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REDUCTIVE FORMATION OF 1,5-BENZOTHIAZEPINES¹

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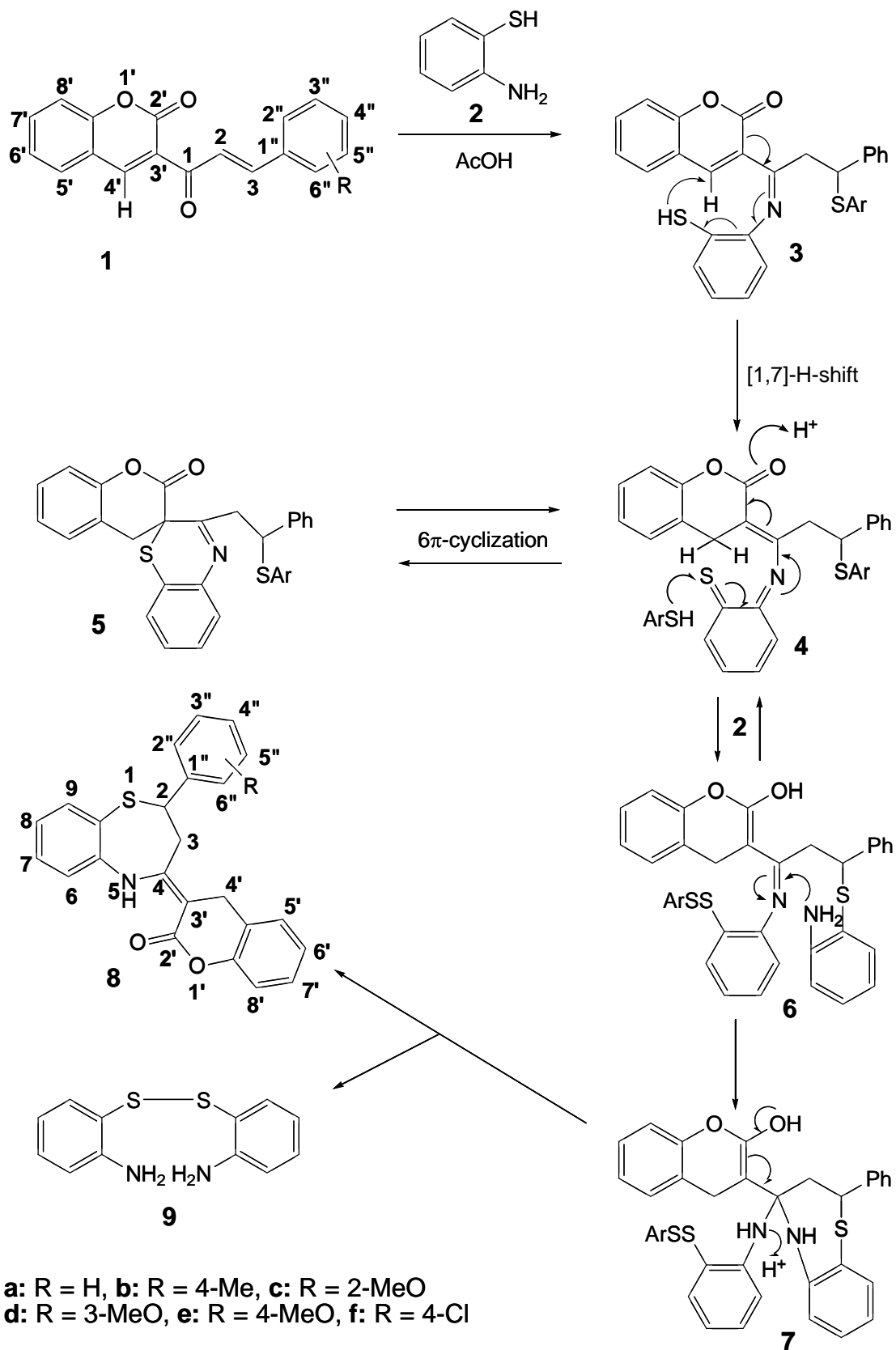
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Abstract – An unprecedented formation of a new type of 1,5-benzothiazepines with exocyclic double bond at position 4 has been achieved by the reaction of 3-aryl-1-(3-coumarinyl)propen-1-ones with 2-aminothiophenol.

Owing to their bioactivities, natural, semisynthetic and synthetic coumarins^{2,3} are important substances in the drug research. As a result, numerous coumarin type substances have been synthesized, some of which can be utilized as convenient starting materials for the synthesis of heterocyclic ring systems. 3-Cinnamoyl coumarins⁴ prepared by the reaction of 3-acetylcoumarins with aromatic aldehydes proved to be especially versatile intermediates for this purpose. 3-Cinnamoyl coumarins have been used for the synthesis of pyridine,^{3b} pyrazoline^{4a} and isoxazoline^{4g} derivatives. 1,5-Benzodiazepines and 1,5-benzothiazepines possessing a coumarin moiety have also been synthesized by the reaction of various coumarinylchalcones with 1,2-phenylenediamine and 2-aminothiophenol.⁵

Synthesis of 2,4-disubstituted 2,3-dihydro-1,5-benzothiazepines by the reaction of α,β -unsaturated ketones with 2-aminothiophenol (**2**) under various reaction conditions is well established in the chemical literature.⁶ As a continuation of our studies in this field, synthesis of newer representatives of such

1,5-benzothiazepines has been attempted by the reaction of 3-aryl-1-(3-coumarinyl)propen-1-ones (**1a-f**) with 2-aminothiophenol (**2**). Compounds (**1a-f**) and 2-aminothiophenol (**2**) were allowed to react in



Scheme 1

hot toluene in the presence of acetic acid (Scheme 1).⁷ For a complete conversion of the starting coumarinylchalcones (**1a-f**) the use of two or three equivalents of 2-aminothiophenol (**2**) was required.

On the basis of previous experiences concerning the reaction of various α,β -unsaturated ketones with 2-aminothiophenol (**2**),⁶ the formation of 2-aryl-4-(3-coumarinyl)-2,3-dihydro-1,5-benzothiazepines was expected. However, electron impact (70 eV) mass spectra of all isolated products (**8a-f**) revealed molecular ions higher by two Daltons than those of the expected 2-aryl-4-(3-coumarinyl)-2,3-dihydro-1,5-benzothiazepines. The structures of compounds (**8a-f**) were elucidated by NMR spectroscopy using ^1H , ^{13}C , DEPT-135, ^1H - ^{13}C HSQC, ^1H - ^{13}C HMBC, ^1H - ^1H COSY and ^1H - ^1H NOESY techniques, using widely accepted strategies.⁸ The route of the signal and structure assignments of **8d** is discussed as a representative example.⁹ Utilizing the ^1H and ^1H - ^1H COSY spectra we identified one 1,2-disubstituted aromatic ring with S- and N-, one another 1,2-disubstituted aromatic ring with O- and C-substituents. Furthermore, one 1,3-disubstituted aromatic ring with C- and CH_3O -groups. Moreover, one isolated $-\text{CH}_2-$ and the spin system of a $-\text{CH}_2\text{CH}-$ moiety have also been detected. The long-range $J_{\text{C,H}}$ HMBC correlations of the NH, SCH and the isolated $-\text{CH}_2-$ hydrogen atoms provided an unambiguous assignment of the aromatic rings of the benzothiazepine and coumarin moieties. The NH/C-3' correlation proved the C-4 position of the coumarinyl moiety, whereas the NH/C-3 cross-peak revealed the presence of the thiazepine ring.

The high chemical shift $\delta\text{NH} = 11.61$ ppm indicates a strong hydrogen bonding, whereas the steric proximity of the $\text{H}_2\text{C}-3$ and $\text{H}_2\text{C}-4'$ hydrogen atoms observed in the NOESY experiment, unambiguously proved the *Z*-configuration of the *exo* double bond.

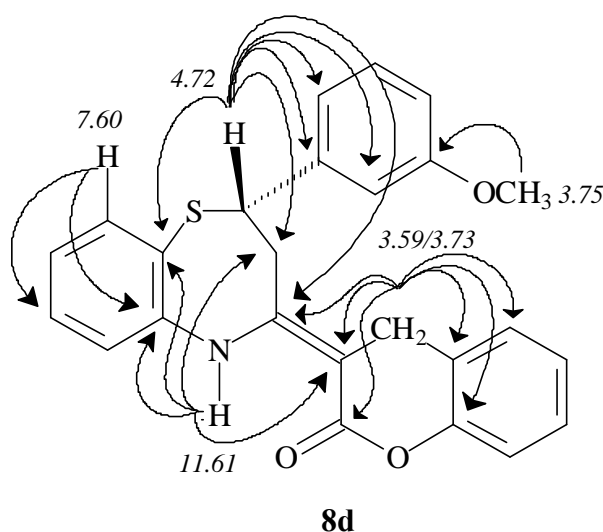


Figure 1. Characteristic HMBC correlations of the NH, H-2, H₂C-4', H-9 and CH₃O hydrogen atoms in compound (**8d**). The arrows indicate the detected $^2J_{\text{CH}}$ and $^3J_{\text{CH}}$ couplings.

Over the major products (**8a-f**), bis(2-aminophenyl) disulfide (**9**) has also been isolated as by-product from the crude reaction mixtures. Presence of this by-product may help the evaluation of the mechanism of the formation of compounds (**8a-f**). As far as the reaction mechanism is concerned, we assume that compound (**3**) is formed as first intermediate which may then be converted into substances (**4** and **5**) as indicated in Scheme 1. Compound (**4**) reacts with another 2-aminothiophenol (**2**) molecule to afford intermediate (**6**) which gives compound (**7**) on a ring closure. This intermediate provides the isolated benzothiazepines (**8a-f**) together with the by-product (**9**) (Scheme 1). The 2-aminothiophenol (**2**) has been found to reduce disulfide bonds in proteins under weakly acidic conditions.¹⁰ Our experiments are in progress to corroborate this plausible reaction mechanism.

Although the yields of the isolated major products (**8a-f**) are only medium, an unprecedented formation of new type of 1,5-benzothiazepines with exocyclic double bond at position 4 has been achieved in our present study. It is worth mentioning the high stereoselectivity of the ring closure reaction providing the (*Z*)-isomers of (**8a-f**) as stereohomogeneous products.

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7. **Representative Experimental Procedure. Synthesis of Compound 8d:** A mixture of **1d** (1.38 g, 5.0 mmol), 2-aminothiophenol (1.80 g, 15.0 mmol), toluene (50 mL) and acetic acid (5.0 mL) was refluxed for 6 h, then the solvent was evaporated under reduced pressure and the residue was crystallized from methanol to afford compound (**8d**) (Scheme 1).
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9. NMR spectra were recorded at 300 K in CDCl₃ at 500/125 MHz on a Bruker-Avance instrument.
- 8a:** ¹H NMR: δ = 11.47 (s, 1H, NH), 4.65 (dd, 1H, J = 5.0, 10.9 Hz, 2-H), 3.61 (d, 1H, J = 18.6 Hz, 4'-H_β), 3.45 (d, 1H, J = 18.6 Hz, 4'-H_α), 2.91 (dd, 1H, J = 5.0, 13.7 Hz, 3-H_β), 2.74 (dd, 1H, J = 10.9, 13.7 Hz, 3-H_α); ¹³C NMR: δ = 53.2 (C-2), 35.9 (C-3), 159.3 (C-4), 84.6 (C-3'), 26.8 (C-4'); MS (*m/z*) 385; Yield 46%, mp 185-186 °C.
- 8b:** ¹H NMR: δ 11.62 (s, 1H, NH), 4.74 (dd, 1H, J = 4.6, 10.5 Hz, 2-H), 3.71 (d, 1H, J = 18.3 Hz, 4'-H_β), 3.56 (d, 1H, J = 18.3 Hz, 4'-H_α), 3.00 (dd, 1H, 4.6, 13.7 Hz, 3-H_β), 2.84 (dd, 1H, J = 10.5, 13.7 Hz, 3-H_α); ¹³C NMR: δ = 53.2 (C-2), 36.1 (C-3), 159.1 (C-4), 84.9 (C-3'), 27.3 (C-4'); MS (*m/z*) 399; Yield 51%, mp 180-181 °C.
- 8c:** ¹H NMR: δ = 11.58 (s, 1H, NH), 5.23 (dd, 1H, J = 4.6, 12.0 Hz, 2-H), 3.92 (d, 1H, J = 18.4 Hz,

4'-H_β), 3.76 (d, 1H, 18.4 Hz, 4'-H_α), 3.06 (dd, 1H, J = 4.6, 13.6 Hz, 3-H_β), 2.67 (dd, 1H, J = 12.0, 13.6 Hz, 3-H_α); ¹³C NMR: δ = 46.7 (C-2), 34.9 (C-3), 159.9 (C-4), 84.6 (C-3'), 27.0 (C-4'); MS (*m/z*) 415; Yield, 52%, mp 176-177 °C.

8d: ¹H NMR: δ = 11.61 (s, 1H, NH), 4.72 (dd, 1H, J = 5.0, 10.7 Hz, 2-H), 3.73 (d, 1H, J = 18.1 Hz, 4'-H_β), 3.59 (d, 1H, J = 18.1 Hz, 4'-H_α), 3.02 (dd, 1H, J = 5.0, 13.8 Hz, 3-H_β), 2.84 (dd, 1H, J = 10.7, 13.8 Hz, 3-H_α); ¹³C NMR: δ = 53.0 (C-2), 36.2 (C-3), 159.0 (C-4), 142.2 (C-5a), 123.8 (C-6), 130.3 (C-7), 126.0 (C-8), 135.6 (C-9), 126.1 (C-9a), 144.6 (C-1''), 112.4 (C-2''), 159.9 (C-3''), 113.3 (C-4''), 129.9 (C-5''), 118.7 (C-6''), 166.3 (C-2'), 85.0 (C-3'), 27.3 (C-4'), 120.6 (C-4a'), 128.1 (C-5'), 123.7 (C-6'), 127.8 (C-7'), 116.6 (C-8'), 151.0 (C-8a'), 55.2 (3''-OCH₃); MS (*m/z*) 415; Yield 39%, mp 166-167 °C.

8e: ¹H NMR: δ = 11.62 (s, 1H, NH), 4.76 (dd, 1H, J = 5.0, 10.1 Hz, 2-H), 3.69 (d, 1H, J = 18.1 Hz, 4'-H_β), 3.50 (d, 1H, J = 18.1 Hz, 4'-H_α), 2.99 (dd, 1H, J = 5.0, 13.6 Hz, 3-H_β), 2.82 (dd, 1H, J = 10.1, 13.6 Hz, 3-H_α); ¹³C NMR: δ = 53.0 (C-2), 36.2 (C-3), 159.0 (C-4), 84.9 (C-3'), 27.2 (C-4'); MS (*m/z*) 415; Yield 59%, mp 161-162 °C.

8f: ¹H NMR: δ = 11.60 (s, 1H, NH), 4.73 (dd, 1H, J = 5.1, 10.6 Hz, 2-H), 3.70 (d, 1H, J = 18.0 Hz, 4'-H_β), 3.56 (d, 1H, J = 18.0 Hz, 4'-H_α), 3.00 (dd, 1H, J = 5.1, 13.9 Hz, 3-H_β), 2.80 (dd, 1H, J = 10.6, 13.9 Hz, 3-H_α); ¹³C NMR: δ = 52.7 (C-2), 36.0 (C-3), 159.5 (C-4), 85.2 (C-3'), 27.3 (C-4'); MS (*m/z*) 419; Yield 57%, mp 170-171 °C.

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