dimethylthiophane (80%).

EXPERIMENTAL

Thiophenes were hydrogenated using the following common procedure. Trifluoroacetic acid was slowly added to the mixture of thiophene and triethylsilane with heating under reflux at 50°. To maintain a homogeneous soln in the case of phenylthiophene hydrogenation and when HSL-94 was employed as the donor of hydride-ions solvent was added to the mixture.

Qualitative and quantitative analyses of the mixture were performed on a GLC. Chromatographic conditions: for Chrom-3, detector-catharometer, carrier gas—helium, column I–15% polyethyleneglycoladipate on risorb BLK, l-2,5 m, inner diameter 4 mm (stainless steel). Operation conditions: t 130°, P_{He} 0·6 (1), t 200°, P_{He} 0·8 (2); for Chrom-2, flame ionization detector, carrier gas-nitrogen, column II–12% fluorosilicon on Celite 545 l-1·5 m, inner diameter 4 mm (copper), operation conditions t 200°, P_{N_2} 0·7 (3).

PMR spectra were obtained on Brucker HX-90, 0·5 Hz in 1 cm.

In order to separate the hydrogenation products, the mixture was neutralized with Na_2CO_3 aq, the aqueous layer extracted with ether, the combined organic phase dried over $MgSO_4$, the ether evaporated and the residue distilled under vacuum. 2-Methyl and 2,5-dimethylthiophanes were separated from the silane products by complexation with mercuric chloride[26] followed by heating under reflux in 15% HCl. In the synthesis of thiophanevaleric acid and the solid residue left after vacuum distillation of all low-boiling components was crystallized from n-hexane. The physical properties of new hydrogenation products are shown in Table 2.

The structures of new compounds were confirmed by IR and PMR spectra and elemental analyses (Table 2).

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