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Cycloaddition of 4,5-Dihydrooxazol-5-one Derivatives to 4-Methylbenzene-1,2-dithiol*

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Abstract—Reactions of 4,5-dihydrooxazol-5-one derivatives with 4-methylbenzene-1,2-dithiol in the presence of triethylamine includes nucleophilic attack by the thiol group on the carbonyl carbon atom in the oxazole ring, followed by opening of the latter and recyclization to 1,4-benzodithiine derivatives.

In the recent years, a considerable impetus was given to study of dihydrooxazolone derivatives, specifically 4,5-dihydrooxazol-5-ones which are key intermediate products in the synthesis of drugs, e.g., levothyroxine, anticancer agents, D-penicillamine, and fungicides [1–2]. In addition, these compounds are used in the preparation of metal-selective electrodes, in particular those selective for transition metals [3–4]. 4,5-Dihydrooxazolones exhibit specific reactivity toward nucleophiles. Some their reactions involve cleavage of the O–C^5 bond, while other reactions follow a substitution mechanism [5–6].

The present communication reports on reactions of a series of 4-methylidene-4,5-dihydrooxazol-5-ones **Ia**–**Id** with 4-methylbenzene-1,2-dithiol, which result in formation of new compounds. Initial oxazolones **Ia**, **Ib**, and **Id** were synthesized by condensation of *N*-benzoylaminoacetic acid with the corresponding carbonyl compounds in acetic anhydride in the presence of anhydrous sodium acetate. Compound **Ic** was obtained by reaction of 2-phenyl-4,5-dihydrooxazol-5-one with *p*-chlorobenzaldehyde. The reactions of oxazolones **Ia**–**Id** with 4-methylbenzene-1,2-dithiol were carried out in dry benzene in the presence of triethylamine. These mild conditions were sufficient to ensure cleavage of the C^5–O bond in the oxazole ring via nucleophilic attack by the thiol group on the carbonyl carbon atom in **I** [7–8]. Taking into account the presence of two thiol groups in the nucleophile molecule, formation of two regioisomeric products **II** and **III** might be expected (Scheme 1). Insofar as the electron density on the thiol sulfur atom in the *para* position with respect to the methyl group is greater, isomer **II** predominates in the product mixture, and it can readily be isolated by crystallization.

When the reaction of 4,5-dihydrooxazol-5-ones **Ia**–**Id** with 4-methylbenzene-1,2-dithiol in the presence of triethylamine was performed at elevated temperature (120–130°C) initially formed product **II** or **III** underwent intramolecular cyclization leading to 1,4-benzodithiine derivatives **IV** or **V**, respectively. As in the previous case, the major isomer (**IVa**–**IVd**) was isolated from the reaction mixture.

EXPERIMENTAL

The melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The mass spectra were recorded on a Shimadzu QP 1100 EX mass spectrometer. The IR spectra were obtained on an Amatson 1000 FT-IR spectrophotometer. The NMR spectra were measured on a Bruker DRX-500 Avance instrument using tetramethylsilane as internal reference.

4-(1-Methylethylidene)-2-phenyl-4,5-dihydrooxazol-5-one (Ia) [9]**.** A mixture of 2.4 g (26 mmol) of anhydrous sodium acetate, 4.8 g (26 mmol) of *N*-benzoylaminoacetic acid, 9.0 g (77 mmol) of acetic anhydride, and 12.0 g (0.2 mol) of freshly distilled acetone was heated under shaking until a pinkish solution was obtained (6 h). The solution was poured into water, and the precipitate was filtered off, washed with a solution of $NaHCO_3$ to remove acetic anhydride, and recrystallized from 96% ethanol. Yield 1.8 g (33%), colorless crystals, mp 99–100°C.

(*E*,*Z*)-2-Phenyl-4-propylidene-4,5-dihydrooxazol-5-one (Ib) [10]**.** A mixture of 3.3 g (36 mmol) of

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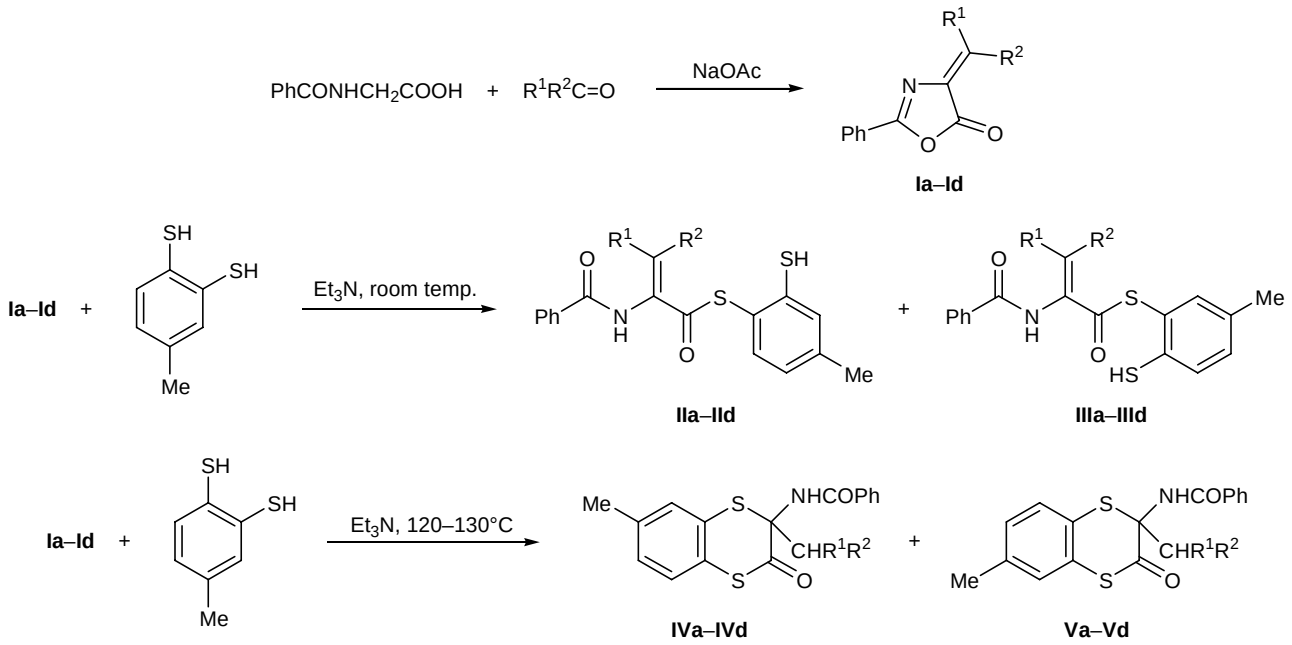
Scheme 1.



I–V, $R^1 = R^2 =$ Me (**a**); $R^1 =$ H, $R^2 =$ Et (**b**), $R^2 = 4\text{-}ClC_6H_4$ (**c**), $R^2 =$ 2-furyl (**d**).

anhydrous sodium acetate, 7.2 g (40 mmol) of *N*-benzoylaminoacetic acid, 20 ml of acetic anhydride, and 25 ml of propionaldehyde was heated under shaking until an orange solution was obtained (45 min). The mixture was cooled and poured onto crushed ice, and the precipitate was filtered off, washed with water, and treated with 70% aqueous ethanol. The precipitate was filtered off and recrystallized from 50% aqueous ethanol. Yield 4.0 g (46%), colorless needles, mp 81–83°C.

(*E*,*Z*)-4-(4-Chlorobenzylidene)-2-phenyl-4,5-dihydrooxazol-5-one (Ic) [9]**.** A mixture of 1.61 g (0.01 mol) of 2-phenyl-4,5-dihydrooxazol-5-one and 1.36 g (0.01 mol) of *p*-chlorobenzaldehyde was heated for 5 min on a water bath. The mixture was poured onto crushed ice, and the precipitate was filtered off and washed with 96% ethanol. Yield 1.84 g (65%), pale yellow crystals, mp 191–192°C.

(*E*,*Z*)-4-(2-Furylmethylidene)-2-phenyl-4,5-dihydrooxazol-5-one (Id) [11]**.** A mixture of 6.2 g (0.065 mol) of 2-furaldehyde, 4.9 g (27 mmol) of *N*-benzoylaminoacetic acid, 2.5 g (27 mmol) of anhydrous sodium acetate, and 9.0 g (77 mmol) of acetic anhydride was heated for 30 min at 80°C. The mixture was poured onto crushed ice, and the precipitate was filtered off, washed with cold water, dried, and recrystallized from 96% ethanol. Yield 13.2 g (85%), yellow needles, mp 170–171°C.

***S*-(4-Methyl-2-sulfanylphenyl) 2-benzoylamino-3-methyl-2-butenethioate (IIa).** A mixture of 0.2 g (1 mmol) of oxazole (**Ia**), 0.16 g (1 mmol) of 4-methylbenzene-1,2-dithiol, and 0.2 g of triethylamine was stirred for 1 h at room temperature. It was then dissolved in 10 ml of hot 96% ethanol, the solution was cooled, and the precipitate was filtered off and recrystallized from 96% ethanol. Yield 0.2 g (57%), mp 145–146°C. IR spectrum (KBr), ν, cm^{-1}: 3329 (N–H), 1716 (C=O), 1641 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.38 s (6H, CH_3), 2.40 s (3H, CH_3), 4.10 m (1H, SH), 5.88 m (1H, NH), 7.2–7.7 m (8H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.6, 28.7, 55.7, 61.2, 127.1–141.5, 166.7, 199.8. Mass spectrum, *m*/*z* (I_{rel}, %): 357 $[M]^+$ (33), 202 (100), 105 (10), 154 (12), 77 (100). Found, %: C 64.01; H 5.47; N 4.11. $C_{19}H_{19}NO_2S_2$. Calculated, %: C 63.83; H 5.36; N 3.92.

***S*-(4-Methyl-2-sulfanylphenyl) (*E*,*Z*)-2-benzoylamino-2-pentenethioate (IIb).** Oxazole **Ib**, 0.2 g (1 mmol), was dissolved in 20 ml of dry benzene, and 0.16 g (1 mmol) of 4-methylbenzene-1,2-dithiol and 0.2 g of triethylamine were added. The mixture was stirred for 30 min at room temperature, and the precipitate was filtered off, washed with dry benzene, and recrystallized from dry benzene. Yield 0.27 g (76%), colorless crystals, mp 189–190°C. IR spectrum (KBr), ν, cm^{-1}: 3303 (N–H), 1697 (C=O), 1642 (C=O).

^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.4 t (3H, CH_3), 2.10–2.22 m (2H, CH_2), 2.4 s (3H, CH_3), 3.96 m (1H, SH), 5.03 m (1H, NH), 6.99–7.75 m (9H, H_{arom}, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.50, 21.10, 25.3, 57.3, 59.40, 127.12–141.49, 166.79, 200.84. Mass spectrum, *m*/*z* (I_{rel}, %): 357 $[M]^+$ (35), 202 (10), 154 (14), 105 (100), 77 (100). Found, %: C 63.67; H 5.00; N 3.84. $C_{19}H_{19}NO_2S_2$. Calculated, %: C 63.83; H 5.36; N 3.92.

***S*-(4-Methyl-2-sulfanylphenyl) (*E*,*Z*)-2-benzoylamino-3-(4-chlorophenyl)-2-propenethioate (IIc).** Oxazole **Ic**, 0.29 g (1 mmol), was dissolved in 20 ml of dry benzene, and 0.16 g (1 mmol) of 4-methylbenzene-1,2-dithiol and 0.2 g of triethylamine were added. The mixture was stirred for 25 min at room temperature, and the precipitate was filtered off, washed with dry benzene, and recrystallized from dry benzene. Yield 0.35 g (81%), colorless crystals, mp 184–185°C. IR spectrum (KBr), ν, cm^{-1}: 3280 (N–H), 1691 (C=O), 1641 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.41 s (3H, CH_3), 4.35 m (1H, SH), 5.7 m (1H, NH), 7.0–7.7 m (13H, H_{arom}, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.1, 21.3, 55.8, 57.3, 57.5, 126.9–142.1, 166.6, 200.5. Mass spectrum, *m*/*z* (I_{rel}, %): 439 $[M]^+$ (10), 105 (30), 77 (100). Found, %: C 62.91; H 4.03; N 3.24. $C_{23}H_{18}ClNO_2S_2$. Calculated, %: C 62.79; H 4.12; N 3.18.

***S*-(4-Methyl-2-sulfanylphenyl) (*E*,*Z*)-2-benzoylamino-3-(2-furyl)-2-propenethioate (IId).** A mixture of 0.24 g (1 mmol) of oxazole **Id**, 0.16 g (1 mmol) of 4-methylbenzene-1,2-dithiol, and 0.2 ml of triethylamine in 20 ml of dry benzene was stirred for 1 h at room temperature. The precipitate was filtered off, washed with cold benzene, and recrystallized from 96% ethanol. Yield 0.18 g (46%), colorless crystals, mp 207°C (decomp.). IR spectrum (KBr), ν, cm^{-1}: 3354 (N–H), 1691 (C=O), 1641 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.44 s (3H, CH_3); 3.85 m (1H, SH); 5.59 m (1H, NH); 6.06 s, 6.23 s, 6.71 s (3H, furyl), 7.2–7.6 m (9H, H_{arom}, =CH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.2, 50.4, 56.8, 107.0, 110,5, 127.0–142.6, 151.5, 166.3, 199.4. Mass spectrum, *m*/*z* (I_{rel}, %): 395 $[M]^+$ (15), 245 (100), 105 (70), 77 (20). Found, %: C 63.92%; H 4.46; N 3.69. $C_{21}H_{17}NO_3S_2$. Calculated, %: C 63.77; H 4.33; N 3.54.

***N*-(2-Isopropyl-7-methyl-3-oxo-2,3-dihydro-1,4-benzodithiin-2-yl)benzamide (IVa).** A mixture of 0.4 g (2 mmol) of oxazole **Ia**, 0.32 g (2 mmol) of 4-methylbenzene-1,2-dithiol, and 0.4 g of triethylamine was stirred for 1 h at 120–130°C. It was then dissolved in chloroform, the solvent was removed, and the residue was crystallized from ethanol and purified by column chromatography. Yield 39%, colorless crystals, mp 107–108°C. IR spectrum (KBr), ν, cm^{-1}: 3339 (N–H), 1742 (C=O), l612 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.2 s (6H, CH_3), 2.12 s (3H, CH_3), 3.18 m (1H, CH), 5.57 m (1H, NH), 6.88–7.7 m (8H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.4, 20.7, 33.8, 102.9, 130.8–144.4, 170.1, 192.7. (10), 202 (60), 77 (100). Found, %: C 63.66; H 5.50; N 3.76. $C_{19}H_{19}NO_2S_2$. Calculated, %: C 63.83; H 5.36; N 3.92.

***N*-(7-Methyl-3-oxo-2-propyl-2,3-dihydro-1,4-benzodithiin-2-yl)benzamide (IVb).** A mixture of 0.4 g (2 mmol) of oxazole **Ib**, 0.32 g (2 mmol) of 4-methylbenzene-1,2-dithiol, and 0.4 g of triethylamine was stirred for 1 h at 120–130°C. It was then dissolved in chloroform, the solvent was removed, and the residue was crystallized from ethanol and purified by column chromatography. Yield 40%, colorless crystals, mp 109–110°C. IR spectrum (KBr), ν, cm^{-1}: 3315 (NH), 1722 (C=O), 1600 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.01 t (3H, CH_3), 2.03–2.34 m (4H, CH_2), 2.41 s (3H,CH_3), 5.12 s (1H, NH), 6.77–7.95 m (8H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 11.2, 20.1, 22.9, 42.3, 100.1, 129.9–142.2, 164.8, 196.9. Mass spectrum, *m*/*z* (I_{rel}, %): 357 $[M]^+$ (25), 202 (10), 105 (10), 77 (100). Found, %: C 64.11; H 5.45; N 4.18. $C_{19}H_{19}NO_2S_2$. Calculated, %: C 63.83; H 5.36; N 3.92.

***N*-[2-(4-Chlorophenyl)-7-methyl-3-oxo-2,3-dihydro-1,4-benzodithiin-2-yl]benzamide (IVc).** A mixture of 0.32 g (2 mmol) of oxazole **Ic**, 0.32 g (2 mmol) of 4-methylbenzene-1,2-dithiol, and 0.4 g of triethylamine was stirred for 1 h at 120–130°C. It was then dissolved in chloroform, the solvent was removed, and the residue was crystallized from ethanol and purified by column chromatography. Yield 31%, colorless crystals, mp 112–113°C. IR spectrum (KBr), ν, cm^{-1}: 3292 (N–H), 1719 (C=O), 1608 (C=O). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.39 s (3H, CH_3), 3.71 s (2H, CH_2), 6.91–7.77 m (12H, H_{arom}), 5.57 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.1, 39.3, 109.1, 125.9–146.6, 168.9, 198.5. Mass spectrum, *m*/*z* (I_{rel}, %): 439 $[M]^+$ (15), 105 (20), 77 (100). Found, %: C 62.55; H 3.96; N 3.20. $C_{23}H_{18}ClNO_2S_2$. Calculated, %: C 62.79; H 4.12; N 3.18.

***N*-[2-(2-Furyl)-7-methyl-3-oxo-2,3-dihydro-1,4-benzodithiin-2-yl]benzamide (IVd).** A mixture of 0.48 g (2 mmol) of oxazole **Id**, 0.32 g (2 mmol) of 4-methylbenzene-1,2-dithiol, and 0.4 g of triethylamine was stirred for 1 h at 120–130°C. It was then dissolved in chloroform, the solvent was removed, and

the residue was crystallized from ethanol and purified by column chromatography. Yield 35%, colorless crystals, mp 113–114°C. IR spectrum (KBr), ν, cm^{-1}: 3367 (N–H), 1732 (C=O), 1633 (C=O). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.21 s (3H, CH_3), 3.46–3.63 m (2H, CH_2), 5.72 m (1H, NH), 6.07–7.00 m (3H, furyl), 7.2–7.92 m (8H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.9, 40.1, 105.6, 124.9–143.2, 155.9, 161.8, 197.3. Mass spectrum, *m*/*z* (I_{rel}, %): 395 $[M]^+$ (10), 245 (55), 77 (100). Found, %: C 63.58; H 4.17; N 3.66. $C_{21}H_{17}NO_3S_2$. Calculated, %: C 63.77; H 4.33; N 3.54.

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