Novel Synthesis of Thiophen-3-malonic Esters and their Selenophen Analogues

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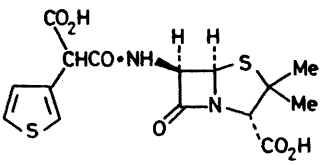
Summary Condensation of 1,4-dichlorobut-3-en-2-one with malonic esters gives the corresponding Knoevenagel adducts which may be cyclised directly to thiophen-3-malonic esters or their selenophen analogues.

THIOPHEN-3-MALONIC ACID (**1a**) has pharmaceutical importance as the side-chain intermediate used in the production of the semisynthetic β-lactam antibiotic ticarcillin (**2**).[1,2] Currently, this intermediate is prepared by elaboration of preformed 3-substituted thiophens.[3] We now report the first example known to us of a direct cyclisation to thiophen-3-malonates.

It was thought that a suitable substrate for such a cyclisation would be a diene of type (**3**). Such a species



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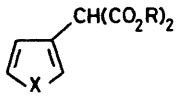
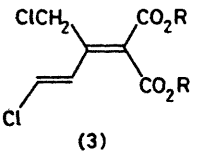


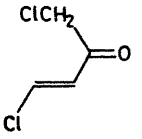
(1)

a: R = H, X = S
b: R = Me, X = S
c: R = Et, X = S
d: R = $PhCH_2$, X = S
e: R = Et, X = Se



(3)

a: R = Me
b: R = Et
c: R = $PhCH_2$



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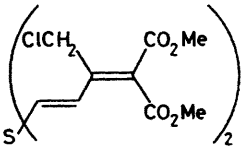

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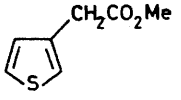

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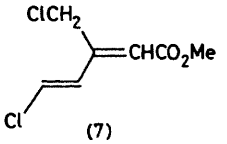

(7)

would possess, in its chlorine atoms, two reactive leaving groups which might be displaced by a single dibasic sulphur nucleophile. The initial transient cyclic product should then undergo double bond migration to the desired thiophen (**1b**—**d**). The diene diesters (**3a**–**c**) were prepared in two steps from chloroacetyl chloride. Typically, reaction of chloroacetyl chloride with acetylene and aluminium chloride in dichloromethane gave, in improved yield (75%), 1,4-dichlorobut-3-en-2-one,[4] predominantly as the *trans*-isomer (**4**). Although the chlorovinyl group of the ketone (**4**) is susceptible to nucleophilic attack,[5] Knoevenagel condensations with malonic esters were successfully carried out by employing the method of Lehnert[6] (titanium tetrachloride–pyridine). For example, condensation with dimethyl malonate (3 h, ambient temperature) afforded methyl-5-chloro-3-chloromethyl-2-methoxycarbonylpenta-2,4-dienoate as the *trans*-isomer (**3a**) (m.p. 56 °C; 48% yield).

Cyclisation of the dienes (**3a**–**c**) to the thiophens (**1b**–**d**) was carried out in several different ways:[7] by treatment with hydrogen sulphide in the presence of base (KOH–EtOH, or NEt_3–CH_2Cl_2[8]); with sodium hydrogen sulphide in aqueous methanol; or preferably, with sodium sulphide. Thus, a solution of the dichloride (**3a**) in tetrahydrofuran, stirred for 16 h with sodium sulphide nonahydrate (1·4 equiv.), gave dimethyl thiophen-3-malonate (**1b**) (b.p. 93—95 °C at 0·2 mmHg; 53% yield). When this reaction was carried out using a deficiency of sodium sulphide, the symmetrical sulphide (**5**)[9] was isolated in low yield after chromatography on silica. This suggests that the initial attack of sodium sulphide in the above cyclisation occurs at the vinyl chloride group.

Some broadening of the scope of this synthesis has been possible. Reaction of the dichloride (**3b**) with sodium selenide in the usual way afforded the corresponding selenophen (**1e**) (b.p. 137—138 °C at 1 mmHg; 47% yield). Although the yields are inferior, the chloro-ketone (**4**) has also been elaborated to the thiophen-3-acetic ester (**6**) by reaction with methyl triphenylphosphoranylideneacetate (90° C; 16 h) to give methyl 5-chloro-3-chloromethylpenta-2,4-dienoate (**7**), which was subsequently cyclised (H_2S–KOH–EtOH) to methyl thiophen-3-acetate (**6**).[10]

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