CYCLOADDITION OF BENZOTHIAZOLIUM N-PHENACYLIDE WITH OLEFINIC DIPOLAROPHILES

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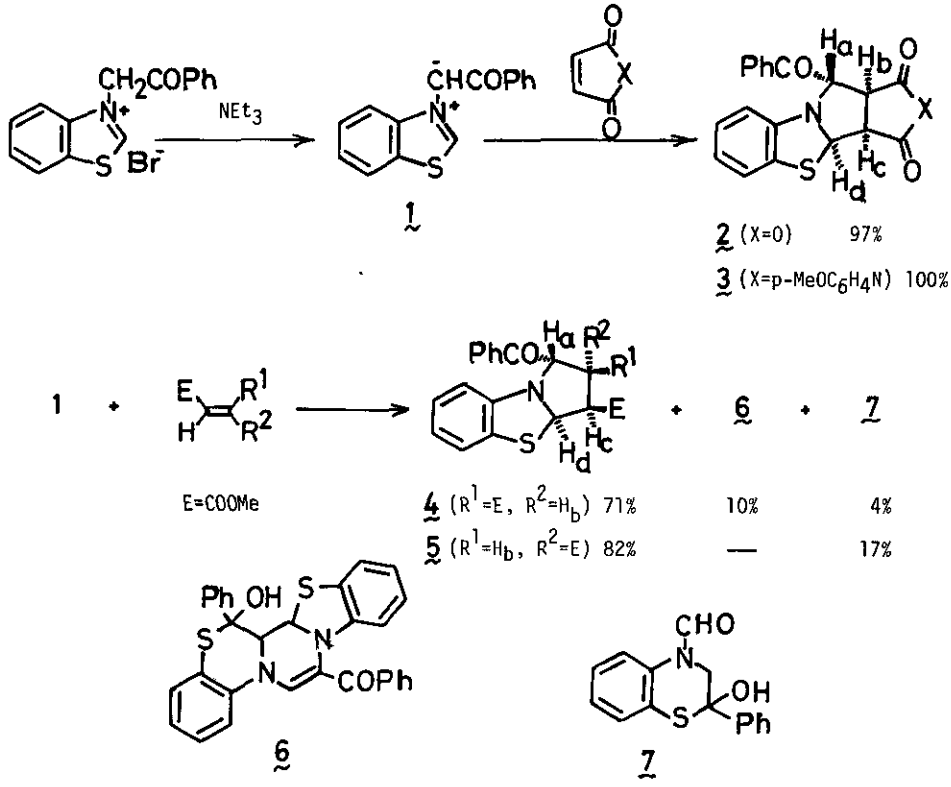
Abstract — Benzothiazolium N-phenacylide, generated in situ from 3-phenacylbenzothiazolium bromide and triethylamine, reacted with maleic anhydride, N-(p-methoxyphenyl)maleimide, dimethyl maleate, and fumarate to give the corresponding tetrahydropyrrolo[2,1-b]benzothiazole derivatives, all of which were stable on treatment with triethylamine, in good yields respectively. With maleonitrile the sole cycloadduct was formed, whereas fumaronitrile gave a mixture of two stereoisomeric cycloadducts. In some cases, dimer and/or hydrated compound of ylide were formed as by-products. On treatment with triethylamine epimerization and ring-transformation of cycloadducts obtained from both the dinitriles were observed.

Potts and his co-workers[1] have reported that 4-methylthiazolium N-phenacylide reacted with N-phenylmaleimide to give the cycloadduct whose stereochemistry was not fully established, whereas no identifiable cycloadducts were obtained in the reaction with other olefinic dipolarophiles.
We have now found that benzothiazolium N-phenacylide (1), generated in situ from 3-phenacylbenzothiazolium bromide[2] and triethylamine, reacted with a variety of olefinic dipolarophiles to afford the corresponding cycloadducts in good yields.
The typical procedure for the cycloaddition is as follows: under nitrogen, a solution of triethylamine (3 mmol) in dry chloroform (1 ml) was added, drop by drop, to a mixture of 3-phenacylbenzothiazolium bromide (3 mmol) and an olefin (3 mmol) in dry chloroform (30 ml) at 20°C, and then the reaction mixture was stirred at the same temperature for 3 h. The mixture was poured into water (200 ml), and extracted with chloroform. The extract was evaporated in vacuo, and the residue was purified by recrystallization and/or chromatography on silica gel.
The ylide 1 reacted with maleic anhydride and N-(p-methoxyphenyl)maleimide to give the corresponding cycloadducts 2 and 3 in excellent yields respectively. However, the reactivity of 1 toward dimethyl maleate and fumarate was somewhat lower, and the cycloadducts 4 and 5 were formed, together with

small amounts of dimer 6 and/or 4-formylbenzo[1,4]thiazine derivative 7 (Scheme 1). In the absence of an olefinic dipolarophile under similar conditions, the ylide 1 was transformed into 6 and 7 in 37 and 51% yields respectively[3].



Scheme 1

Structural elucidation of cycloadducts 2 — 5 was accomplished on the basis of spectral data and of chemical conversions.

2: pale yellow prisms; mp 173-174°C; IR (KBr) 1850, 1780, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.73 (1H, dd, H_c, J=8.6, 8.6 Hz), 4.23 (1H, dd, H_b, J=1.0, 8.6 Hz, changed to a doublet when irradiated at δ 6.02), 5.33 (1H, d, H_d, J=8.6 Hz, changed to a singlet when irradiated at δ 3.73), 6.02 (1H, d, H_a, J=1.0 Hz), 6.65-7.70 (7H, m), 7.95-8.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 47.9, 51.1, 69.3, 71.9 (tert. C), 167.6, 172.1, 193.2 (C=O); MS m/e 351 (M^+).

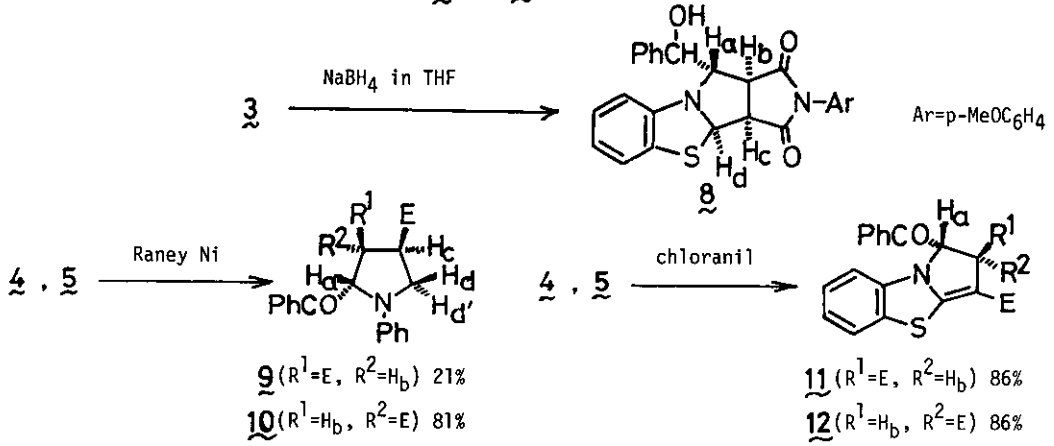
3: colorless plates; mp 195-196°C; IR (KBr) 1780, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (1H, dd, H_c, J=7.9, 7.9 Hz), 3.73 (3H, s), 4.03 (1H, dd, H_b, J=7.9, 0.5 Hz), 5.41 (1H, d, H_d, J=7.9 Hz, changed to a singlet when irradiated at δ 3.59), 6.05 (1H, d, H_a, J=0.5 Hz), 6.37, 6.77 (each 2H, d), 6.90-8.30 (9H, m); ^{13}C NMR ($CDCl_3$) δ 47.6, 50.6 (tert. C), 55.3 (CH_3), 68.4, 71.9 (tert. C), 173.3, 176.5, 194.0 (C=O); MS m/e 456 (M^+).

4: pale yellow needles; mp 119-122°C; IR (KBr) 1780, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.53, 3.59 (each

3H, s), 3.65 (1H, dd, H_b, J=7.3, 5.5 Hz), 3.94 (1H, dd, H_c, J=7.3, 7.3 Hz, changed to a doublet when irradiated at δ 5.67), 5.67 (1H, d, H_d, J=7.3 Hz, changed to a singlet when irradiated at δ 3.94), 5.88 (1H, d, H_a, J=5.5 Hz, changed to a singlet when irradiated at δ 3.65), 6.29 (1H, m), 6.62-7.07, 7.47-7.78 (each 3H, m), 8.05-8.35 (2H, m); ^{13}C NMR ($CDCl_3$) δ 50.1, 51.8, 52.2, 52.4 (tert. C), 67.1, 73.0 (CH_3), 170.0, 170.5, 199.7 (C=O); MS m/e 397 (M^+).

5: colorless needles; mp 104-105°C; IR (KBr) 1780, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42, 3.73 (each 3H, s), 3.77 (1H, dd, H_c, J=9.8, 7.4 Hz), 4.26 (1H, dd, H_b, J=9.8, 7.9 Hz, changed to a doublet when irradiated at δ 5.89), 5.50 (1H, d, H_d, J=7.4 Hz, changed to a singlet when irradiated at δ 3.77), 5.89 (1H, d, H_a, J=7.9 Hz, changed to a singlet when irradiated at δ 4.26), 6.55-7.13 (4H, m), 7.36 -7.65 (3H, m), 7.87-8.15 (2H, m); ^{13}C NMR ($CDCl_3$) δ 47.6 (tert. C), 52.1 (CH_3), 69.4, 72.2 (tert. C), 170.0, 170.8, 196.4 (C=O); MS m/e 397 (M^+).

Reduction of 3 with sodium borohydride in tetrahydrofuran afforded the corresponding alcohol 8 in a quantitative yield. On the basis of ^1H NMR data of 8, it was deduced that H_a appeared at lower field than H_d in all cycloadducts. Reductive desulfurization of 4 and 5 with Raney nickel (W-2) in ethanol gave the pyrrolidine derivatives 9 and 10, whereas 4 and 5 were treated with chloranil in ethanol to give the dehydrogenated products 11 and 12 respectively (Scheme 2).



9 (R^1=E, R^2=H_b) 21%
10 (R^1=H_b, R^2=E) 81%
11 (R^1=E, R^2=H_b) 86%
12 (R^1=H_b, R^2=E) 86%

Scheme 2

Structural elucidation of 8 — 12 was accomplished on the basis of spectral data.

8: colorless needles; mp 105-108°C; IR (KBr) 3500, 1780, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.07 (1H, broad s, OH, exchanged with D_2O), 3.29-3.60 (2H, complex signal, H_b and H_c), 3.67 (3H, s), 4.58 (1H, d, H_a, J=4.7 Hz), 4.83 (1H, broad d, CHOH, J=4.7 Hz), 5.68 (1H, d, H_d, J=7.1 Hz), 6.21 (1H, m), 6.49-7.63 (12H, m); MS m/e 458 (M^+).

9: pale yellow prisms; mp 81-82°C; IR (KBr) 1740, 1690 cm^{-1}; ^1H NMR (C_6D_6 in the presence of Eu $(dpm)_3$) δ 3.37, 3.65 (each 3H, s), 3.77 (1H, dd, H_b, J=7.4, 0.8 Hz), 3.70-3.94 (1H, dt, H_c, J=8.1,

8.1, 7.4 Hz), 4.12, 4.54 (each 1H, dd, H_d and H_d', J=8.1, 8.1 Hz), 5.96 (1H, d, H_a, J=0.8 Hz), 6.41-7.20 (8H, m), 8.17-8.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ 43.2, 49.0 (tert. C), 48.4 (CH_2), 51.2, 52.8 (CH_3), 65.7 (tert. C), 171.0, 197.5 (C=O); MS m/e 367 (M^+).

10: pale yellow needles; mp 113-114°C; IR (KBr) 1740, 1790 cm^{-1}; ^1H NMR (C_6D_6 in the presence of $Eu(dmp)_3$) δ 2.94, 3.64 (each 3H, s), 3.77 (1H, dd, H_d, J=9.0, 9.0 Hz), 4.20 (1H, dd, H_d', J=9.0, 9.0 Hz), 4.29 (1H, apparent dd, H_b, J=10.6, 8.1 Hz, changed to a sharp dd (J=10.6, 0.8 Hz) when irradiated at δ 5.65), 4.66 (1H, dt, H_c, J=10.6, 9.0, 9.0 Hz), 5.65 (1H, d, H_a, J=8.1 Hz), 6.31-7.19 (8H, m), 7.83-8.06 (2H, m); ^{13}C NMR ($CDCl_3$) δ 43.6, 49.9 (tert. C), 50.1 (CH_2), 51.8, 52.4 (CH_3), 62.3 (tert. C), 169.5, 172.3, 199.1 (C=O); MS m/e 367 (M^+).

11: yellow needles; mp 189-190°C; IR (KBr) 1735, 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72, 3.82 (each 3H, s), 4.34 (1H, d, H_b, J=4.0 Hz), 6.18 (1H, d, H_a, J=4.0 Hz), 6.58 (1H, m), 6.58-7.66 (6H, m), 7.97-8.11 (2H, m); MS m/e 395 (M^+).

12: yellow needles; mp 208-209°C; IR (KBr) 1745, 1690, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.18, 3.65 (each 3H, s), 4.85 (1H, d, H_b, J=12.0 Hz), 5.96 (1H, d, H_a, J=12.0 Hz), 6.46 (1H, m), 6.86-7.65 (6H, m), 7.78-8.06 (2H, m); MS m/e 395 (M^+).

Stereochemistry of 2 — 5, and 8 — 12 was deduced on the basis of values of coupling constants in ^1H NMR spectra respectively[4].

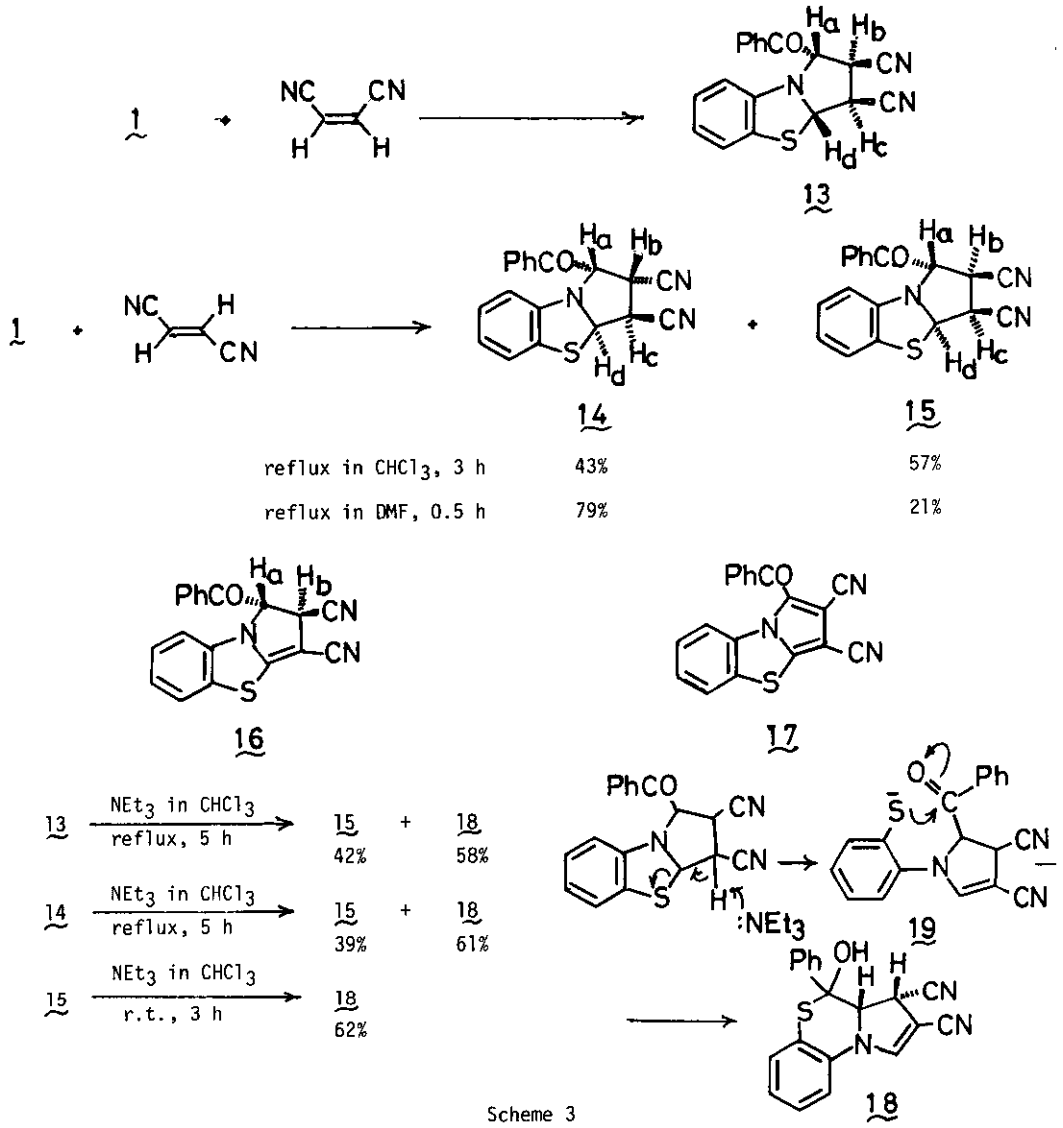
Next, the reaction of 1 with maleonitrile and fumaronitrile was investigated. With maleonitrile the sole cycloadduct 13 was obtained in 91% yield. On the other hand, 1 reacted with fumaronitrile to give two isomeric cycloadducts 14 and 15, whose relative yields depended on the reaction conditions (Scheme 3). Structural elucidation of cycloadducts 13 — 15 was accomplished on the basis of spectral data and of chemical conversions.

13: colorless plates; mp 181-183°C; IR (KBr) 2230, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.95 (1H, dd, H_c, J=8.5, 6.1 Hz), 4.04 (1H, dd, H_b, J=8.5, 3.5 Hz), 5.47 (1H, d, H_d, J=6.1 Hz), 5.68 (1H, d, H_a, J=3.5 Hz), 6.72-8.29 (9H, m); MS m/e 331 (M^+).

14: colorless needles; mp 190-191°C; IR (KBr) 2240, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.42 (1H, dd, H_c, J=9.5, 7.2 Hz, changed to a doublet when irradiated at δ 5.58), 4.31 (1H, dd, H_b, J=7.2, 7.2 Hz, changed to a doublet when irradiated at δ 5.70), 5.58 (1H, d, H_d, J=7.2 Hz, changed to a singlet when irradiated at δ 3.42), 5.70 (1H, d, H_a, J=7.2 Hz), 6.64-7.33 (4H, m), 7.45-7.76 (3H, m), 7.88-8.25 (2H, m); ^{13}C NMR ($CDCl_3$) δ 34.4, 41.4, 68.0, 71.0 (tert. C), 193.2 (C=O); MS m/e 331 (M^+).

15: colorless prisms; mp 133-135°C; IR (KBr) 2240, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.25 (1H, dd, H_c, J=8.4, 8.4 Hz), 4.16 (1H, dd, H_b, J=8.4, 3.8 Hz), 4.99 (1H, d, H_d, J=8.4 Hz), 5.67 (1H, d, H_a, J=3.8 Hz), 6.84-7.28 (4H, m), 7.37-7.74 (3H, m), 7.90-8.13 (2H, m); ^{13}C NMR ($CDCl_3$) δ 31.9, 41.8, 69.4, 73.1 (tert. C), 192.2 (C=O); MS m/e 331 (M^+).

When 13 or 15 was treated with an equimolar amount of chloranil in refluxing ethanol for 2 h or in



Scheme 3

refluxing toluene for 4 h, the same dehydrogenated product 16 was obtained in 53 or 61% yield respectively. In similar conditions in toluene for 4 h, however, 14 afforded a 50% yield of the fully dehydrogenated product 17, which was also formed in 47% yield together with a 2% yield of 16 when 15 was treated with chloranil in refluxing xylene for 4 h.[5]

16: colorless prisms; mp 234-236°C; IR (KBr) 2200, 1695 cm^{-1}; ^1H NMR (C_5D_5N) δ 5.63 (1H, d, H_b, J= 4.1 Hz), 6.94-7.32 (3H, m), 7.37 (1H, d, H_a, J=4.1 Hz), 7.45-7.82 (4H, m), 8.24-8.46 (2H, m); MS m/e 329 (M^+).

17: colorless prisms; mp 304-305°C; IR (KBr) 2210, 1640 cm^{-1}; ^1H NMR (CF_3COOD) δ 7.35-8.45 (m); MS m/e 327 (M^+).

It has been found that on treatment with triethylamine cycloadducts 13 — 15 underwent epimerization and/or ring-transformation, whereas cycloadducts 2 — 5 were unchanged under similar conditions. Thus, 13 and 14 were transfomed into a mixture of 15 and benzo[1,4]thiazine derivative 18 when treated with an equimolar amount of triethylamine in refluxing chloroform. However, 15 was readily converted to 18 at room temperature: in this case no 13 or 14 was formed and 15 was recovered (Scheme 3). The structure of 18 was deduced on the basis of spectral data.

18: colorless needles; mp 197-198°C; IR (KBr) 3380, 2250, 2190 cm^{-1}; ^1H NMR (acetone-d_6) δ 4.23 (1H, dd, ≥C<u>H</u>, J=8.5, 1.7 Hz), 5.11 (1H, d, ≥C<u>H</u>, J=8.5 Hz), 6.54 (1H, s, O<u>H</u>, exchanged with D_2O), 6.96-7.95 (9H, m), 8.15 (1H, d, =C<u>H</u>, J=1.7 Hz); MS m/e 331 (M^+).

The transformation into 18 can be interpreted as shown in Scheme 3: the intermediate phenyl sulfide 19 arising from deprotonation of a cycloadduct, the most likely 15, would give rise to 18 through the nucleophilic attack on the carbonyl carbon as illustrated for the formation of 6 and 7.[3]

On the basis of the above facts, it seems reasonable to assume that the cycloaddition reaction of 1 with olefinic dipolarophiles proceeds stereoselectively, and that the initial cycloadduct derived from cis-olefin has the H_a,H_b—trans—H_b,H_c—cis—H_c,H_d-trans configuration like 13, and then undergoes epimerization to the more stable H_a,H_b—trans—H_b,H_c—cis—H_c,H_d—cis cycloadduct.

References and Notes

1. K. T. Potts, D. R. Choudhury, and T. R. Westby, J. Org. Chem., 1976, 41, 187.

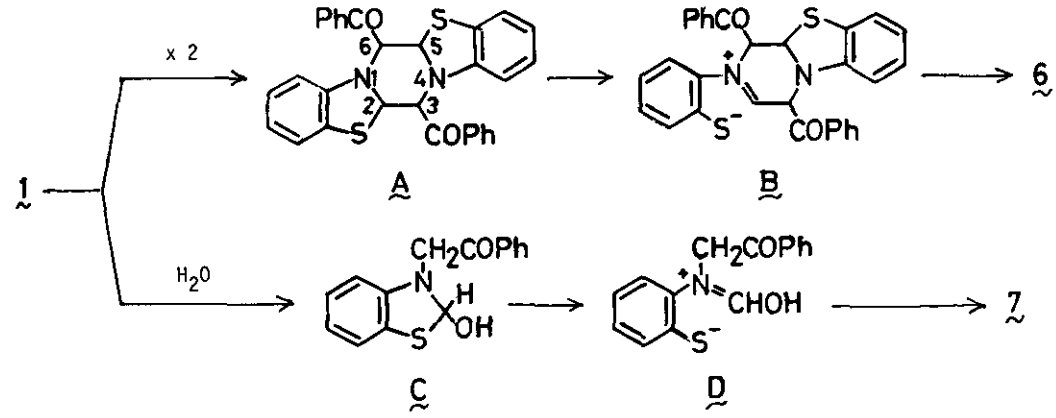
2. 3-Phenacylbenzothiazolium bromide was prepared by the reaction of benzothiazole with phenacyl bromide in refluxing benzene [colorless needles; mp 249-250°C; IR (KBr) 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 6.82 (2H, s, CH_2), 7.50-8.72 (9H, m), 10.86 (1H, s, =CH).

   All new compounds in this communication gave satisfactory elemental analyses.

3. The compound has solvent of crystallization. 6·EtOH: yellow needles (from EtOH); mp 161-164°C (dec); IR (KBr) 3500, 1620, 1250 cm^{-1}; ^1H NMR (C_5D_5N) δ 1.31 (3H, t), 3.87 (2H, q), 4.58, 5.76 (each 1H, d, >CH, J=7.7 Hz), 5.25 (2H, broad s, OH), 6.60-7.73 (15H, m), 7.95 (1H, s, =CH), 7.97-8.29 (3H, m); MS m/e 506 (6^+). 6·isoPrOH: yellow needles (from isoPrOH); mp 158-162°C (dec); ^1H NMR (C_5D_5N) δ 2.33 (6H, d, CH_3), 4.16 (1H, dq, $CHMe_2$), 4.49, 5.66 (each 1H, d, J=8 Hz), 6.20 (2H, broad s, OH, exchanged with D_2O), 6.52-7.60 (15H, m), 7.84 (1H, s, =CH), 7.88-8.10 (3H, m); ^{13}C NMR (C_5D_5N) δ 26.0 (q, CH_3), 63.3 (d, $CHMe_2$), 66.5, 69.7 (each d, tert. C), 80.6 (s, quat. C), 188.3 (s, C=O).

   7: colorless plates; mp 152-153°C; IR (KBr) 3260, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.28, 4.80 (each 1H, d, J=13.5 Hz), 3.67 (1H, s, OH, exchanged with D_2O), 7.05-7.86 (9H, m), 8.70 (1H, s, CHO); ^{13}C NMR ($CDCl_3$) δ 50.0 (CH_2), 83.0 (quat. C), 162.3 (CHO); MS m/e 271 (M^+).

   The formation of 6 and 7 can be accounted for as follows. In analogy to the rearrangement observed in adducts derived from 4-methylthiazolium N-phenacylide and acetylenic dipolarophiles,[1] the C_2—S (or C_5—S) bond in the initially formed dimer A would be broken to yield the intermediate phenyl sulfide B. Subsequent rotation and condensation at the carbonyl group initially at C_6 (or C_3) would give rise to the rearranged dimer 6.



On the other hand, the remaining ylide 1 would react with water during work-up to yield the benzothiazoline derivative C, followed by the fission of C_2—S bond to generate the phenyl sulfide D. A similar intramolecular nucleophilic attak at the carbonyl carbon would give rise

to 7.

4. It has been reported that in pyrrolidine derivatives cis coupling constants $J_{2,3}$ and $J_{4,5}$ (8-10[6], 6.3-9.8 Hz[7]) exhibited larger values than those of trans coupling constants (1.2-2.6[6], 0.0-5.7 Hz[7]). It has also been observed that cis coupling constants $J_{3,4}$ (8.0-10.3 Hz) revealed larger values than those of trans coupling constants (3.0 Hz), but in some cases trans coupling constants exhibited unexpectedly large values (11.0-11.5 Hz) because of steric repulsion between the substituents at C_2 and C_3 and at C_4 and C_5.
5. In all cases, the corresponding starting cycloadducts were recovered.
6. H. W. Heine, R. Peavy, and A. J. Durbetaki, J. Org. Chem., 1966, 31, 3924.
7. P. B. Woller and N. H. Cromwell, ibid., 1970, 35, 888.

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