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

![Scheme 1](image)

Structural elucidation of cycloadducts \( \mathbf{2} - \mathbf{5} \) was accomplished on the basis of spectral data and of chemical conversions.

\( \mathbf{2} \): pale yellow prisms; mp 173-174°C; IR (KBr) 1850, 1780, 1680 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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 \( \delta \) 6.02), 5.33 (1H, d, \( H_d, J=8.6 \) Hz, changed to a singlet when irradiated at \( \delta \) 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\(_3\)) \( \delta \) 47.9, 51.1, 69.3, 71.9 (tert. \( \mathbf{C} \)), 167.6, 172.1, 193.2 (\( \mathbf{C} \)); MS m/e 351 (\( M^+ \)).

\( \mathbf{3} \): colorless plates; mp 195-196°C; IR (KBr) 1780, 1700, 1680 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 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 \( \delta \) 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\(_3\)) \( \delta \) 47.6, 50.6 (tert. \( \mathbf{C} \)), 55.3 (\( \mathbf{CH}_3 \)), 68.4, 71.9 (tert. \( \mathbf{C} \)), 173.3, 176.5, 194.0 (\( \mathbf{C} \)); MS m/e 456 (\( M^+ \)).

\( \mathbf{4} \): pale yellow needles; mp 119-122°C; IR (KBr) 1780, 1680 cm\(^{-1}\); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 3.53, 3.59 (each
3H, s), 3.65 (1H, dd, Hb, J=7.3, 5.5 Hz), 3.94 (1H, dd, Hc, J=7.3, 7.3 Hz, changed to a doublet when irradiated at δ 5.67), 5.67 (1H, d, Hd, J=7.3 Hz, changed to a singlet when irradiated at δ 3.94), 5.88 (1H, d, Ha, 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); 13C NMR (CDCl3) δ 50.1, 51.8, 52.2, 52.4 (tert. C), 67.1, 73.0 (CH3), 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 (CDCl3) δ 3.42, 3.73 (each 3H, s), 3.77 (1H, dd, Ha, J=9.8, 7.4 Hz), 4.26 (1H, dd, Hb, J=9.8, 7.9 Hz, changed to a doublet when irradiated at δ 3.77), 5.89 (1H, d, Hd, J=7.4 Hz, changed to a singlet when irradiated at δ 3.77), 5.89 (1H, d, Hb, 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); 13C NMR (CDCl3) δ 47.6 (tert. C), 52.1 (CH3), 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 Ha appeared at lower field than Hd 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).

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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 (CDCl3) δ 3.07 (1H, broad s, OH, exchanged with D₂O), 3.29-3.60 (2H, complex signal, Hb and Hc), 3.67 (3H, s), 4.58 (1H, d, Hg, J=4.7 Hz), 4.83 (1H, broad d, CH₂OH, J=4.7 Hz), 5.68 (1H, d, Hg, J=7.1 Hz), 6.21 (1H, m), 6.49-7.63 (12H, m); MS m/e 458 (M+).

9 (R¹=E, R²=Hb) 21%
10 (R¹=Hb, R²=E) 81%

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 (CDCl3) δ 3.07 (1H, broad s, OH, exchanged with D₂O), 3.29-3.60 (2H, complex signal, Hb and Hc), 3.67 (3H, s), 4.58 (1H, d, Hg, J=4.7 Hz), 4.83 (1H, broad d, CH₂OH, J=4.7 Hz), 5.68 (1H, d, Hg, 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 (CDCl₃) δ 3.37, 3.65 (each 3H, s), 3.77 (1H, dd, Hb, J=7.4, 0.8 Hz), 3.70-3.94 (1H, dt, Hc, J=8.1,
8.1, 7.4 Hz), 4.12, 4.54 (each 1H, dd, Hg and Hg', J=8.1, 8.1 Hz), 5.96 (1H, d, Hg, J=0.8 Hz), 6.41-7.20 (8H, m), 8.17-8.38 (2H, m); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \& 43.2, 49.0 (tert. \greek{q}), 48.4 (CH2), 51.2, 52.8 (CH3), 65.7 (tert. \greek{q}), 171.0, 197.5 (\greek{q}=0); MS m/e 367 (M\textsuperscript{+}).

\textsuperscript{10}: pale yellow needles; mp 113-114\textdegree C; IR (KBr) 1740, 1790 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CD\textsubscript{3}OD in the presence of Eu(dmp\textsubscript{3}) \& 2.94, 3.64 (each 3H, s), 3.77 (1H, dd, Hg, J=9.0, 9.0 Hz), 4.20 (1H, dd, Hg', J=9.0, 9.0 Hz), 4.29 (1H, apparent dd, Hg, J=10.6, 8.1 Hz, changed to a sharp dd (J=10.6, 0.8 Hz) when irradiated at \& 5.65), 4.66 (1H, dt, Hg, J=10.6, 9.0, 9.0 Hz), 5.65 (1H, d, Hg, J=8.1 Hz), 6.31-7.19 (8H, m), 7.83-8.06 (2H, m); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \& 43.6, 49.9 (tert. \greek{q}), 50.1 (CH\textsubscript{2}), 51.8, 52.4 (CH\textsubscript{3}), 62.3 (tert. \greek{q}), 169.5, 172.3, 199.1 (\greek{q}=0); MS m/e 367 (M\textsuperscript{+}).

\textsuperscript{11}: yellow needles; mp 189-190\textdegree C; IR (KBr) 1735, 1690, 1670 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \& 3.72, 3.82 (each 3H, s), 4.34 (1H, d, Hg, J=4.0 Hz), 6.18 (1H, d, Hg, 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\textsuperscript{+}).

\textsuperscript{12}: yellow needles; mp 208-209\textdegree C; IR (KBr) 1745, 1690, 1650 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \& 3.18, 3.65 (each 3H, s), 4.85 (1H, d, Hg, J=12.0 Hz), 5.96 (1H, d, Hg, 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\textsuperscript{+}).

Stereochemistry of \textsuperscript{2} and \textsuperscript{3} was deduced on the basis of values of coupling constants in \textsuperscript{1}H NMR spectra respectively.\textsuperscript{4}

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

\textsuperscript{13}: colorless plates; mp 181-183\textdegree C; IR (KBr) 2230, 1670 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \& 3.95 (1H, dd, Hg, J=8.5, 6.1 Hz), 4.04 (1H, dd, Hg, J=8.5, 3.5 Hz), 5.47 (1H, d, Hg, J=6.1 Hz), 5.68 (1H, d, Hg, J=3.5 Hz), 6.72-8.29 (9H, m); MS m/e 331 (M\textsuperscript{+}).

\textsuperscript{14}: colorless needles; mp 190-191\textdegree C; IR (KBr) 2240, 1680 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \& 3.42 (1H, dd, Hg, J=9.5, 7.2 Hz, changed to a doublet when irradiated at \& 5.58), 4.31 (1H, dd, Hg, J=7.2, 7.2 Hz, changed to a doublet when irradiated at \& 5.70), 5.58 (1H, d, Hg, J=7.2 Hz, changed to a singlet when irradiated at \& 3.42), 5.70 (1H, d, Hg, J=7.2 Hz), 6.64-7.33 (4H, m), 7.45-7.76 (3H, m), 7.88-8.25 (2H, m); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \& 34.4, 41.4, 68.0, 71.0 (tert. \greek{q}), 193.2 (\greek{q}=0); MS m/e 331 (M\textsuperscript{+}).

\textsuperscript{15}: colorless prisms; mp 133-135\textdegree C; IR (KBr) 2240, 1680 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (CDCl\textsubscript{3}) \& 3.25 (1H, dd, Hg, J=8.4, 8.4 Hz), 4.16 (1H, dd, Hg, J=8.4, 3.8 Hz), 4.99 (1H, d, Hg, J=8.4 Hz), 5.67 (1H, d, Hg, J=3.8 Hz), 6.84-7.28 (4H, m), 7.37-7.74 (3H, m), 7.90-8.13 (2H, m); \textsuperscript{13}C NMR (CDCl\textsubscript{3}) \& 31.9, 41.8, 69.4, 73.1 (tert. \greek{q}), 192.2 (\greek{q}=0); MS m/e 331 (M\textsuperscript{+}).

When \textsuperscript{13} or \textsuperscript{15} was treated with an equimolar amount of chloranil in refluxing ethanol for 2 h or in
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.\(^5\)

\[ \text{16: colorless prisms; mp 234-236^\circ C; IR (KBr) 2200, 1695 cm}^{-1}; \text{ }^1\text{H NMR (CD}_2\text{OD)} \delta 5.63 (1H, d, H_b, J=4.1 Hz), 6.94-7.32 (3H, m), 7.37 (1H, d, H_a, J=4.1 Hz), 7.45-7.82 (4H, m), 8.24-8.46 (2H, m); MS m/e 329 (M^+)\].

\[ \text{17: colorless prisms; mp 304-305^\circ C; IR (KBr) 2210, 1640 cm}^{-1}; \text{ }^1\text{H NMR (CD}_3\text{COOD)} \delta 7.35-8.45 (m); MS m/e 327 (M^+)\].
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 transformed 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-d₆) δ 4.23 (1H, dd, 3J, 5.8, 1.7 Hz), 5.11 (1H, d, 3J, 5.8 Hz), 6.54 (1H, s, O-H, exchanged with D₂O), 6.96-7.95 (9H, m), 8.15 (1H, d, 3J, 5.8 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 2.³

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 H₂₃-H₂₆-trans-H₅₅-cis-H₅₆-trans configuration like 13, and then undergoes epimerization to the more stable N₂₃-H₂₅-trans-H₅₅-cis-H₅₆-cis cycloadduct.
References and Notes


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 -d₆) δ 6.82 (2H, s, CH₂), 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 (C₅D₅N) δ 1.31 (3H, t), 3.87 (2H, q), 4.58, 5.76 (each 1H, d, =CH), 7.53 (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 (M⁺). 6-isoPrOH: yellow needles (from isoPrOH); mp 158-162°C (dec); 1H NMR (C₅D₅N) δ 2.33 (6H, d, CH₃), 4.16 (1H, dq, CHMe₂), 4.49, 5.66 (each 1H, d, J=8 Hz), 6.20 (2H, broad s, OH, exchanged with D₂O), 6.52-7.60 (15H, m), 7.84 (1H, s, =CH), 7.88-8.10 (3H, m); 13C NMR (C₅D₅N) δ 26.0 (q, CH₃), 63.3 (d, CHMe₂), 66.5, 69.7 (each d, tert. C), 80.6 (s, quat. C), 188.3 (s, =0). 7: colorless plates; mp 152-153°C; IR (KBr) 3260, 1650 cm⁻¹; 1H NMR (CDCl₃) δ 3.28, 4.80 (each 1H, d, J=13.5 Hz), 3.67 (1H, s, OH, exchanged with D₂O), 7.05-7.86 (9H, m), 8.70 (1H, s, CH=O); 13C NMR (CDCl₃) δ 50.0 (CH₂), 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, the C₂-S (or C₅-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 C₆ (or C₃) 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 C₂-S bond to generate the phenyl sulfide D. A similar intramolecular nucleophilic attack at the carbonyl carbon would give rise to: [Diagram]

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4. It has been reported that in pyrrolidine derivatives cis coupling constants $J_{2,3}$ and $J_{4,5}$ (8-10, 6.3-9.8 Hz\textsuperscript{7}) exhibited larger values than those of trans coupling constants (1.2-2.6, 0.0-5.7 Hz\textsuperscript{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.


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