A New Route to 3,4-Disubstituted Tetrahydrothiophenes

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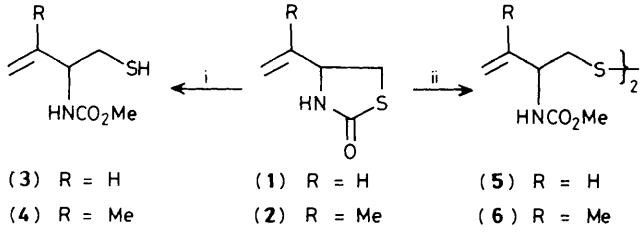
Reaction of readily available thiazolidinones with *N*-bromosuccinimide affords 3,4-disubstituted tetrahydrothiophenes.

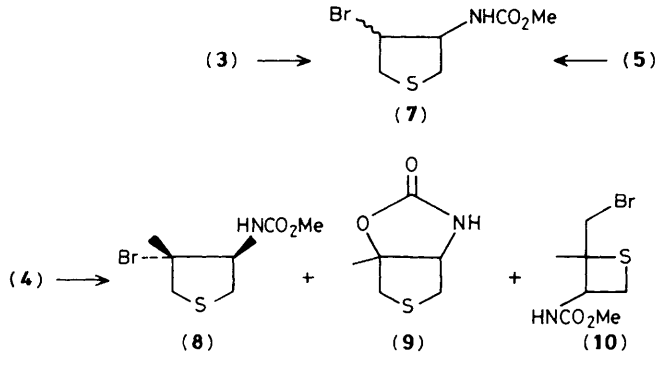
A route to 3,4-disubstituted tetrahydrothiophenes can be envisaged by the attack of electrophiles on derivatives of 2-aminobut-3-ene-1-thiols. Such a cyclisation of acyclic derivatives is of interest because of recent reports[1] of the synthesis of such thiophenes stimulated by the need[2] to establish new routes to biotin. We have recently described[3] the preparation of derivatives of 2-aminobut-3-ene-1-thiols from the unsaturated thiazolidinones (**1**) and (**2**) which are available in high yield from the appropriate 1,4-dihalogenobut-2-enes. We now describe not only the multistep conversion of the thiazolidinones (**1**) and (**2**) into 3,4-disubstituted tetrahydrothiophenes *via* derivatives of 2-aminobut-3-enes-1-thiols, but also the remarkably simple direct conversion of the thiazolidinones (**1**) and (**2**) with *N*-bromosuccinimide into 3-bromo-4-isocyanatotetrahydrothiophenes.

The thiols (**3**) and (**4**) and the disulphides (**5**) and (**6**) have been obtained[3] in good yield from the respective thiazolidinones (Scheme 1). Bromination of the thiol (**3**) or the disulphide (**5**) in dichloromethane gives the carbamates (**7**) in 63 and 61% yield, respectively (Scheme 2). In contrast, bromination of the thiol (**4**) gives three major products: the tetrahydrothiophene (**8**) (20%), the bicyclic compound (**9**) (28%), and the thietane (**10**) (35%) (Scheme 2). Bromination of the disulphide (**6**) gives the thietane (**10**) in 75% yield. The structures of the products were established by a combination of spectroscopy (^1H and ^{13}C n.m.r.), microanalysis, and reactions to establish the skeleton (debromination with $Zn/MeCO_2H$ or Bu^n_3SnH) and the stereochemistry (with sodium hydride *trans*-derivatives afford aziridines,† in accord with literature precedent[4]).

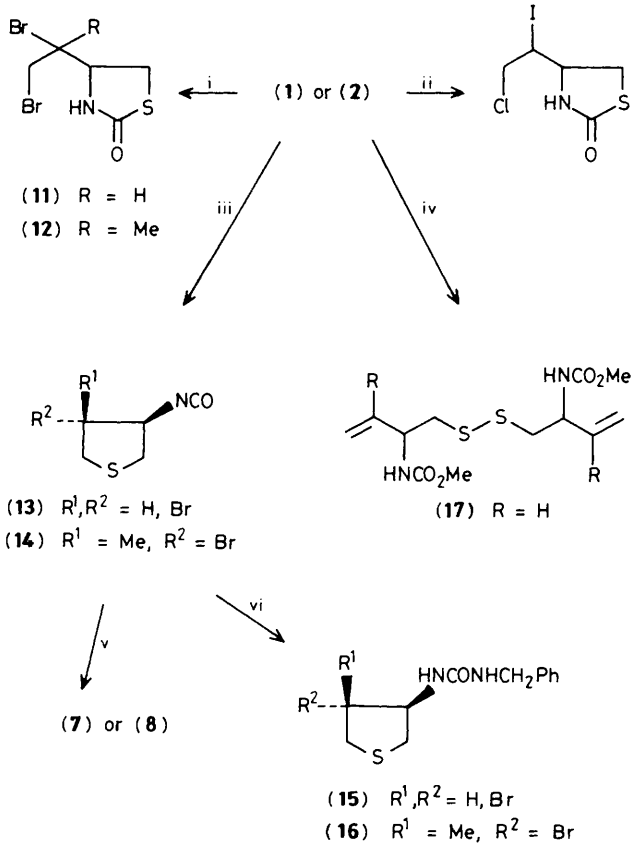
Direct bromination of the thiazolidinones (**1**) and (**2**) in dichloromethane gives mixtures of the diastereoisomeric dibromides (**11**) and (**12**), respectively, although we note that addition of iodine monochloride to the thiazolidinone (**1**) proceeds in an anti-Markovnikov sense (Scheme 3). However reaction of the thiazolidinones (**1**) and (**2**) with *N*-bromosuccinimide in dichloromethane gives the bromo isocyanates (**13**) and (**14**), respectively, in 87 and 96% yields. From the thiazolidinone (**1**) a mixture of *cis*- and *trans*-isomers is obtained but from the thiazolidinone (**2**) the single isomer (**14**) is isolated (Scheme 3). The isocyanates (**13**) and (**14**) are sufficiently stable to permit distillation, but react readily with



Scheme 1. *Reagents:* i, KOH, MeOH, N_2; ii, KOH, MeOH, O_2.



Scheme 2



Scheme 3. *Reagents:* i, Br_2, CH_2Cl_2; ii, ICl, CH_2Cl_2; iii, *N*-bromosuccinimide, CH_2Cl_2; iv, *N*-iodosuccinimide, CH_2Cl_2 MeOH; v, MeOH; vi, $PhCH_2NH_2$.

† Whereas *cis*-derivatives afford unsaturated monocyclic products.

alcohols and amines, *e.g.* with methanol the carbamates (**7**) and (**8**) are obtained, and with benzylamine the ureas (**15**) and (**16**) are formed in high yield.

Although the nature of the variety of products isolated from the foregoing reactions implies mechanistic complexities, which will be discussed in a full paper, it is likely that reaction of the thiazolidinones (**1**) and (**2**) with *N*-bromosuccinimide proceeds *via* initial electrophilic attack at sulphur with formation of an acyclic isocyanate. In support of this view we find that the thiazolidinone (**1**) on treatment with *N*-iodosuccinimide in dichloromethane gives the disulphide (**17**). In the reaction with *N*-bromosuccinimide the ready cyclisation of an intermediate sulphenyl bromide is expected, by analogy with results obtained in the penicillin[5] and prostacyclin[6] areas. Reaction of unsaturated thiols with iodine gives sulphenyl iodides, and their ready conversion, even in the absence of oxygen, into disulphides has been described.[7] Our results not only suggest the use of unsaturated thiazolidinones as precursors of unsaturated sulphenyl halides; they also establish a route *via* the bromo isocyanates (**13**) and (**14**) to 3,4-disubstituted tetrahydrothiophenes in high yield.

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