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A NEW RING-OPENING REACTION OF 3-CHLORO-1,2-BENZISOTHIAZOLE

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German workers[1] have reported recently that the reaction of 3,4-dichloro-1,2-benzisothiazole with sodium alkoxides or with secondary amines gives the expected nucleophilic substitution product, together with small amounts of material formed by fission of the isothiazole ring. In an attempt to prepare 1,2-benzisothiazole-3-carbonitrile, we boiled 3-chloro-1,2-benzisothiazole[2] for 30 min with sodium cyanide in aqueous acetone. None of the required product could be detected; instead we obtained 2-thiocyanatobenzonitrile (62%), bis(2-cyanophenyl)disulphide (22%), and crystalline basic material (6%).** Obviously, the ring-opening reaction observed by Becke and Hagen[1] had become the major reaction under the conditions used. Physical evidence [M^+ 191.0373 ($C_{10}H_9NOS$ requires 191.0405); δ (in $CDCl_3$) 7.77-7.28 (4H, m, arom.H), 6.73 (2H, br, NH_2), and 2.42 p.p.m. (3H, s, Ac); $\nu_{max.}$(KCl) 3410, 3310 (NH_2), and 1615 (C=O) cm^{-1}] suggested that the basic material was the hitherto unknown 2-acetyl-3-aminobenzo[b]thiophen. Moreover, it was readily diazotised, and the resulting diazonium salt reacted with hypophosphorous acid to give the known[3] 2-acetylbenzo[b]thiophen. It seemed probable that 2-acetyl-3-aminobenzo[b]thiophen had been formed by reaction between 3-chloro-1,2-benzisothiazole

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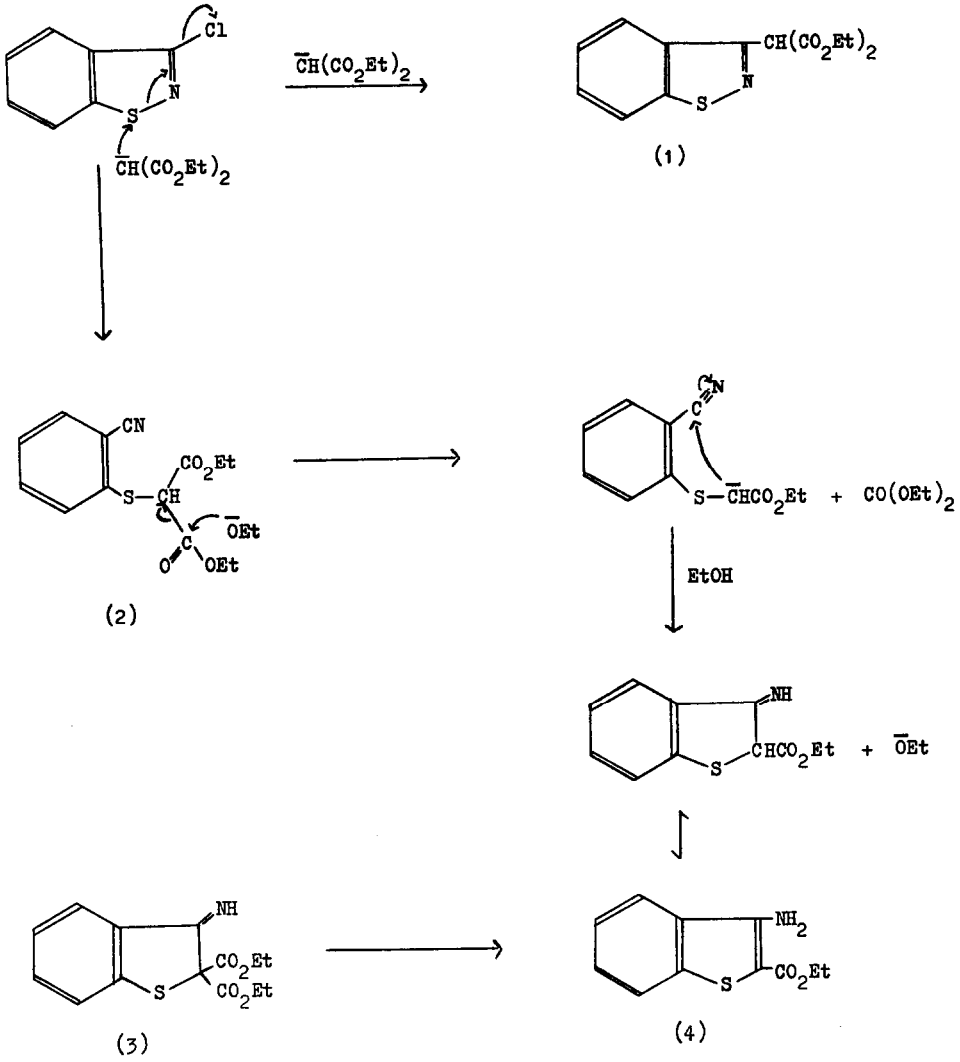
** The percentage composition of the mixture was obtained from a quantitative study of the i.r. spectrum of the crude mixture, using the pure components as standards.

and the carbanion generated from acetone under the basic reaction conditions.

In order to investigate this hypothesis further, we treated 3-chloro-1,2-benzisothiazole with a series of 1,3-dicarbonyl compounds in the presence of sodium ethoxide, since carbanions are produced very readily from such compounds under these conditions. Treatment with sodio diethyl malonate at room temperature for 30 min, and then under reflux for 30 min, gave a mixture of diethyl (1,2-benzisothiazol-3-yl)malonate (1) (46%) and ethyl 3-aminobenzo[b]thiophen-2-carboxylate (4) (28%). The latter compound was the major product (70%) when the reaction was carried out at room temperature for 48 h. Its structure was confirmed by successive deamination (hypophosphorous acid on the diazonium salt) and alkaline hydrolysis, to give the known[4] benzo[b]thiophen-2-carboxylic acid. Alternatively, the ester (4) could be hydrolysed and decarboxylated to give the unstable 3-aminobenzo[b]thiophen, which could then be characterised as the known[5] N-acetyl derivative.

Heating 3-chloro-1,2-benzisothiazole under reflux for 4 h with pentan-2,4-dione in ethanolic sodium ethoxide gave 2-acetyl-3-aminobenzo[b]thiophen (80%); this was identical with the minor product of the reaction with sodium cyanide in aqueous acetone. Similar treatment of 3-chloro-1,2-benzisothiazole with sodio ethyl acetoacetate gave mainly ethyl 3-aminobenzo[b]thiophen-2-carboxylate (4), and a small amount (<5%) of 2-acetyl-3-aminobenzo[b]-thiophen.

Clearly, the diester (1) is formed by the direct nucleophilic displacement of the 3-chloro-group, and at first it seemed possible that the ester (4) could be formed from it by opening of the alkali-sensitive isothiazole ring in the presence of sodium ethoxide, followed by recyclisation to give the more stable benzo[b]thiophen system. However, when the diester (1) was boiled with ethanolic sodium ethoxide, none of the expected mono-ester (4) could be detected. Consequently, we now believe that the ester (4) results from an initial attack by the carbanion on the sulphur atom of the isothiazole ring, with extrusion of chloride ion and formation of the nitrile (2). This could then lose an ethoxycarbonyl group in a retro-Claisen reaction (as outlined in the reaction scheme) and cyclise to give the observed product (4). Alternatively, intermediate (2) may first cyclise to give (3) which could then lose an ethoxycarbonyl group to give the observed product (4). Analogous mechanisms would explain the formation of the products obtained from the reaction with pentan-2,4-dione or ethyl acetoacetate. Some confirmation of the proposed mechanism comes from the identification (g.l.c.) of diethyl carbonate in the crude mixture from the diethyl malonate reaction, and of


Cl
N
S
$\bar{C}H(CO_2Et)_2$
$\bar{C}H(CO_2Et)_2$
$CH(CO_2Et)_2$
(1)
CN
CO_2Et
S—CH
$\bar{O}Et$
C
O
OEt
(2)
C≡N
$S-\bar{C}HCO_2Et$ + $CO(OEt)_2$
EtOH
NH
$CHCO_2Et$ + $\bar{O}Et$
NH
CO_2Et
CO_2Et
(3)
NH_2
CO_2Et
(4)

ethyl acetate in the mixture from the reaction with pentan-2,4-dione or with ethyl acetoacetate. In addition, we have found that ethyl (2-cyanophenylthio)acetate and (2-cyanophenylthio)acetone cyclise spontaneously in alkaline solution to give ethyl 3-aminobenzo[b]thiophen-2-carboxylate (4) and 2-acetyl-3-aminobenzo[b]thiophen respectively.

The above reactions appear to form the basis of an excellent method for preparing certain 2-substituted 3-aminobenzo[b]thiophens. Hitherto such compounds have been inaccessible. The scope of the reaction is being investigated.

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