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PHOTOCYCLOADDITIONS TO 2-PHENYLBENZOTHIAZOLE

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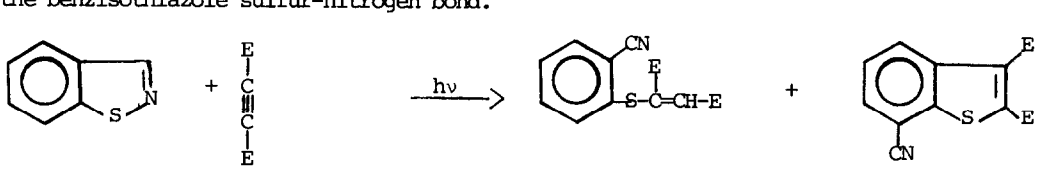
Photocycloadditions to 2-phenylbenzothiazoles proceed in high yield with certain alkenes to produce 1,5-benzothiazepines. We report herein the first example of an intermolecular photoaddition to a benzothiazole in which a seven membered heterocyclic system is obtained. The cycloaddition reactions are both regiospecific and stereospecific.

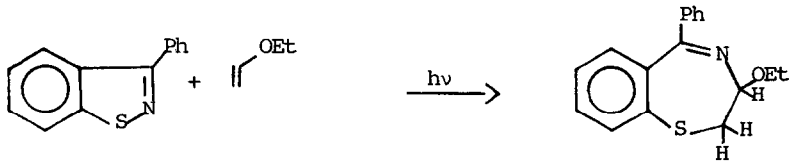
As an extension of our interest in photocycloadditions of condensed heteroaromatic systems containing one heteroatom [benzo(b)thiophene, benzo(b)furan, indole][1a-e] and two heteroatoms, benzisothiazole[2a,b], we have spent considerable effort investigating the photochemistry of derivatives of benzothiazole. The rationale had it that [2+2]π photocycloaddition of an alkyne to a benzothiazole - followed by thermal ring opening - would provide direct one-step entry into 1,5-benzothiazepines.

As we have previously indicated[2a,b] photocycloaddition of benzisothiazoles (1) to alkynes, such as dimethyl acetylenedicarboxylate, or two alkenes such as ethyl vinyl ether results in the formation of the photoproducts (II), (III) and (IV). We suggest these products derive from trapping the intermediate biradical obtained after homolytic cleavage of the benzisothiazole sulfur-nitrogen bond.[3]



(I a) E = $COOCH_3$ (II) (III)

(1)

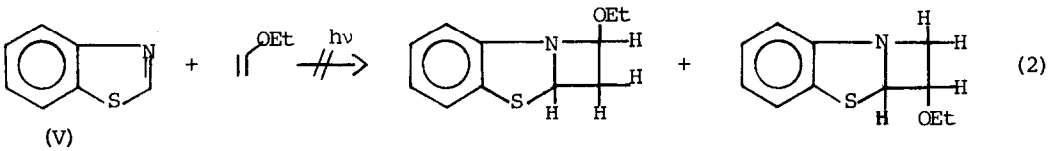


(I b) (IV)

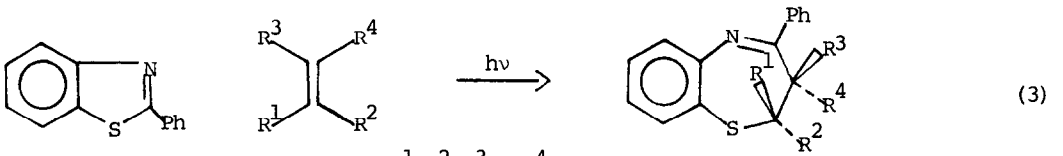
As an example reaction, ethyl vinyl ether and 3-phenylbenzisothiazole (Ib) produced the substituted 2,3-dihydro-1,4-benzothiazepine (IV) - a potentially pharmacologically active system.

We anticipated that benzothiazole (V) and its derivatives might undergo [2+2] photocycloadditon at the carbon-nitrogen double bond,[4] providing the potential benzothiazepine system. It is also so that this cycloadduct is a penicillin precursor. Contrary to our expectation, unsubstituted benzothiazole was photostable in the presence of alkenes (2) as were some other simple benzothiazoles tested. Instead of undergoing cycloaddition, most benzothiazoles simply fluoresced.

Irradiation of 2-phenylbenzothiazole (VI) under the same conditions, gave cyclic adducts and produced derivatives of 2,3-dihydro-1,5-benzothiazepine (VIII) (3), the product structures being suggested by spectroscopic and chemical evidence.



(V) (2)

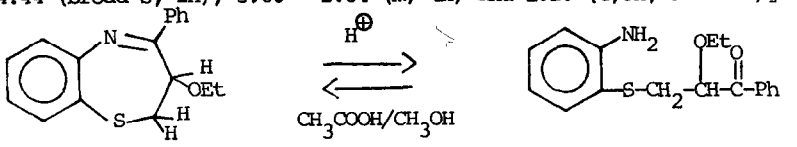


(VI) (VII) a) $R^1=R^2=R^3=H;R^4=OEt$ (VIII) a) (3)
b) $R^1=R^3=H;R^2=R^4=CH_3$ b)
c) $R^2=R^3=H;R^1=R^4=CH_3$ c)

This is the first known example of an intermolecular photoaddition to a benzothiazole in which either a $[2+2]\pi$ cycloadduct, or a seven membered heterocyclic system, derives and the reaction proceeds both regioselectively and stereospecifically. We suggest 2-arylbenzothiazoles are photochemically reactive because they are analogous - spectroscopically - to Schiff bases and take advantage of the extended conjugation the aryl group provides.[5]

In a particular example, irradiation, through Pyrex, of 2-phenylbenzothiazole (VI)[6] in ethyl vinyl ether ($5\text{-}10^{-2}$M) (VII a) purged with nitrogen using a high pressure mercury arc for 45 hours gave, after evaporation of the ethyl vinyl ether and chromatographic separation on silica gel one product, 3-ethoxy-4-phenyl-2,3-dihydro-1,5-benzothiazepine (VIII a) - in 75% yield as a yellow oil. Spectroscopic data supports the proposed structure. Thus, the mass spectrum showed a molecular ion of 283 (1:1 adduct) and a base peak with m/e 211 (M^+-72, i.e. $M^+ - CH_2{=}CH{-}OC_2H_5$). In the NMR spectrum the 3 hydrogens on C-2 and C-3 appeared as a typical ABX system: δ 4.43 (X,dd), δ 3.9 and 3.61 (A and B, 2dd) with J_{AX}=6, J_{BX}=10 and J_{AB}=11.5 Hz.[7] Chemical evidence for the 1,5-benzothiazepine structure was obtained by acid hydrolysis of the product (VIII a), which hydrolysed at the room

temperature[8] giving α-ethoxy-β-(2-aminophenylmercapto)-propiophenone (IX) [IR: 3440 and 3340 cm^{-1} (NH_2), 1690 cm^{-1} (C = O);[9] NMR: δ7.91-6.57 (m,9H), 4.60 (dd,1H, J= 5 and 8 Hz), 4.44 (broad s, 2H), 3.66 - 2.84 (m, 4H) and 1.20 (t,3H, J = 7Hz)].

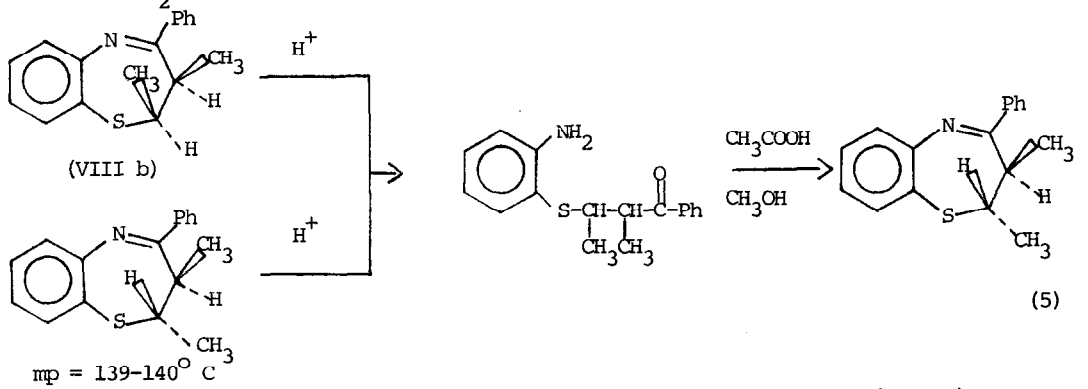


(4)

(VIII a) (IX)

After recondensation[10] of (IX) in methanol with a catalytic amount of acetic acid the cyclized product (VIII a) was reobtained, unequivocally proving that the compound (VIII a) has the structure ascribed.

The stereospecificity of the cycloaddition reaction with 2-phenylbenzothiazole was shown by the reactions with cis-butene (VII b) and trans-butene (VII c). In both cases only one photoproduct (VIII b) and (VIII c) was obtained. The reaction with cis-butene was much faster. Thus, degassed solution ($8x10^{-2}$M) of 2-phenylbenzothiazole (VI) in cis-butene (VII b) in a sealed Pyrex tube irradiated with a Hg high pressure lamp for 120 hrs. produced 57% of the product (VIII b). Under the same conditions the reaction with trans-butene produced only 10% of the product (VIII c). The cis-isomer of 2,3-dimethyl substituted 2,3 dihydro-4-phenyl-1,5-benzothiazepine (VIII c) isomerized to trans-isomer upon standing for one month at room temperature. Acidic hydrolysis of either (VIII b) or (VIII c) produces α,β-dimethyl-b-(2-aminophenylmercapto)-propiophenone (X) [IR:3480 and 3370 cm^{-1} (NH_2), 1690 cm^{-1} (C = O)].



(5)

(VIII b)

(VIII c) mp = 139-140° C

(X)

(VIII c)

Recondensation, (X) in the presence of acetic acid in methanol, produced the thermodynamically more stable trans-isomer (VIII c). The NMR spectrum of this product shows two separated multiplets (double quartets with J_{vic} = 10.5 Hz[11]) at δ 3.80 and 2.70 assigned to the hydrogens on C-2 and C-3 respectively.[12] From spin decoupling it was obvious that the doublet at δ 1.40 belonged to the methyl group which is coupled with the hydrogen at δ 3.80 and the doublet at δ 1.04 to the hydrogen at δ 2.70.

The mechanism of these reactions is not yet completely investigated. It might be

possible that sulfur-carbon cleavage in the excited state of 2-phenylbenzothiazole produces an intermediate (either a diradical or a zwitterion) the latter being trapped by unsaturated compounds. More experiments are in progress to elucidate the specific pathways of these interesting novel, and synthetically useful new photocycloaddition reactions.

Acknowledgement

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