HETEROCYCLES, Vol. 68, No. 7, 2006, pp. 1319 - 1324. © The Japan Institute of Heterocyclic Chemistry
Received, 17th February, 2006, Accepted, 29th May, 2006, Published online, 30th May, 2006. COM-06-10702

REDUCTIVE FORMATION OF 1,5-BENZOTHIAZEPINES[1]

Albert Lévai,[a*] Gábor Tóth,[b*] Tímea Gondos,[b] József Jekő,[c] and D. I. Brahmbhatt[d]

[a]Department of Organic Chemistry, University of Debrecen, Egyetem tér 1, H-4010 Debrecen, Hungary. E-mail: alevai@puma.unideb.hu

[b]Institute of General and Analytical Chemistry, Budapest University of Technology and Economics, Szent Gellért tér 4, H-1111 Budapest, Hungary and Drug Research Institute Ltd., H-1325 Budapest, Hungary. E-mail: gabor.toth@mail.bme.hu

[c]Department of Chemistry, College of Nyíregyháza, Sóstói u. 31/b, H-4400 Nyíregyháza, Hungary

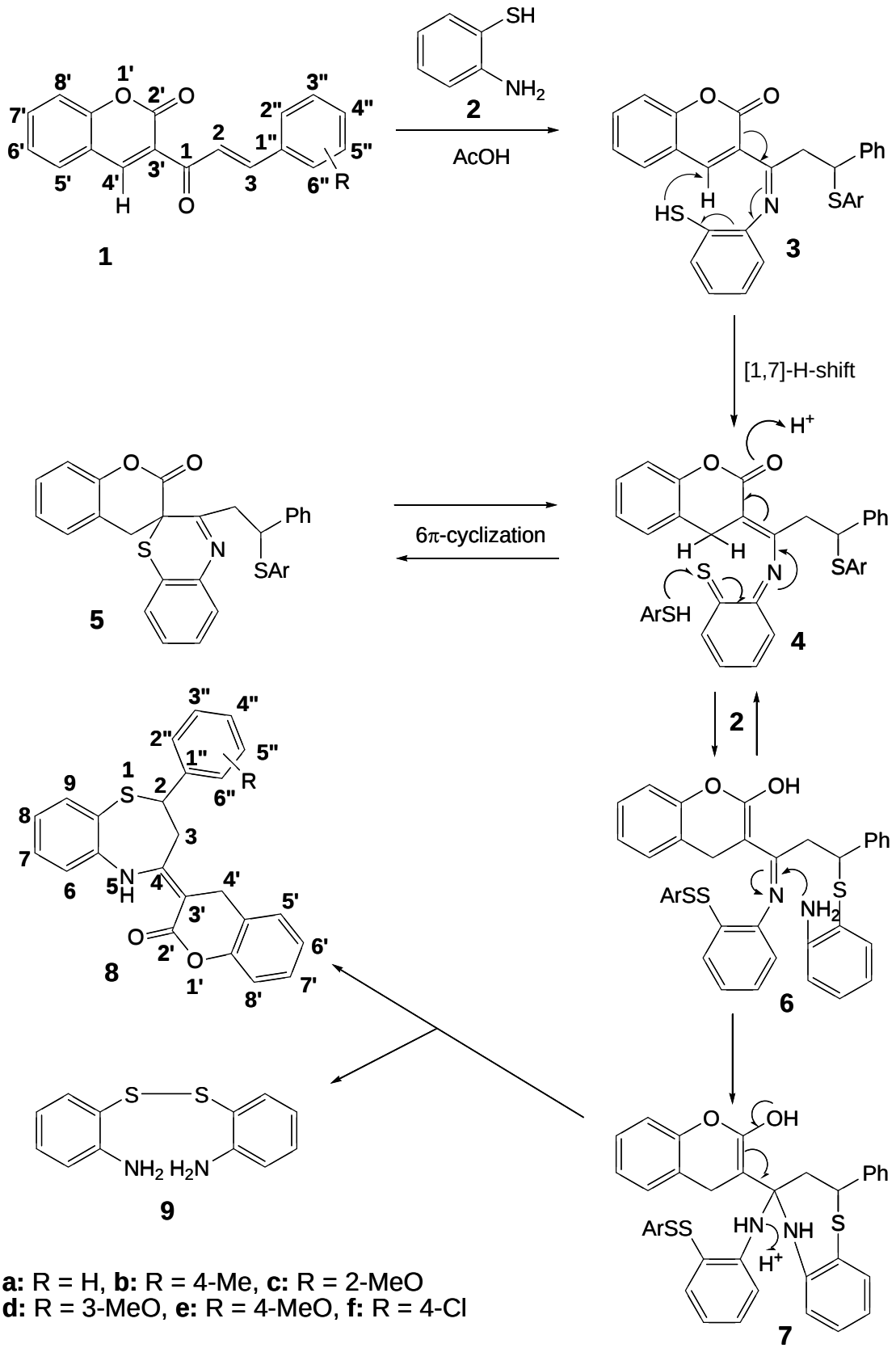
[d]Department of Chemistry, Sardar Patel University, Vallabh Vidyanagar 388 120 Gujarat, India

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 coumarins[4] 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

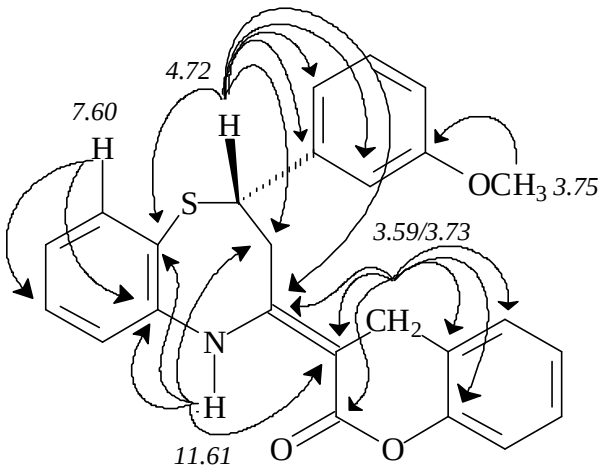


Scheme 1

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 ^{1}H, ^{13}C, DEPT-135, ^{1}H-^{13}C HSQC, ^{1}H-^{13}C HMBC, ^{1}H-^{1}H COSY and ^{1}H-^{1}H 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 ^{1}H and ^{1}H-^{1}H 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 -CH_2- and the spin system of a -CH_2CH- moiety have also been detected . The long-range $J_{C,H}$ HMBC correlations of the NH, SCH and the isolated -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 shif δNH = 11.61 ppm indicates a strong hydrogen bonding, whereas the steric proximity of the H_2C-3 and H_2C-4' hydrogen atoms observed in the NOESY experiment, unambiguously proved the *Z*-configuration of the *exo* double bond.



8d

Figure 1. Characteristic HMBC correlations of the NH, H-2, H_2C-4', H-9 and CH_3O hydrogen atoms in compound (**8d**). The arrows indicate the detected $^{2}J_{CH}$ and $^{3}J_{CH}$ 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 intermedaite 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.

ACKNOWLEDGEMENTS

The present study was sponsored by the Hungarian National Research Foundation (Grant Nos. OTKA T046127 and T049468) for which our gratitude is expressed. Technical assistance of Mrs. M. Nagy is highly appreciated.

REFERENCES AND NOTES

1. Oxazepines and Thiazepines, 44. For Part 43, see: S. Kéki, L. Nagy, Gy. Deák, A. Lévai, and M. Zsuga, *Rapid Commun. Mass Spectrom.,* 2005, **19**, 1263.
2. (a) T. A. Geismann, "The Chemistry of Flavonoid Compounds," Pergamon Press, London, 1962. (b) J. B. Harborne, "The Flavonoids: advances in research since 1980," Chapman and Hall, London, 1988. (c) J. B. Harborne, "The Flavonoids: advances in research since 1986," Chapman and Hall, London, 1993.
3. (a) M. S. Y. Khan and P. Sharma, *Indian J. Chem.,* 1995, **34B**, 237. (b) D. I. Brahmbhatt, G. B. Raolji, S. U. Pandya, and U. R. Pandya, *Indian J. Chem.,* 1999, **38B**, 212.
4. (a) J. A. A. Miky and A. A. Farrag, *Indian J. Chem.,* 1997, **36B**, 357. (b) A. I. Essawy, M. Elkady, and A. Y. Mohamed, *Indian J. Chem.,* 1980, **19B**, 567. (c) J. A. M. van den Goorbergh, M. van der Steeg, and A. van der Gen, *Synthesis,* 1984, 859. (d) E. Dimitrova and Y. Anghelova, *Synth. Commun.,* 1986, **16**, 1195. (e) J. A. M. van den Goorbergh, M. van der Steeg, and A. van der Gen, *Synthesis,* 1987, 314. (f) P. I. Yagodinets, O. V. Skripskaya, I. N. Chernyuk, and M. I. Shevchuk, *Zh. Obschch. Khim.,* 1991, **61**, 1856.
5. (a) R. Djudjic and M. Trkovnik, *Croat. Chem. Acta,* 1990, **63**, 13. (b) A. Prashant, S. Srinivas Rao, K.

S. Chowdary, and V. S. H. Krishnan, *Heterocycl. Commun.,* 2001, **7**, 61. (c) V. V. Mulwad and R. B. Pawar, *Indian J. Chem.*, 2003, **42B**, 2091.

6. (a) W. Ried and W. Marx, *Chem. Ber.*, 1957, **90**, 2683. (b) W. D. Stephens and L. Field, *J. Org. Chem.,* 1959, **24**, 1576. (c) O. Hideg-Hankovszky and K. Hideg, *Acta Chim. Acad. Sci. Hung.*,1971, **68**, 403. (d) A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.,* 1976, **88**, 293. (e) A. Lévai and R. Bognár, *Acta Chim. Acad. Sci. Hung.*, 1977, **92**, 415. (f) A. Lévai, *Pharmazie,* 1979, **34**, 439. (g) A. Lévai, R. Bognár, and J. Kajtár, *Acta Chim. Acad. Sci. Hung.*,1980, **103**, 27. (h) A. Lévai, *Pharmazie*, 1981, **36**, 449. (i) R. A. Mane and D. B. Ingle, *Indian J. Chem.,* 1982, **21B**, 973. (j) V. D. Orlov, N. N. Kolos, and N. N. Ruzhinckaya, *Khim. Geterotsikl. Soedin.,* 1983, 1638. (k) A. K. Gupta, V. K. Singh, and U. C. Pant, *Indian J. Chem.,* 1983, **22B**, 1057; (l) K. P. Jadhav and D. B. Ingle, *Indian J. Chem.*, 1983, **22B**, 180. (m) U. C. Pant, B. S. Gaur, and M. Chugh, *Indian J. Chem.*, 1988, **27B**, 752. (n) A. Lévai, *Pharmazie,* 1989, **44**, 317. (o) A. Lévai, *Heterocycl. Commun.,* 1999, **5**, 359. (p) R. H. Swellen, Y. A. Allam, and G. A. M. Nawwar, *Z. Naturforsch.,* 1999, **54b**, 1197. (q) A. R. Katritzky, B. V. Rogovoy, C. Chassaing, V. Vedensky, B. Forood, B. Flatt, and H. Nakai, *J. Heterocyclic Chem.*, 2000, **37**, 1655. (r) A. Lévai, *J. Heterocyclic Chem.*, 2000, **37**, 199. (s) M., Kodomari, T. Noguchi, and T. Aoyama, *Synth. Commun.,* 2004, **34**, 1783. (t) L. Nagarapu, R. Narendar, and K. Sucheta, *Heterocycl. Commun.,* 2003, **9**, 35.

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 crystalllized from methanol to afford compound (**8d**) (Scheme 1).

8. E. Pretsch, G. Tóth, M. E. Munk, and M. Badertscher, "Computer-Aided Structure Elucidation, Spectra Interpretation and Structure Generation," Wiley-VCH, Weinheim, 2002.

9. NMR spectra were recorded at 300 K in $CDCl_3$ at 500/125 MHz on a Bruker-Avance instrument.

8a: ^{1}H 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); ^{13}C 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 ^{o}C.

8b: ^{1}H 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); ^{13}C 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 ^{o}C.

8c: ^{1}H 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); ^{13}C 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 ^{o}C.

8d: ^{1}H 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); ^{13}C 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"-OCH_3); MS (*m/z*) 415; Yield 39%, mp 166-167 ^{o}C.

8e: ^{1}H 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); ^{13}C 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 ^{o}C.

8f: ^{1}H 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); ^{13}C 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 ^{o}C.

10. Y. Abe, T. Ueda, and T. Imoto, *J. Biochem.*, 1994, **115**, 52.