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Studies on the Furan Series

Part III. Some Secondary Reactions in the Friedel-Crafts Acylation of Methyl 2-Furoate and Related Compounds. The First Synthesis of a Thienofulvene Ring System

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When methyl 2-furoate (I) is treated with $FeCl_3$ and an excess of an aliphatic acid chloride, the product formed is methyl (Z)-5-(1-chloro-1-alkenyl)-2-furoate instead of the expected ketone. The sulphur analogue of I ethyl 2-thenoylate under similar conditions gave ethyl (Z)-5-(1-chloro-1-alkenyl)-2-thenoylate and ethyl (4E)-6-chloro-5-alkyl-4-alkylidene-4H-cyclopenta[b]-2-thenoylate. Reactions with certain benzene analogues are described and reaction mechanisms are discussed.

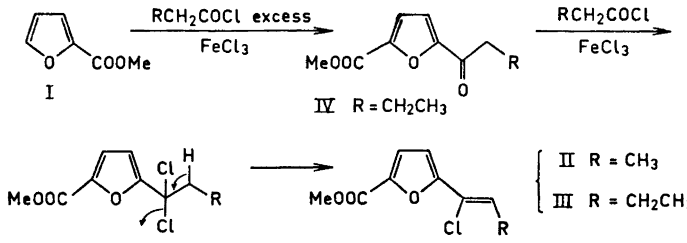
Acylation of methyl 2-furoate (I) has been reported as giving both 5- and 4-ketones.[1–3] Acylation has now been performed in refluxing alkanoyl chloride in the presence of $FeCl_3$. Only one product could be separated from the black, tarry reaction mixture. The compound was identified according to the spectra and elemental analyses as methyl (Z)-5-(1-chloro-1-alkenyl)-2-furoate (II alkenyl = propenyl; III alkenyl = butenyl; AcCl gave only resinous material). The problem of stereoisomerism was solved by comparing the NMR spectra of the products II and III with the NMR spectra of (E)- and (Z)-2-furyl-1-propene. The thermodynamic control under the reaction conditions results in the more stable (Z)-isomer being dominant.

When methyl 5-butyryl-2-furoate (IV) was treated in refluxing butyryl chloride/$FeCl_3$ in the usual manner, III resulted. Refluxing toluene/$FeCl_3$ failed to affect IV; but when HCl was bubbled into the boiling mixture, III was produced. The butyric anhydride/$FeCl_3$ treatment of I gave no reaction. In the preparation of IV, according to the method of Galust'yan,[3] 6 % of III was formed as a byproduct.

While this work was in progress, Torii *et al.*[4] reported that they have isolated 4 – 10 % of ethyl 5-(1-chloro-1-hexenyl)-2-furoate (no mention of the isomerism) and the quite labile ethyl 5-(1,1-dichloro-1-hexyl)-2-furoate from

the reaction of ethyl 2-furoate and hexanoic anhydride in the presence of $SnCl_4$.

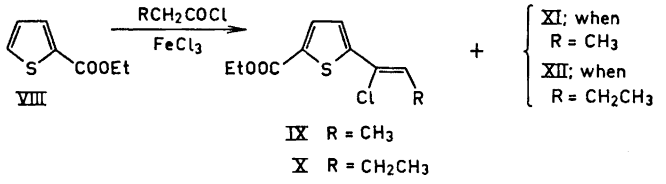
The overall reaction seems to consist of an initial Friedel-Crafts acylation, which is followed by the chlorination of the ketone group and the elimination of HCl from the labile geminal dichloride intermediate (Scheme 1).



Scheme 1.

When butyrophenone was treated with $PrCOCl/FeCl_3$ as above, 4 % of a compound having an identical NMR [5] spectrum to that of (Z)-1-chloro-1-phenyl-1-butene (V), was produced. *p*-Methoxybutyrophenone (VI) gave 28 % of (Z)-1-chloro-1-(*p*-methoxyphenyl)-1-butene (VII) after stirring in $PrCOCl/FeCl_3$ at room temperature. The electron-donating methoxy group in the benzene ring explains the better yield as VI is chlorinated more easily than butyrophenone.

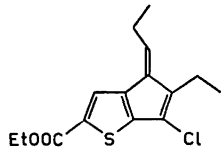
Ethyl 2-thenoylate (VIII) gave the S-heterocyclic analogues of II and III [ethyl (Z)-5-(1-chloro-1-alkenyl)-2-thenoylate; IX alkenyl = propenyl; X alkenyl = butenyl; AcCl gave tar] in refluxing acid chloride. Besides IX and X, 14 – 21 % of a yellow solid was obtained in both cases (XI in propionyl chloride and XII in butyryl chloride; Scheme 2).



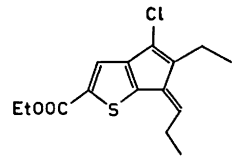
Scheme 2.

The mass spectrum of XII gave the molecular weight as 296 and indicated that the compound contained chlorine. According to the NMR spectrum only one thiophenic proton was present. Four possible isomers result from

the spectral data, *i.e.* the two thienofulvenes, each with (E)- or (Z)-configuration, in the alkylidene position:

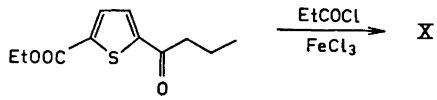


XII



XII a

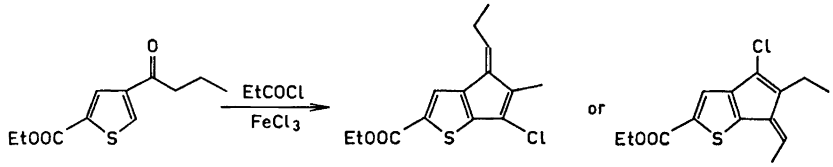
When ethyl 5-butyryl-2-thenoylate (XIII; prepared by a modified method of Robinson [2]) was treated with $EtCOCl/FeCl_3$, X resulted (Scheme 3). This proves that X is not an intermediate of XII.



XIII

Scheme 3.

On the other hand ethyl 4-butyryl-2-thenoylate [2] (XIV), on treatment with $EtCOCl/FeCl_3$, gave a yellow solid (XV; Scheme 4), the alternative structure XVa being ruled out by the presence of an 1-H triplet at τ 3.78 and a 3-H singlet at τ 7.94.



XIV XV XV a

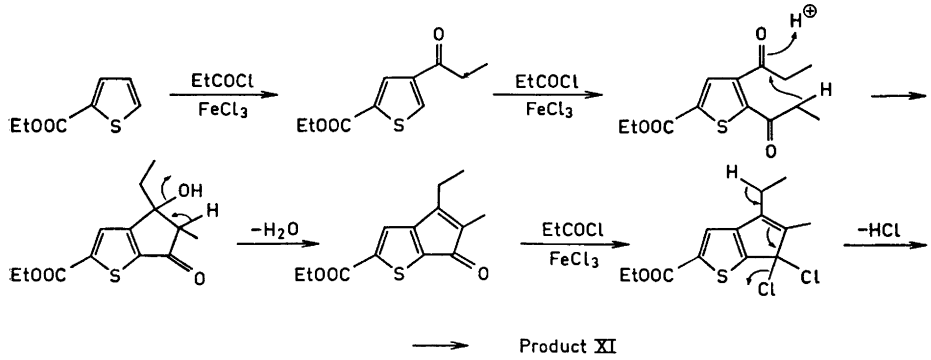
Scheme 4.

Molecular models indicate that the propylidene group is likely to exist in the (E)-configuration, due to the severe steric crowding in the (Z)-form.

Thus the compounds XI, XII, and XV are ethyl (4E)-6-chloro-5-methyl-4-ethylidene-4H-cyclopenta[b]-2-thenoylate, ethyl (4E)-6-chloro-5-ethyl-4-propylidene-4H-cyclopenta[b]-2-thenoylate, and ethyl (4E)-6-chloro-5-methyl-4-propylidene-4H-cyclopenta[b]-2-thenoylate, respectively.

The 4- and 5-acylations of ethyl 2-thenoylate are competitive reactions. However, when the 5-acylation into the thiophene ring has occurred, the electrophilic sulphur and the acyl carbonyl reduce the nucleophility of the 4-

position, and the reaction gives IX and X. The electron-repelling effects of sulphur and the acyl carbonyl after 4-acylation are opposite, and another acylation into the 5-position can now take place. Subsequently acid-catalysed condensation, the chlorination of the ketone group, and elimination of H_2O and HCl, lead to the observed products (Scheme 5).



Scheme 5.

The resonance factors of carbonyls conjugated with the thiophene ring probably cause only 4H-cyclopenta[b]thiophene to be formed.

Thienofulvenes XI, XII, and XV have a new structure system, which is not mentioned in literature. In fact, no one of the four possible thienofulvenes seems to be described earlier. However, some papers,[6–9] which deal with 4H- and 6H-cyclopenta[b]thiophene derivatives, are published.

Methyl 2-furoate (I) did not give any analogous compound such as XI and XII. This is explained by the fact that oxygen has a greater electronegativity than sulphur, and so the 4-acylation of I is difficult under the reaction conditions used.

EXPERIMENTAL

The spectra were determined on the instruments described earlier.[10] All melting points are uncorrected. Butyrophenone and *p*-methoxybutyrophenone were prepared with the Friedel-Crafts acylation. Other chemicals were of commercial quality.

Methyl (Z)-5-(1-chloro-1-butenyl)-2-furoate (III). 5.00 g of methyl 2-furoate (I) and 1.00 g of anh. $FeCl_3$ were refluxed in 50 ml of butyryl chloride for 10 h. The mixture was cooled, poured into ice water and extracted with ether. After the $NaHCO_3$ washing and $MgSO_4$ drying ether was evaporated and the residue, black oil, was purified in a silica gel column (elution with benzene). Yield 4.16 g (41 %) of viscous oil; m.p. of he hydrolyzed compound 132 – 133°C (recryst. from EtOH/H_2O); ν_{max} 2960, 2920, 1730, 1630, 980 cm^{-1}; λ_{max} 290 (ε 28 000) nm; τ 2.92 (1H d 3.5 Hz), 3.50 (1H d 3.5 Hz), 3.48 (1H t 7 Hz), 6.13 (3H s), 7.62 (2 H quintet 7 Hz), 8.88 (3H t 7 Hz); *m/e* 214 (100 %), 199 (63 %), 179 (39 %), 171 (17 %), 155 (19 %), 139 (44 %), 119 (42 %), 105 (18 %), 91 (43 %), 65 (41 %), 63 (32 %), 59 (27 %). (Found: C 50.54; H 4.40 Calc. for $C_{10}H_{11}ClO_3$: C 50.47; H 4.21.)

Methyl (Z)-5-(1-chloro-1-propenyl)-2-furoate (II). 5.00 g of I was refluxed in propionyl chloride and treated like above. Yield 2.40 g (31 %); m.p. of hydrolyzed II 141°C(re-

cryst. from EtOH/H_2O); λ_{max} 289 (ε 27 400) nm; τ 2.92 (1H d 3.5 Hz), 3.48(1H d 3.5 Hz 3.45(1H q 7 Hz), 6.15(3H s), 8.04(3H d 7 Hz). (Found: C 53.67; H 4.86. Calc. for $C_9H_9ClO_3$ C 54.00; H 4.50.)

Treatment of methyl 5-butyryl-2-furoate (IV). When IV was prepared,[3] 6 % of III was separated with the column chromatography from the reaction mixture. 2.00 g of IV and 0.50 g of $FeCl_3$ were refluxed in 20 ml of butyryl chloride for 5 h. After usual treatments 1.80 g of III (81 %) was obtained. When 1.56 g of IV was refluxed with 1.00 g of $FeCl_3$ in toluene 16 h, no reaction occurred. But when HCl was bubbled into the refluxing mixture for 4 h, 0.92 g of III (61 %) formed.

(Z)-1-Chloro-1-phenyl-1-butene (V). 5.00 g of butyrophenone was treated like I in butyryl chloride. Yield 0.32 g (4 %); b.p. 105–110°C/11 mmHg (in a capillary); τ 2.80 (5H m), 4.02(1H t 7 Hz), 7.66(2H quintet 7 Hz), 8.90(3Ht 7 Hz). Literature [5] gives b.p. as 90–94°C/5 mmHg and τ 2.76(5H m), 3.98(1H), 7.63(2H), 8.93(3H).

(Z)-1-Chloro-1-p-methoxyphenyl-1-butene (VII). 5.00 g of *p*-methoxybutyrophenone was stirred for 20 h with 1.00 g of anh. $FeCl_3$ in 50 ml of butyryl chloride at room temperature and treated after that like V. Yield 1.60 g (28 %); b.p. 158–163°C/11 mmHg (in a capillary); τ 2.60(2H d 9 Hz), 3.27(2H d 9 Hz), 4.08(1H t 7 Hz), 6.33(3H s), 7.67(2H quintet 7 Hz), 8.94(3H t 7 Hz). (Found: C 67.22; H 6.48. Calc. for $C_{11}H_{13}ClO$: C 67.35; H 6.63.)

Ethyl (Z)-5-(1-chloro-1-butenyl)-2-thenoylate (X) and ethyl (4E)-6-chloro-5-ethyl-4-propylidene-4H-cyclopenta[b]-2-thenoylate (XII). 5.00 g of ethyl 2-thenoylate (VIII) and 1.00 g of anh. $FeCl_3$ were refluxed in 50 ml of butyryl chloride for 12 h. Purification like V. Yield 3.95 g (51 %) of X (viscous oil); m.p. of hydrolyzed X 139–140°C (recryst. from EtOH/H_2O); λ_{max} 303 (ε 16 700) nm; ν_{max} 2960, 1720, 1620, 1525 cm^{-1}; τ 2.53(1H d 4Hz), 2.94(1H d 4 Hz), 3.84(1H t 7 Hz), 5.75(2H 7 Hz), 7.63(2H quintet 7 Hz), 8.65(3H t 7 Hz), 8.80(3H t 7 Hz); *m/e* 244(60 %), 229(10 %), 209(15 %), 199(40 %), 171(100 %), 157(42 %), 135(44 %), 121(47 %). (Found: C 53.68; H 5.03. Calc. for $C_{11}H_{13}ClO_2S$: C 53.98; H 5.31.) Yield 2.10 g (21 %) of XII (yellow solid); m.p. 85°C (recryst. from EtOH/H_2O); λ_{max} 254 (ε 10 050), 292sh (ε 14 400), 299 (ε 15 400), 375 (ε 2700) nm; ν_{max} 2960, 1680, 1625 cm^{-1}; τ 2.34 (1H s), 3.81(1H t 7 Hz), 5.73(2H q 7 Hz), 7.05–7.80(4H m), 8.40–9.00(9H m); *m/e* 296(100 %), 281(100 %), 267(42 %), 261(12 %), 253(68 %), 244(21 %), 299(19 %), 209(24 %), 174(36 %), 173(51 %), 171(55 %). (Found: C 60.45; H 5.93. Calc. for $C_{15}H_{17}ClO_2S$: C 60.81; H 5.74.)

Ethyl (Z)-5-(1-chloro-1-propenyl)-2-thenoylate (IX) and ethyl (4E)-6-chloro-5-methyl-4-ethylidene-4H-cyclopenta[b]-2-thenoylate (XI). 5.00 g of VIII was refluxed in propionyl chloride and treated as above. Yield 4.60 g (62 %) of IX (viscous oil); m.p. of hydrolyzed IX 169–170°C (recryst. from EtOH/H_2O); τ 2.45(1H d 4 Hz), 2.92(1H d 4 Hz), 3.70(1H q 7 Hz), 5.72(2H q 7 Hz), 8.08(3H d 7 Hz), 8.67(3H 7 Hz). (Found: C 51.97; H 4.48. Calc. for $C_{10}H_{11}ClO_2S$: C 52.17; H 4.78.) Yield 0.76 g (18 %) of XI yellow solid); m.p. 79–80°C; λ_{max} 255 (ε 10 400), 292sh (ε 18 700), 298 (ε 19 500), 377 (ε 2700) nm; τ 2.27(1H s), 3.68(1H q 7 Hz), 5.70(2H q 7 Hz), 7.73(3H d 7 Hz), 7.88(3H s), 8.60(3H d 7 Hz). (Found: C 57.98; H 4.88. Calc. for $C_{13}H_{13}ClO_2S$: C 58.21; H 4.86.)

Treatment of ethyl 5-butyryl-2-thenoylate (XIII). 1.00 g of XII [2] and 0.20 g of anh. $FeCl_3$ were treated in propionyl chloride as above. TLC showed that only X was formed.

Ethyl (4E)-6-chloro-5-methyl-4-propylidene-4H-cyclopenta[b]-2-thenoylate (XV). 0.16 g of ethyl-4-butyryl-2-thenoylate (XIV) [2] and 0.05 g of anh. $FeCl_3$ were treated like XIII. Yield 0.07 g (37 %); m.p. 78–79°C; τ 2.55(1H s), 3.78(1H t 7 Hz), 5.78(2H q 7 Hz), 7.66(2H quintet 7 Hz), 7.94(3H s), 8.60–9.10(6H m).

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REFERENCES

1. Gillman, H. and Calloway, N. D. *J. Am. Chem. Soc.* **55** (1933) 4197.
2. Robinson, G. C. *J. Org. Chem.* **31** (1966) 4252.
3. Galust'yan, G. G. and Tsukervanik, I. P. *Zh. Obshch. Khim.* **34** (1964) 1478. Ref. *Chem. Abstr.* **61** (1964) 5590b.

4. Torii, S., Tanaka, H., Ogo, H. and Yamasita, S. *Bull. Chem. Soc. Japan* **44** (1971) 1079.
5. Newman, S. and Kaugars, G. *J. Org. Chem.* **30** (1965) 3295.
6. Meth-Cohn, O. and Gronowitz, S. *Acta Chem. Scand.* **20** (1966) 1577.
7. Meth-Cohn, O. and Gronowitz, S. *Acta Chem. Scand.* **20** (1966) 1733.
8. Sam, J. and Thompson, A. C. *J. Pharm. Sci.* **52** (1963) 898.
9. MacDowell, D. W. H., Patrick, T. B., Frame, B. K. and Ellison, D. L. *J. Org. Chem.* **32** (1967) 1226.
10. Pennanen, S. I. and Nyman, G. A. *Acta Chem. Scand.* **26** (1972) 1018.

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