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Hetero-Diels–Alder Reaction of 5-Ylidene-4-sulfanylidene-1,3-thiazolidin-2-ones with *N*,*N*′-Bis(methoxycarbonyl)-1,4-benzoquinone Diimine

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Abstract—Hetero-Diels–Alder reaction of 5-(propan-2-ylidene)-4-sulfanylidene-1,3-thiazolidin-2-one with *N*,*N*′-bis(methoxycarbonyl)-1,4-benzoquinone diimine in boiling toluene afforded 87% of dimethyl 9,9-dimethyl-2-oxo-8a,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8(3*H*,4a*H*)-diylidenedicarbamate. Analogous reactions of 5-benzylidene-, 5-{[4-(dimethylamino)phenyl]methylidene}-, and 5-[(2-hydroxyphenyl)-methylidene]-4-sulfanylidene-1,3-thiazolidin-2-ones led to the formation of the corresponding dimethyl 9-aryl-2-oxo-3,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8-diyldicarbamates in 64–82% yield.

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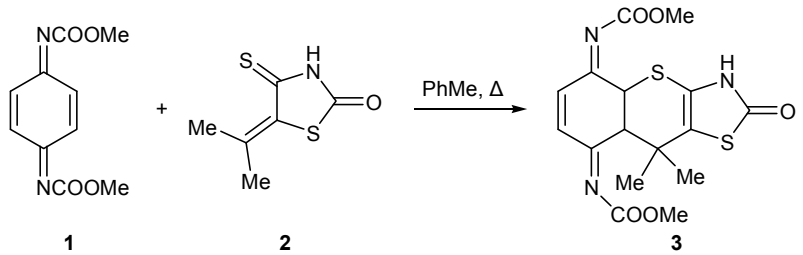
5-(Arylmethylidene)-4-sulfanylidene-1,3-thiazolidin-2-ones are known not only as highly reactive heterodienes [1] but also as compounds exhibiting antitumor activity and affinity for such anticancer targets as PPARγ-receptors [2]; in addition, they inhibit Bcl-XL/BH3 [3] and $TNF_{\alpha}/TNFR_{c}1$ interactions [4] and cell growth via inhibition of translation initiation [5].

Hetero-Diels–Alder reactions of 5-(arylmethylidene)-1,3-thiazolidin-2-ones with acrolein, diethyl acetylenedicarboxylate, norbornene, maleimides derived from amino acids, and norbornene-2,3-dicarboxylic acid imides lead to the formation of the corresponding fused heterocyclic compounds containing a thiazolidine ring. 3,5a,6,11b-Tetrahydro-2*H*,5*H*-chromeno-[4′,3′:4,5]thiopyrano[2,3-*d*][1,3]thiazol-2-ones were synthesized in 60–80% yield by the base-catalyzed Knoevenagel–hetero-Diels–Alder domino reaction of 4-sulfanylidene-1,3-thiazolidin-2-one with 3,7-dimethyloct-6-enal, 2-allyloxybenzaldehydes, and 2-formylphenyl (*E*)-3-arylprop-2-enoates [6]. 5-(Arylmethylidene)-4-sulfanylidene-1,3-thiazolidin-2-ones reacted with 2 equiv of 1,4-naphthoquinone in acetic acid to give 11-aryl-3,5,10,11-tetrahydro-2*H*-benzo-[6,7]thiochromeno[2,3-*d*][1,3]thiazole-2,5,10-triones [7]; in this reaction, 1 equiv of 1,4-naphthoquinone was consumed for the oxidation of initially formed aromatic adduct.

The synthesis of new fused thiopyrano[2,3-*d*][1,3]-thiazole derivatives mimicking structural fragments of 5-ylidene-4-sulfanylidene-1,3-thiazolidin-2-ones seems to be an important line of research.

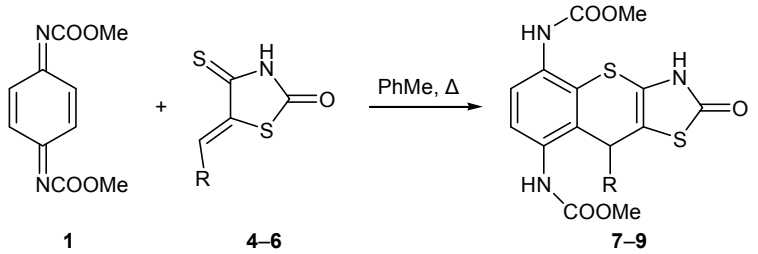
N,*N*′-Bis(methoxycarbonyl)-1,4-benzoquinone diimine (**1**) [8, 9] reacted with 5-(propan-2-ylidene)-4-sulfanylidene-1,3-thiazolidin-2-one (**2**) in boiling toluene to give bis-carbamate **3** in 87% yield (Scheme 1). Unlike 1,4-naphthoquinone [7], hetero-Diels–Alder re-

Scheme 1.



1 **2** **3**

Scheme 2.



1 **4–6** **7–9**

4, **7**, R = Ph; **5**, **8**, R = 4-$Me_2NC_6H_4$; **6**, **9**, R = 2-HOC_6H_4.

action of **1** with thiazolidinone **2** in acetic acid cannot be accomplished since quinone diimine **1** is capable of reacting with the solvent.

The IR spectrum of **3** contained an absorption band at 1640 cm^{-1} due to C=N stretching vibrations. The olefinic 6-H and 7-H protons resonated in the ^1H NMR spectrum of **3** as doublets at δ 7.38 and 7.53 ppm, and the corresponding carbon signals were located at δ_C 124.69 and 129.78 ppm in the ^{13}C NMR spectrum.

No reduction product of quinone diimine **1**, dimethyl benzene-1,4-diylbiscarbamate [8], was detected in the reaction mixture. This indicates that compound **3** is formed directly via [4+2]-cycloaddition rather than as a result of subsequent oxidation of aromatic adduct.

Under analogous conditions, quinone diimine **1** reacted with dienes **4**–**6** to give biscarbamates **7**–**9** in 64–82% yield (Scheme 2). Compounds **7**–**9** are likely to be formed as racemates since a chiral center (C^9) is generated during the reaction. Presumably, increased steric hindrances in the primary adducts are responsible for their autoaromatization to compounds **7**–**9**.

The structure of **7**–**9** was confirmed by IR and ^1H NMR spectra, and ^{13}C NMR spectrum was additionally recorded for compound **8**. The IR spectra of **7**–**9** lacked C=N stretching band at 1640 cm^{-1}, but absorption bands in the region 1610–1570 cm^{-1} were observed due to stretching vibrations of aromatic C=C bonds; also, NH stretching bands were present in the regions 3225–3226 (N^3–H) and 3360–3370 cm^{-1} (carbamate group). The ^1H NMR spectra of **7**–**9** showed a one-proton singlet at δ 8.66–8.94 ppm and a two-proton singlet at δ 9.54–9.58 ppm (CONH). Aromatic carbon nuclei of biscarbamate **8** resonated in the ^{13}C NMR spectrum at δ_C 116.45–147.02 ppm.

EXPERIMENTAL

The IR spectra were recorded on an InfraLUM FT-02 spectrometer with Fourier transform from samples prepared as KBr disks. The ^1H NMR spectra were recorded on a Bruker DRX 500 instrument (500.13 MHz) using DMSO-d_6 as solvent and tetramethylsilane as internal standard. The ^{13}C NMR spectra were measured with complete decoupling from protons on the same instrument at 126 MHz in DMSO-d_6. The purity of the isolated compounds was checked by TLC on Silufol UV-254 plates using chloroform–diethyl ether (1:2) or tetrahydrofuran–diethyl ether (1:1) as eluent; spots were developed by treatment with iodine vapor. Compounds **2**–**4** were synthesized according to the procedures described in [7, 10].

Dimethyl {9,9-dimethyl-2-oxo-8a,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8(3*H*,4a*H*)-diylidene}biscarbamate (3). A mixture of 1.11 g (5 mmol) of compound **1** and 0.87 g (5 mmol) of heterodiene **2** in 10 mL of anhydrous toluene containing a small amount of hydroquinone was refluxed for 5 h. The mixture was cooled, the solvent was removed, and the residue was recrystallized from ethyl acetate–hexane (1:1). Yield 1.7 g (87%), light yellow crystals, mp 95–97°C. IR spectrum, ν, cm^{-1}: 3225 (NH), 1680, 1650 (C=O), 1640 (C=N). ^1H NMR spectrum, δ, ppm: 1.32 s (3H, Me), 1.42 s (3H, Me), 3.01 s (6H, OMe), 2.65 d (1H, CH, J = 9.0 Hz), 4.53 d (1H, CH, J = 9.0 Hz), 7.38 d (1H, CH=, J = 10 Hz), 7.53 d (1H, CH=, J = 10 Hz), 8.26 br.s (1H, NH). ^{13}C NMR spectrum, δ_C, ppm: 25.65 and 27.31 (Me), 37.45 (C^9), 39.28 (C^{4a}), 48.39 (C^{8a}), 53.58 (OMe), 122.48 (C^{9a}), 124.69 and 129.78 (C^6, C^7), 135.89 (C^{3a}), 155.29 and 155.87 (NC=O), 157.08 and 160.24 (C^5, C^8), 171.26 (C^2). Found, %: C 48.52; H 4.18; N 10.45. $C_{16}H_{17}N_3O_5S_2$. Calculated, %: C 48.61; H 4.30; N 10.63.

Compounds **7**–**9** were synthesized in a similar way.

Dimethyl (2-oxo-9-phenyl-3,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8-diyl)biscarbamate (7). Yield 0.71 g (64%), yellow crystals, mp 182–184°C (from EtOH). IR spectrum, ν, cm^{-1}: 3370, 3226 (NH), 1680, 1650 (C=O), 1620, 1610, 1575 (C=C_{arom}).

^{1}H NMR spectrum, δ, ppm: 3.71 s (6H, OMe), 5.65 s (1H, 9-H), 7.01 t (1H, H_{arom}, J = 7.0 Hz), 7.28–7.40 m (4H, H_{arom}), 7.47 d (1H, H_{arom}, J = 8.6 Hz), 7.82 d (1H, H_{arom}, J = 8.6 Hz), 8.94 br.s (1H, NH), 9.58 br.s (2H, NH). Found, %: C 53.97; H 3.80; N 9.27. $C_{20}H_{17}N_3O_5S_2$. Calculated, %: C 54.18; H 3.84; N 9.48.

Dimethyl {9-[4-(dimethylamino)phenyl]-2-oxo-3,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8-diyl}biscarbamate (8). Yield 0.98 g (81%), dark violet crystals, mp 202–203°C (from EtOH). IR spectrum, ν, cm^{-1}: 3360, 3226 (NH), 1675, 1650 (C=O), 1625, 1610, 1575 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 2.43 s (6H, NMe_2), 3.70 s (6H, OMe), 5.62 s (1H, 9-H), 7.03 d (1H, H_{arom}, J = 8.9 Hz), 7.12 d (1H, H_{arom}, J = 8.9 Hz), 7.48 d (1H, H_{arom}, J = 8.7 Hz), 7.73–7.80 m (3H, H_{arom}), 8.66 br.s (1H, NH), 9.54 br.s (2H, NH). ^{13}C NMR spectrum, δ_C, ppm: 31.52 (C^9), 40.58 (NMe_2), 52.58 (OMe); 116.45, 119.25, 120.05, 125.89, 132.56, 136.78, 136.92, 147.02 (C_{arom}); 127.81 (C^{9a}), 139.56 (C^{3a}), 153.12 and 156.39 (**C**O_2Me), 168.24 (C^2). Found, %: C 54.08; H 4.48; N 11.31. $C_{22}H_{22}N_4O_5S_2$. Calculated, %: C 54.32; H 4.53; N 11.52.

Dimethyl {9-(2-hydroxyphenyl)-2-oxo-3,9-dihydro-2*H*-thiochromeno[2,3-*d*][1,3]thiazole-5,8-diyl}biscarbamate (9). Yield 0.94 g (82%), light yellow crystals, mp 190–192°C (from EtOH). IR spectrum, ν, cm^{-1}: 3580 (OH), 3365, 3225 (NH), 1680, 1650 (C=O), 1615, 1570 (C=C$_{arom}$). ^{1}H NMR spectrum, δ, ppm: 3.71 s (6H, OMe), 5.74 s (1H, OH), 5.82 s (1H, 9-H), 6.84–6.87 m (1H, H_{arom}), 7.01–7.05 m (3H, H_{arom}), 7.50 d (1H, H_{arom}, J = 8.7 Hz), 7.81 d (1H, H_{arom}, J = 8.7 Hz), 8.68 br.s (1H, NH), 9.56 s (2H, NH). Found, %: C 52.05; H 3.43; N 8.94. $C_{20}H_{17}N_3O_6S_2$. Calculated, %: C 52.29; H 3.70; N 9.15.

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