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A novel reaction between benzothiazoles and diaroylacetylenes in the presence of Meldrum's acid: ring expansion of benzothiazoles to functionalized 1,4-benzothiazines

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ABSTRACT

A novel and efficient ring expansion of benzothiazoles to functionalized 1,4-benzothiazines is described. The reactive 1:1 zwitterionic intermediates formed by addition of benzothiazoles to diaroylacetylenes were trapped with Meldrum's acid under mild reaction conditions to produce 2-[2-hydroxy-2-aryl-2*H*-1,4-benzothiazin-3(4*H*)-yliden]-1-aryl-1-ethanones in excellent yields.

Benzothiazine derivatives are best known as pharmaceuticals for the central nervous system serving as neuroleptic, sedative, analgesic, anti-emetic, and antihistamine agents and also for treatment of various mental illnesses. A number of benzothiazine derivatives have been found to exhibit anti-hypertensive, vasorelaxant, anticancer, antibacterial, antifungal, gastroprokinetic, and immunomodulatory activities.[1] Furthermore, a number of benzothiazine-based dyes have been prepared which exhibit a rich variety of colors.[2] Some examples have been used as models for redox-active molecular wires,[3] p- and n-type semiconductors,[4] and food flavoring additives.[5]

The most common synthetic methods reported for the preparation of 1,4-benzothiazines involve: (i) cyclizations, classified on the basis of the number of ring atoms in each of the components being cyclized: (a) single bond formation, adjacent to sulfur or nitrogen, or between two carbons, (b) formation of two bonds, from [5+1], [4+2], or [3+3] atom fragments, (c) formation of three or four bonds;[1] (ii) transformation of three- to eight-membered heterocyclic rings, of these, ring expansion of five-membered rings is the most common leading to 1,4-benzothiazines. These include the Takamizawa reaction,[6] ring expansion of thiazolidine S-oxides,[7] hydroxide-induced ring expansion of *N*-alkylthiazolium iodides,[8] ring expansion of substituted benzothiazoles with organolithium reagents[9] or alcohols,[10] reaction of azides with 2-alkylidenebenzothiazolines,[11] N-alkylation of thiazoles followed by treatment with base,[12] reaction of 4-acetoacetamido-1,2-dithiol-3-one with sodium ethoxide,[13] and reaction of 4-chloro-5*H*-1,2,3-dithiazol-5-one with α,β-unsaturated β-amino esters.[14]

As part of our continuing efforts on the development of new routes for the preparation of biologically active heterocyclic compounds,[15–20] herein, we describe a novel reaction leading to

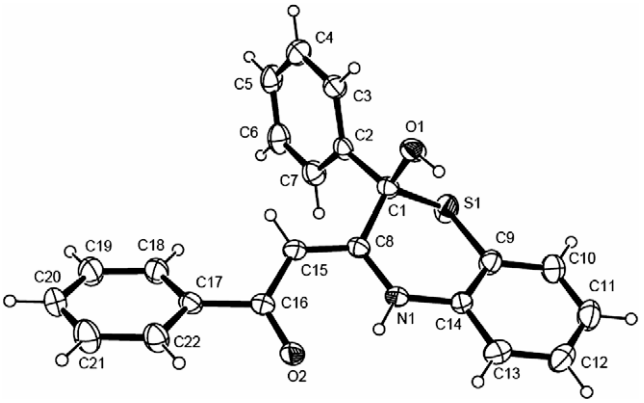

Figure 1. ORTEP diagram of the molecular structure of **4a**.

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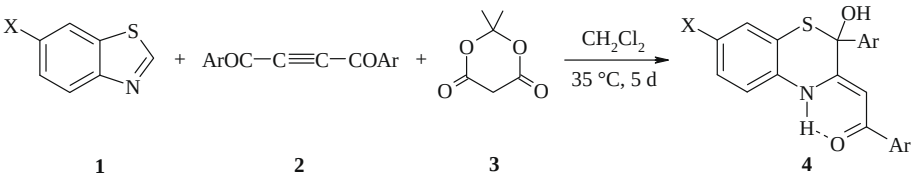


1 2 3 4

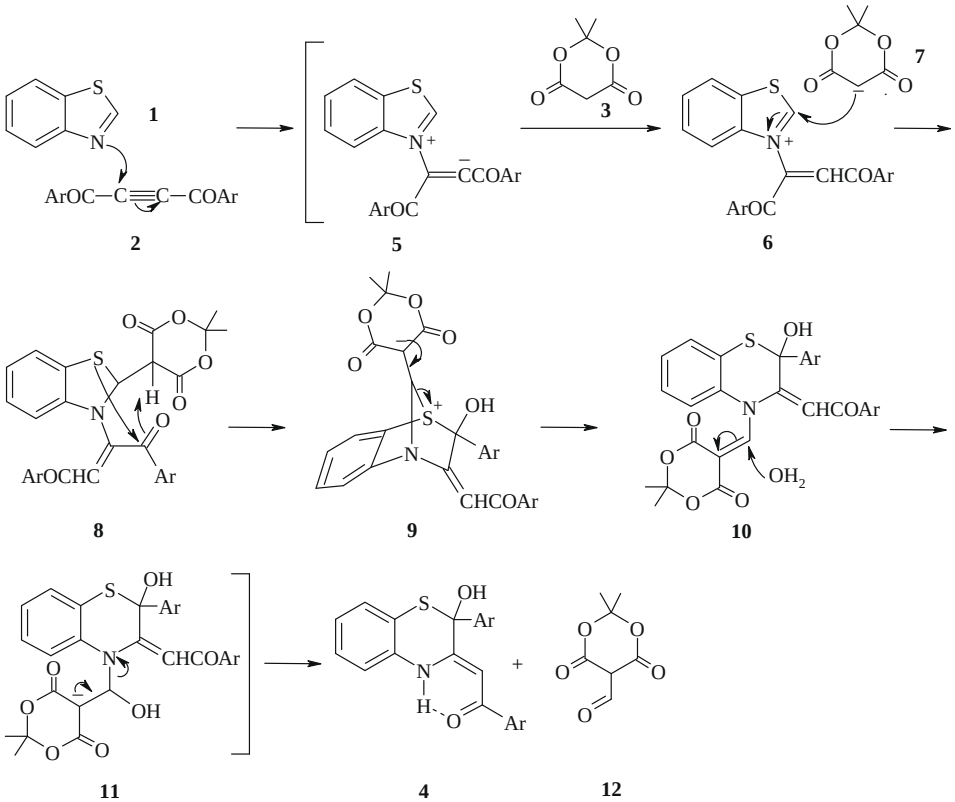
4	Ar	X	% Yield [a]
a	C_6H_5	H	97
b	C_6H_5	Br	94
c	4-Me-C_6H_4	H	93
d	4-Me-C_6H_4	Br	91
e	2,5-$Me_2C_6H_3$	H	92
f	2,5-$Me_2C_6H_3$	Br	90

[a] Isolated yield

Scheme 1.

functionalized 1,4-benzothiazines. Thus, a mixture of a benzothiazole **1** and a diaroylacetylene **2**, in the presence of Meldrum's acid **3**, underwent a novel reaction to afford 2-[2-hydroxy-2-aryl-2*H*-1,4-benzothiazin-3(4*H*)-yliden]-1-aryl-1-ethanones **4a**–**f** in 90–97% yields (Scheme 1). The reactions were carried out smoothly at 35 °C by mixing the three components in anhydrous CH_2Cl_2, and were complete within five days to afford the functionalized 1,4-benzothiazines **4**. The ^{1}H NMR spectra of the crude products clearly indicated the formation of 1,4-benzothiazines **4**.[21]

The isolated products **4** were characterized on the basis of ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and elemental analysis. The mass spectrum of **4a** displayed the molecular ion (M^+) peak at *m/z* 359, which was ten mass units lower than that of the 1:1 adduct of benzothiazole and dibenzoylacetylene indicating elimination of a carbon atom from the adduct and addition of two hydrogen atoms. The ^{1}H NMR spectrum of **4a** exhibited a fairly sharp signal (δ 3.29) due to the OH group, a sharp singlet (δ 5.58) due to the vinylic H-atom, as well as characteristic signals with appropriate chemical shifts and coupling constants for the 14 aromatic H-atoms. A fairly broad signal (δ 13.55) was observed for the NH group resulting from strong intramolecular hydrogen bonding with the adjacent carbonyl group in the enaminone moiety. The ^{1}H-decoupled ^{13}C NMR spectrum of **4a** consisted of a signal at δ 80.0 due to the COH quaternary carbon atom. Another strong signal appeared at δ 90.2 which was assigned to the electron-rich vinylic CH and the signal at δ 191.4 was due to the



Scheme 2.

carbonyl group. Another 15 distinct resonances (10CH and 5C) were in agreement with the proposed structure.[21]

Single-crystal X-ray analysis of **4a** conclusively confirmed its structure and those of **4b**–**f** by analogy. An ORTEP diagram of **4a** is shown in Figure 1.[22]

This transformation and ring expansion to a thiazine scaffold probably involve a multistep sequence of events. A plausible mechanism for this reaction is depicted in Scheme 2. It is reasonable to assume that the first step could involve initial addition of the benzothiazole **1** to the electron-deficient acetylenic compound **2** and formation of 1:1 zwitterionic intermediate **5**, which is subsequently protonated by Meldrum's acid **3**. Next, the positively charged ion **6** is attacked by the conjugate base of the acid **7** to form 1:1:1 adduct **8**. Nucleophilic attack of the sulfur atom on the carbonyl group, facilitated by protonation with the adjacent CH-acid would yield 1-thionia-4-azabicyclo[2.2.1]heptane intermediate **9**, which could undergo ring opening to form N-substituted benzothiazine intermediate **10**. This intermediate could undergo hydrolysis leading to adduct **11**, from which formyl Meldrum's acid **12** may be removed to afford the observed 1,4-benzothiazine **4**. The isolation and identification of formyl Meldrum's acid from the reaction mixture are consistent with this mechanism.[23]

In summary, we have developed a novel and efficient ring expansion of benzothiazoles to give functionalized 1,4-benzothiazines. The reaction proceeds via addition between benzothiazoles and diaroylacetylenes in the presence of Meldrum's acid leading to 2-[2-hydroxy-2-aryl-2*H*-1,4-benzothiazin-3(4*H*)-yliden]-1-aryl-1-ethanones which are of potential synthetic and pharmacological interest. The excellent yields of the products, simple starting materials, and mild reaction conditions are the main advantages of this reaction.

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21. The procedure for the preparation of *2-[2-hydroxy-2-phenyl-2H-1,4-benzothiazin-3(4H)-yliden]-1-phenyl-1-ethanone* (**4a**) is described as an example: A mixture of benzothiazole (0.270 g, 2 mmol), dibenzoylacetylene (0.468 g, 2 mmol), and Meldrum's acid (0.288 g, 2 mmol) in dry CH_2Cl_2 (10 mL) was stirred at 35 °C for 5 d. The solvent was removed and the residue was purified by column chromatography using *n*-hexane–EtOAc (1:1) as eluent to afford the product as yellow crystals, mp 155 °C, yield 0.70 g, 97%. EI-MS, *m/z* (%): 359 (M^+, 12), 254 (100), 236 (28), 211 (35), 176 (8), 120 (13), 105 (98), 77 (92). Anal. Calcd for $C_{22}H_{17}NO_2S$ (359.45): C, 73.5; H, 4.8; N, 3.9. Found: C, 73.3; H, 4.9; N, 3.7. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 3.29 (1H, s, OH), 5.58 (1H, s, CH), 7.01 (1H, t, J = 7.5 Hz, CH), 7.14 (1H, d, J = 8.0 Hz, CH), 7.22 (1H, dd, J = 7.5 Hz, J = 7.8 Hz, CH), 7.25 (1H, d, J = 7.8 Hz, CH), 7.34 (2H, dd, J = 7.2 Hz, J = 8.0 Hz, 2CH), 7.41–7.50 (4H, m, 4CH), 7.65 (2H, d, J = 7.9 Hz, 2CH), 7.72 (2H, d, J = 8.0 Hz, 2CH), 13.55 (1H, br s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 80.0 (C), 90.2 (CH), 118.2 (CH), 119.9 (C), 123.4, 126.9, 127.2, 127.5, 128.3, 128.4, 128.5, 129.2, 131.6 (9 CH), 134.6, 138.9, 139.4, and 155.6 (4C), 191.4 (C=O). *1-(2,5-Dimethylphenyl)-2-[2-(2,5-dimethylphenyl)-2-hydroxy-2H-1,4-benzothiazin-3(4H)-yliden]-1-ethanone* (**4e**): yellow crystals, mp 164–165 °C, yield 0.76 g, 92%. EI-MS, *m/z* (%): 415 (M^+, 7), 292 (10), 282 (92), 269 (17), 146 (33), 133 (100), 105 (59). Anal. Calcd for $C_{26}H_{25}NO_2S$ (415.56): C, 75.2; H, 6.1; N, 3.4. Found: C, 75.1; H, 6.2; N, 3.3. ^{1}H NMR (500.1 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3), 2.29 (3H, s, CH_3), 2.36 (3H, s, CH_3), 2.56 (3H, s, CH_3), 3.22 (1H, s, OH), 5.30 (1H, s, CH), 7.00–7.07 (4H, m, 4CH), 7.10–7.17 (3H, m, 3CH), 7.21–7.25 (2H, m, 2CH), 7.68 (1H, s, CH), 13.51 (1H, br s, NH). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.7, 20.8, 21.1 and 21.7 ($4CH_3$), 80.3 (C), 94.1 (CH), 118.3 (CH), 119.2 (C), 123.5, 127.3, 127.5, 128.1, 128.2, 129.9, 130.4 and 130.9 (8CH), 132.6 (C), 132.7 (CH), 133.3, 134.2, 135.0, 135.5, 136.1, 141.2 and 154.2 (7C), 196.5 (C=O).
22. *Selected X-ray crystallographic data for compound* **4a**: $C_{22}H_{17}NO_2S$, monoclinic, space group = *Cc*, a = 16.9745(22) Å, b = 12.4018(15) Å, c = 10.2729(13) Å, β = 123.437(2)°, V = 1804.67(29) Å^3, T = 295(2) K, Z = 4, D_{calcd} = 1.32 g cm^{-3}, μ = 0.195 mm^{-1}, 2619 observed reflections, final R_1 = 0.040, wR_2 = 0.083 and for all data R_1 = 0.0533, wR_2 = 0.092. CCDC 719858 contains the supplementary crystallographic data for the structure reported in this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
23. The amount of formyl Meldrum's acid isolated from the reaction mixture of benzothiazole (2 mmol) and dibenzoylacetylene by column chromatography was 0.19 g, 55% (relative to benzothiazole).