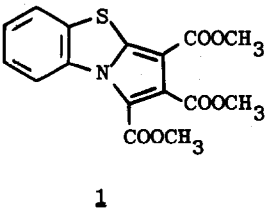
Tetrahedron Letters No. 35, pp 3081 - 3084, 1975. Pergamon Press. Printed in Great Britain.

# ELUCIDATION OF THE REACTIONS OF BENZOTHIAZOLE WITH DIMETHYL ACETYLENEDICARBOXYLATE

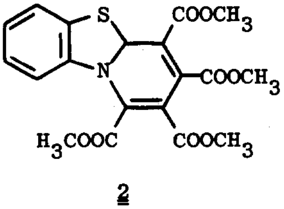
Alexander McKillop* and Trevor S.B. Sayer
School of Chemical Sciences, University of East Anglia
Norwich NR4 7TJ, England

(Received in France 20 February 1975; received in U.K. for publication 17 July 1975*)

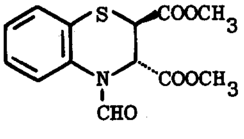
There have been a number of conflicting reports during the last few years on the structures of the products obtained from the reaction of benzothiazole with dimethyl acetylenedicarboxylate (DMAD). Reid *et al*. claimed in 1964 that condensation of benzothiazole with two equivalents of DMAD in methanol gave trimethyl pyrrolo[2,1-*b*]benzothiazole-1,2,3-tricarboxylate 1 in 40% yield as a colourless solid, mp 135-136°; they did not, however, present any evidence in substantiation of the proposed structure.[1] One year later, Acheson and his coworkers reported that tetramethyl 5*a*H-dibenzo[*bd*]thiazole-6,7,8,9-tetracarboxylate 2, mp 234°, was formed in 21% yield when the reaction was carried out in the absence of solvent.[2] Finally, Ogura and his colleagues found in 1974 that the reaction in methanol at room temperature gave 2 in 5% yield together with an 8% yield of *trans*-dimethyl 4-formyl-2,3-dihydrobenzothiazine-2,3-dicarboxylate 3, mp 135-136°, the structure of which was established by X-ray diffraction analysis.[3,4]



1



2



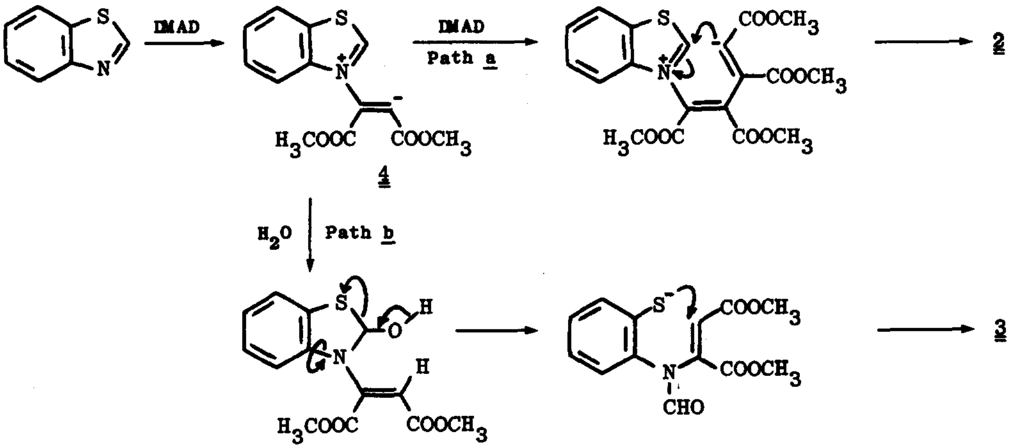
3

We have reinvestigated the reactions carried out in methanol, and our results show that (a) structure 1 proposed by Reid is incorrect; (b) formation of 2 and 3 is fully compatible with current ideas on the mechanisms of additions of DMAD to heterocyclic systems; and (c) the potential utility of heterocycle/

DMAD condensations for the construction of novel heterocyclic systems has not nearly been fully explored.

The tricyclic compound 2 is the "expected" reaction product[5] and its formation can readily be rationalised as shown in the Scheme (path a). Formation of the "anomalous" product 3 can also be simply explained as shown in the Scheme (path b), provided it is assumed that there are small amounts of water present in the methanol used as solvent. This assumption was easily verified:

Scheme



reaction of equimolar amounts[6] of benzothiazole and DMAD in aqueous methanol (1:6, v/v) proceeded smoothly without formation of polymeric material,[7] and after either three days at room temperature or five hours at reflux temperature, crude 3 was obtained in virtually quantitative yield. Recrystallisation from absolute alcohol gave an 85% yield of pure 3 as colourless prisms, mp 135-136$^{\circ}$ (Anal. Calcd. for $C_{13}H_{13}NO_5S$: C, 52.88; H, 4.41; N, 4.76; S, 10.85. Found: C, 52.63; H, 4.42; N, 4.79; S, 10.88); IR (Nujol): $\nu_{C=O}$ 1745 (ester), 1740 (ester) and 1690 (amide); NMR (DMSO-$d_6$): singlets at $\delta$3.65 (6H, $COOC\underline{H}_3$), and 8.9 (1H, N-C$\underline{H}$O), a multiplet at $\delta$7.10-7.70 (4H, aromatic protons), and two doublets at $\delta$4.70 and 6.15 (1H each, $J$ = 5 Hz, $C\underline{H}COOCH_3$).

That production of 3 is only possible when there is water present was also readily demonstrated; the results obtained from a number of reactions in which the amount of water was varied systematically are summarised in the Table. That is, in anhydrous methanol the only product which is formed, in low yield, is the "expected" product 2; compound 3 is formed in low yield when small amounts of water are present, and the yield increases gradually with increasing water content, while formation of 2 is simultaneously suppressed, even when very small amounts of water are present.

Table

Effect of added water on the reaction of benzothiazole (0.01 mol) with DMAD (0.01 mol) in methanol (30 ml) to give 2 and/or 3

| Water, ml | 0 | 0.05 | 0.10 | 0.15 | 5 |
|---|---|---|---|---|---|
| 2 yield, %[a] | 5 | 3 | 0 | 0 | 0 |
| 3 yield, %[a] | 0 | 8 | 14 | 20 | 85 |

[a] Refers to pure, isolated material

From these results it follows that structure 1 is incorrect, and that the product isolated by Reid *et al*. is in fact 3. Moreover, from the data in the Table it follows that either the methanol or the DMAD used by both Reid *et al*. and by Ogura *et al*. must have contained small amounts of water.[8]

The above results clearly indicate that in this reaction the initial addition product 4 formed from benzothiazole and DMAD can be trapped very effectively with water rather than DMAD and that the overall course of reaction can thus be diverted to production of 3. Condensation of DMAD with heterocyclic systems is now a well established procedure for the preparation of many polycyclic heteroaromatic systems,[5] and it is noteworthy that the majority of such reactions have been carried out in the absence of solvent other than DMAD itself. The probability that initial dipolar adducts analogous to 4 can also be trapped in the reactions of other heterocycles with DMAD, and hence that the overall course of the reactions can be altered simply by addition of an external nucleophile or the use of a nucleophilic solvent, should result in the development of novel procedures for the synthesis of many otherwise difficultly accessible heterocycles. We are currently exploring a variety of such reactions.

## References

* The long delay in publication of this paper is due to loss of the original manuscript in the postal service.

1. D.H. Reid, F.S. Skelton, and W. Bonthrone, *Tetrahedron Letters*, 1797 (1964).
2. R.M. Acheson, M.W. Foxton, and G.R. Miller, *J. Chem. Soc.*, 3200 (1965).
3. H. Ogura, H. Takayanagi, K. Furuhata, and Y. Iitaka, *J.C.S. Chem. Comm.*, 759 (1974).
4. H. Ogura and K. Kikuchi, Abstracts of 93rd. Annual Meeting, Pharm. Soc. Japan, II-101 (1973).
5. R.M. Acheson, *Adv. Heterocyclic Chem.*, **1**, 125 (1963).
6. All of the other workers used two equivalents of DMAD, presumably in the expectation of obtaining a 2:1 adduct with the heterocycle. Reaction of benzothiazole with two equivalents of DMAD in aqueous methanol gave 0% of **2** and 75% of **3**; the slight decrease in yield relative to the reaction carried out with equimolar amounts of reactants is due to the fact that **3** is appreciably soluble in DMAD.
7. Addition of benzothiazole to DMAD gives a deep red solution, and reaction proceeds with formation of considerable amounts of tarry, polymeric materials. Reactions carried out in absolute methanol or in methanol containing small amounts of water similarly gave rise to deep red solutions and formation of polymeric materials. In the presence of excess water the reaction mixture is pale yellow in colour, and **3** crystallises from it as a colourless solid. Tlc examination of the crude product showed that the only impurities present were trace amounts of benzothiazole and DMAD.
8. No description is given in Refs. 1 and 3 of the experimental conditions used to effect condensation of DMAD with benzothiazole.