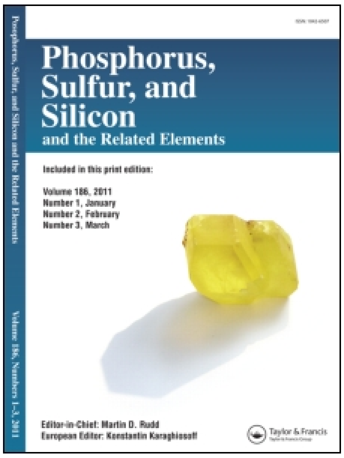

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MODERN FRIEDEL-CRAFTS CHEMISTRY XVI. REACTION OF THIOPHENE WITH BIFUNCTIONAL MOLECULES UNDER DIFFERENT FRIEDEL-CRAFTS CATALYSTS: ATTEMPTED SYNTHESIS OF CYCLOPENTA[b] THIOPHENES AND DIHYDROBENZO[b] THIOPHENES

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MODERN FRIEDEL–CRAFTS CHEMISTRY XVI. REACTION OF THIOPHENE WITH BIFUNCTIONAL MOLECULES UNDER DIFFERENT FRIEDEL–CRAFTS CATALYSTS: ATTEMPTED SYNTHESIS OF CYCLOPENTA[b] THIOPHENES AND DIHYDROBENZO[b] THIOPHENES

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The reaction of thiophene (**1**) with 3-chloropropionyl chloride (**2**), 4-chlorobutyryl chloride (**3**), crotonyl chloride (**4**) and cinnamoyl chloride (**5**) under different Friedel–Crafts catalysts ($AlCl_3$/CH_3NO_2, $FeCl_3$, and $AlCl_3$/CS_2) was investigated. The cyclic products 4,5-dihydro-6H-4-methylcyclopental[b]-thiophen-6-one, 5,6-dihydrobenzo[b]thiophen-7(4H) one and 4-phenyl-6H-cyclopenta[b]thiophen-6-one were formed. The different behaviors of compounds (**2–5**) towards thiophene were discussed.

INTRODUCTION

The growing importance of thiophene derivatives in the design and synthesis of pharmacologically important molecules[1–22] and the little knowledge on the Friedel–Crafts chemistry of thiophene together with our interest in Friedel–Crafts chemistry of sulfur compounds[23–26] stimulated this research in an attempt to find a facile route for the synthesis of cyclic sulfur compounds related to thiophene.

In this investigation we allowed thiophene (**1**) to react with four bifunctional molecules namely 3-chloropropionyl chloride (**2**), 4-chlorobutyryl chloride (**3**), crotonyl chloride (**4**), and cinnamoyl chloride (**5**). The reactions were performed under different Friedel–Crafts catalysts ($AlCl_3$/CH_3NO_2 $FeCl_3$, $AlCl_3$).

RESULTS AND DISCUSSION

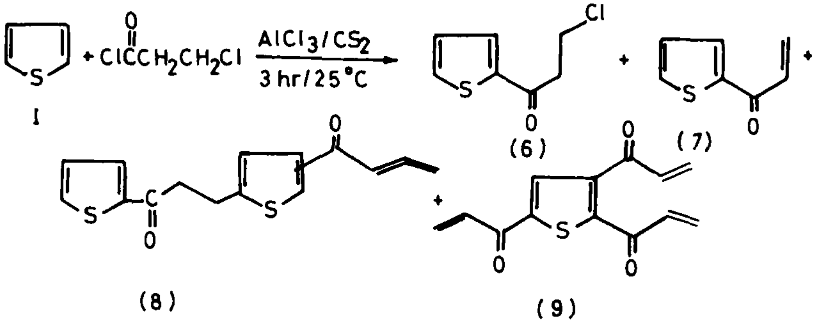
Examination of the results depicted in Table I, showed that, interaction of thiophene with 3-chloropropionyl chloride (**2**) in presence of the mild catalyst, $AlCl_3$/CH_3NO_2 gave only 2-chloroethyl-2-thienyl ketone (6.8%). Using $FeCl_3$ as catalyst afforded a mixture of (**6**; 75%) and 1-(2-thienyl)-2-propen-1-one (**7**; 15%), whereas with $AlCl_3$/CS_2 a mixture of (**6**), (**7**), (**8**) and (**9**) in (46.2, 6.1 and 5%) respectively was obtained; (Scheme I).

TABLE I

Reactions of thiophene with bifunctional compounds under different Friedel–Crafts catalysts

Entry	Bifunctional comp	Catalyst	Observed reaction products (%)	Ref
1	$ClCH_2CH_2COCl$	$AlCl_3/CH_3NO_2$	3-chloro-1-(2-thienyl)propan-1-one (80)	29
2	$ClCH_2CH_2COCl$	$FeCl_3/CS_2$	3-chloro-1-(2-thienyl)propan-1-one (75)	
			1-(2-thienyl)-2-propen-1-one (15)	16
			unidentified (10)	
3	$ClCH_2CH_2COCl$	$AlCl_3/CS_2$	3-chloro-1-(2-thienyl)propan-1-one (46)	
			1-(2-thienyl)-2-propen-1-one (26)	16
			2,3,5-tris(1-propenoyl)thiophene (3)	
			1-(2-thienyl)-3-(2-thienyl)-propan-1-one (15)	
			unidentified (10)	
4	$ClCH_2CH_2CH_2COCl$	$AlCl_3/CH_3NO_2$	4-chloro-1-(2-thienyl)-butan-1-one (75)	
			4-chlorobutanoic acid (17)	
			unidentified (8)	
5	$ClCH_2CH_2CH_2COCl$	$FeCl_3/CS_2$	5-6-dihydrobenzo[b]thiophen-7(4H)-one (18)	
			4-chloro-1-(2-thienyl)-1-butanone (28)	
			3-buten-1-(2-thienyl)-1-one (16)	
			3-butene-1-(3-thienyl)-1-one (10)	
			2-buten-1-(2-thienyl)-1-one (18)	
6	$ClCH_2CH_2CH_2COCl$	$AlCl_3/CS_2$	5,6-dihydrobenzo[b]thiophen-7(4H)-one (37)	
			3-buten-1-(2-thienyl)-1-one (29)	
			tarry material (20)	
7	$CH_3CH{=}CH{-}COCl$	$AlCl_3/CH_3NO_2$	4,5-dihydro-4-methyl-cyclopenta[b]thiophen-6-one (44)	16
			2-buten-1-(2-thienyl)-1-one (8)	16
			3-chloro-1-(2-thienyl)-butan-1-one (20)	
			3-hydroxy-1-(2-thienyl)-butan-1-one (12)	
8	$CH_3CH{=}CH{-}COCl$	$FeCl_3/CS_2$	4,5-dihydro-4-methyl-cyclopenta[b]thiophen-6-one (17)	16
			3-chloro-1-(2-thienyl)-butan-1-one (20)	
			3-hydroxy-1-(2-thienyl)-butan-1-one (6)	
			2-buten-1-(2-thienyl)-1-one (5)	16
			1-(2-thienyl)-butan-1-one (5)	
			unidentified (30)	
9	$CH_3CH{=}CH{-}COCl$	$AlCl_3/CS_2$	4,5-dihydro-4-methyl-cyclopenta[b]thiophen-6-one (26)	16
			3-hydroxy-1-(2-thienyl)-butan-1-one (15)	
			3-chloro-1-(2-thienyl)-butan-1-one (10)	
			unidentified tarry material (45)	
10	$Ph{-}CH{=}CH{-}COCl$	$AlCl_3/CH_3NO_2$	3-phenyl-1-(2-thienyl)-propan-1-one (2)	
			3-phenyl-1-(3-thienyl)-2-propen-1-one (5)	
			3-phenyl-1-(2-thienyl)-2-propen-1-one (91)	16
11	$Ph{-}CH{=}CH{-}COCl$	$FeCl_3/CS_2$	4-phenyl-6H-cyclopenta[b]thiophen-6-one (22)	16
			3-phenyl-1-(2-thienyl)-2-propen-1-one (71)	16
12	$Ph{-}CH{=}CH{-}COCl$	$AlCl_3/CS_2$	3-phenyl-1-(2-thienyl)-2-propen-1-one (75)	16
			cinnamic acid (17)	

It is clear from the above mentioned results, that under mild conditions ($AlCl_3/NO_2$), thiophene is preferentially acylated at position 2, and the produced haloacylthiophene undergoes further reactions in the presence of the stronger catalysts ($FeCl_3/CS_2$, or $AlCl_3/CS_2$). The failure to detect the cyclic products 4,5-dihydro-6H-cyclopenta[b]thiophen-6-one (**10**), or 5,6-dihydro-4H-cyclopenta-[b]thiophen-4-one (**11**) among the reaction products may be attributed to the difficulties encountered with a primary carbocation ring closure to a five-

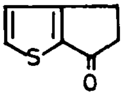


SCHEME 1

membered ring, especially with the carbonyl group deactivation[26] of the thiophene nucleus.

With reference to Table I, the reaction of 4-chlorobutyryl chloride (**4**) with thiophene in the presence of $AlCl_3/CH_3NO_2$ catalyst gave mainly 4-chloro-1-(2-thienyl)-1-butanone (12.7%). The use of stronger catalysts ($FeCl_3/CS_2$, or $AlCl_3/CS_2$) changed the attitude of thiophene toward (**4**). Thus with $FeCl_3$ a mixture of (12.8%), 1-(2-thienyl)-3-buten-1-one (13.1%), 1-(3-thienyl)-3-buten-1-one (14.1%), 1-(2-thienyl)-2-buten-1-one (15.2%) and 5,6-dihydrobenzo[b]thiophen-7(4H)-one (16.2%) was formed. Similarly, using $AlCl_3$ catalyst led to the production of a mixture of (**12**, trace), (**16**; 37%); and 1-(2-thienyl)-3-buten-1-one (**13**; 29%).

It is obvious from the above results that with $FeCl_3$ or $AlCl_3$ the intermediate (**12**) either eliminates HCl to give (**14**) or cyclize to (**16**). Skeletal rearrangement of (**14**) explains the formation of (**14**) and (**15**).



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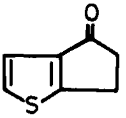


(11)

In the light of the foregoing results, the formation of (**16**) demonstrates, that on the contrary to its reluctance to cyclize to a five-membered ring, a primary carbocation could cyclize fairly into a six-membered ring.

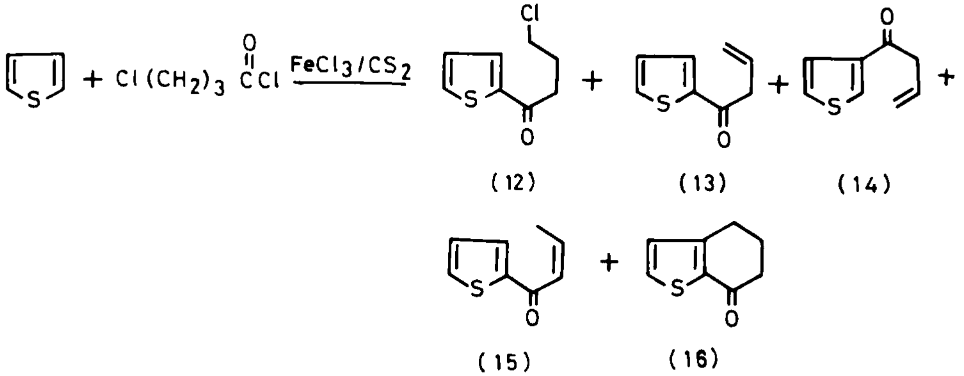


TABLE II

Elementary analysis data

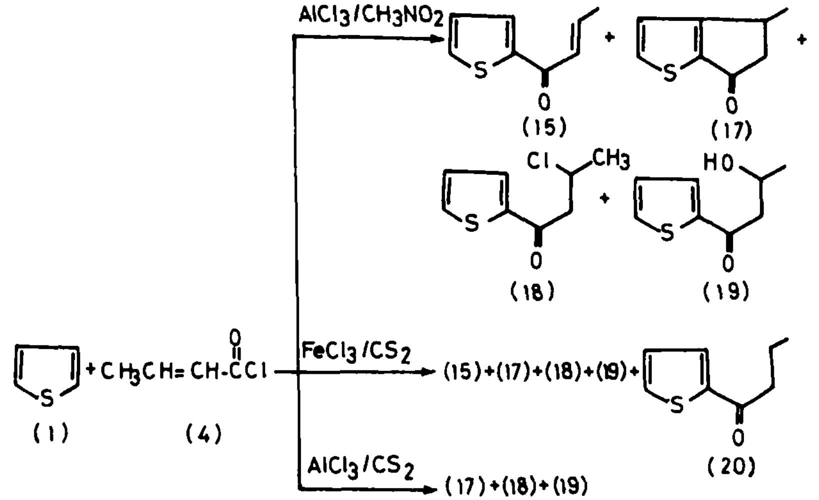
		Calcd.				Found			
Compound	Formula	C	H	Cl	S	C	H	Cl	S
6	C_7H_7ClOS	48.27	4.02	20.11	18.39	48.21	4.00	20.02	17.96
8	$C_{11}H_{13}OS_2$	59.45	4.50	—	28.82	58.93	4.28	—	28.32
9	$C_{13}H_{10}O_3S$	63.41	4.06	—	13.00	63.03	4.00	—	12.87
12	C_8H_9ClOS	51.06	4.78	18.16	17.02	50.86	18.01	18.21	16.81
13	C_8H_8OS	63.15	5.26	—	21.05	63.12	5.07	—	20.90
14	C_8H_8OS	63.15	5.26	—	21.05	63.01	5.10	—	21.00
16	C_8H_8OS	63.15	5.26	—	21.05	63.17	5.24	—	20.84
18	C_8H_9ClOS	51.06	4.78	18.16	17.02	50.79	4.51	17.89	16.71
19	$C_8H_{10}O_2S$	56.47	5.88	—	18.82	56.29	5.69	—	18.56
20	$C_8H_{10}OS$	62.33	6.49	—	20.77	61.88	6.29	—	20.49
24	$C_{13}H_8OS$	73.58	3.77	—	15.09	73.19	3.65	—	14.71

[a] Compounds **7**, **10**, **11**, **15**, **17**, **21**, **22**, and **23** were reported previously (Table I).

[b] ^{1}H NMR was used to differentiate between compounds **13**, **14**, **16** and also between compounds **21**, **18**.

[c] Micro elementary data were obtained using 240 C micro analyzer.

In order to shed some light on the feasibility of a five-membered ring formation through a secondary or more stable carbocation we investigated the interaction of crotonyl and cinnamoyl chlorides with thiophene under different catalysts. The reaction of thiophene with crotonyl chloride is shown in Scheme II.

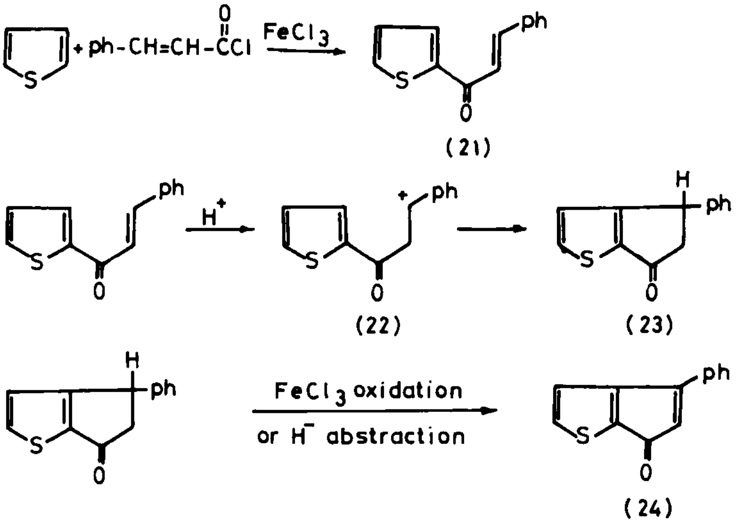


SCHEME 2

The formation of (17; 44%) illustrates the possibility of a five-membered ring closure via an intermediate secondary carbocation. Addition of HCl or H_2O to (**15**) leads to the production (**18**) and (**19**), respectively. Under these reaction conditions hydride abstraction by the intermediate carbocation produced (**20**).

It is of interest to point out that the attitude of thiophene toward cinnamoyl chloride was also, found to be controlled by the catalyst used. Whereas

$AlCl_3/CH_3NO_2$ or $AlCl_3/CS_2$ gave mainly 2-cinnamoylthiophene (**21**) in (90.7%) yield respectively, the use of $FeCl_3/CS_2$ resulted in the production of (**21**; 71%) together with 4-phenyl-6H-cyclopenta[b]thiophen-6-one (**24**; 28%). The whole route to (**24**) can be visualized as follows.



(21)

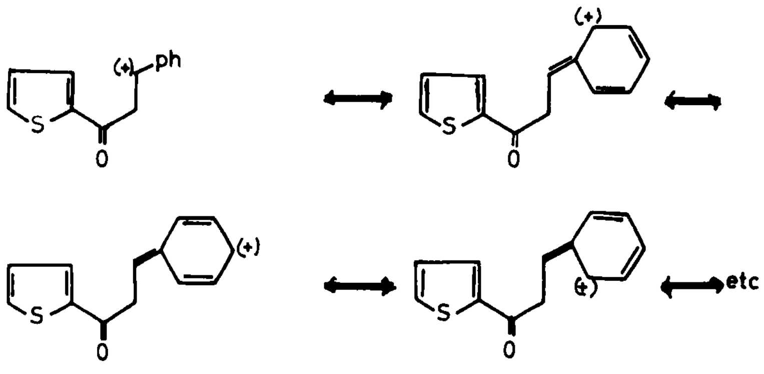
(22)

(23)

(24)

The detection of (**24**) rather than (**23**) could be explained on the ground of either direct oxidation with $FeCl_3$ or tertiary benzylic hydride[27] abstraction by the catalyst followed by loss of a proton to give (**24**).

The lack of formation of (**23**) together with the finding that (**17**) was formed easily under $AlCl_3/CS_2$ conditions directed our attention to the possibility of delocalization of the positive charge in the intermediate carbocation into the adjacent phenyl group and hence its reluctance to cyclize under these conditions. However, such delocalization does not exist in case of the carbocation leading to (**17**).



The intermediacy of (**12**), (**15**), and (**21**) in the formation of (**16**), (**17**), and (**24**) was confirmed by treating (**12**), (**15**), (**21**) separately with the proper catalyst. The major products, as expected were (**16**), (**17**), and (**24**) respectively.

The identities of the products were confirmed by GC/MS, and ^1H NMR spectroscopy.

CONCLUSION

In concluding this paper, we can state that the obtained results are quite interesting, not only from the mechanistic point of view, but also as a demonstration that Friedel–Crafts cyclialkylation reaction can offer facile routes for the synthesis of some thiophene derivatives otherwise difficult to obtain.

EXPERIMENTAL

All melting points were determined on a Kofler melting point apparatus. Chromatographic separation was carried out using 100 × 2 cm glass columns packed with neutral alumina or silica gel as well as 15 × 5 cm glass plates covered with thin film of silica gel. IR spectra were obtained using a Pye-Unicam SP-200 G spectrophotometer. All qualitative and quantitative GC/MS analyses were performed on a Finnigan 4023 quadrupole system equipped with a Model 4500 source upgrade, using a 50-mDB-1 fused Silica WCOT capillary column with a film thickness of 0.25 m. ^{1}H NMR spectra were obtained on an NT-200 spectrometer.

Intermolecular cyclization of thiophene with bifunctional molecules (general procedures)

A) In the presence of $AlCl_3/CH_3NO_2$ catalyst

To a mixture of 0.12 mole of $AlCl_3$ in 50 ml CS_2 placed in two necked flask, 0.12 mole of nitromethane was added slowly while stirring. After stirring for one hour, 0.1 mole of thiophene was added followed by the addition of 0.1 mole of the bifunctional molecule over a period of one hour. The reaction mixture was stirred for an additional two hours at room temperature, decomposed with 10% HCl solution, extracted with methylene chloride and the methylene chloride extract was washed with water, 10% sodium carbonate solution, again with water and dried over magnesium sulfate. The solvents, CH_2Cl_2 and CS_2, were removed by distillation and the residue was subjected to quantitative GC/MS analysis[28] or chromatographed using silica gel in 50 cm × 2 cm column and identified by ^{1}H NMR.

B) In the presence of $AlCl_3$ catalyst

A two necked flask was charged with 0.12 mole $AlCl_3$ and 50 ml dry CS_2. To this mixture, was added 0.1 mole of thiophene followed by dropwise addition of 0.1 mole of the bifunctional compound. The reaction mixture was processed as described previously and the same methods of the products identification were applied.

C) In the presence of $FeCl_3$ catalyst

As in the case of $AlCl_3$ catalyst, with the exception of using $FeCl_3$ instead of $AlCl_3$.

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