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Novel Synthesis of Heterocyclic Ketene N,N-, N,O-, and N,S-Acetals Using Cyanoketene Dithioacetals

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ABSTRACT

A novel synthesis of (2,3-dihydrobenzoimidazole-2-ylidenyl)cyanoacetanilide, (2,3-dihydrobenzoxazole-2-ylidenyl)cyanoacetanilide and (2,3-dihydro-benzothiazole-2-ylidenyl)cyanoacetanilide derivatives **5a–1** via reaction of ketene dithioacetals **2a–d** with *o*-phenylenediamine, *o*aminophenol, and *o*-aminothiophenol **3a–c** is reported and the synthetic potential of the method is demonstrated.

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Key Words: Ketene dithioacetals; *O*-phenylenediamine; *O*-aminothiophenol; *O*-aminophenol; Cyanoketene dithioacetals; Unsaturated nitriles.

Heterocyclic ketene aminals are versatile starting materials for the synthesis of a wide variety of fused heterocycles. Although their synthesis and reactions have received much attention,^[1] the synthesis and reactions of their corresponding sulfur and oxygen analogues-heterocyclic ketene N,S- and N,O-acetals have only been studied in a few cases.^[2] Recently, the synthesis and some reactions of heterocyclic ketene N,S-acetals have been reported by us.^[3,4] Here, we describe the synthesis of some new heterocyclic ketene N,N-, N,O- and N,S-acetals starting with ketene dithioacetals 2.^[5] Compounds 2 are prepared by the reaction of substituted acetanilide derivatives 1 with carbon disulfide in the presence of sodium ethoxide followed by the alkylation with methyl iodide. Compounds 2 reacted with o-phenylenediamine, o-aminophenol and o-aminothiophenol 3a-c in refluxing absolute ethanol to afford the corresponding (benzoimidazol-2-ylidene-, benzoxazole-2-ylidene-, and benzothiazole-2-ylidene)cyanoacetanilides 5 in good yields (Chart 1). The structures of compounds 5 were established and confirmed by their elemental analysis and spectral data (MS, IR, ¹H NMR). Thus, structure of 5a is supported by its mass spectrum which showed a molecular ion corresponding to the formula $C_{16}H_{12}N_4O$ (*m*/*z* 276). The ¹H NMR spectrum contained a multiplet at $\delta = 7.04 - 7.67$ ppm assigned to the aromatic protons and three broad singlets at $\delta = 9.25$, 10.42, and 12.23 ppm assigned to three NH groups. The formation of 5 from the reaction of 2 with 3 is assumed to proceed through nucleophilic attack of the -NH₂, -OH, and -SH groups to the ethylenic double bond followed by elimination of two moles of methyl mercaptan.

This result indicates that the reaction of N-substituted *bis*(methylthiomethylene)-cyanoacetamides with *o*-phenylenediamine, *o*-aminophenol, and *o*-aminothiophenol can be utilized as an excellent route for the synthesis of interesting heterocyclic ketene N,N-, N,O- and N,S-acetal derivatives, which are otherwise accessible only with difficulty. The obtained compounds are now under biological evaluation studies.

EXPERIMENTAL

All melting points are uncorrected on a Gallenkamp melting point apparatus. The ¹H NMR spectra were measured on a Varian 400 MHz

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Chart 1.

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spectrometer for solution $(CD_3)_2SO$ using Si(CH₃)₄ as an internal standard. Mass spectra were recorded on a Varian MAT 112 spectrometer. Analytical data were obtained from The Microanalytical Data Center at Cairo University.

(2,3-Dihydrobenzoimidazole-2-ylidenyl)cyanoacetanilides (5a–d), (2,3dihydrobenzoxazole-2-ylidenyl)cyanoacetanilides (5e–h), and (2,3-dihydrobenzothiazole-2-ylidenyl)cyanoacetanilides (5i–l). General procedure: A mixture of *bis*(methylthiomethylene)-*N*-substituted cyanoacetamides **2a–d** (0.01 mol) and *o*-phenylene diamine, *o*-aminophenol or *o*-aminothiophenol **3a–c** (0.01 mol) was refluxed in ethanol (30 mL) for 4 h. The resulting precipitated solid product was filtered off and recrystallized from the appropriate solvent.

5a: White; m.p., 265–267°C; from ethanol; yield, 80%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3425, 3321 (NH); 2191 (CN); 1649 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 7.04–7.67 (m, 9H, C₆H₅ and C₆H₄); 9.25 (s, 1H, NH); 10.42 (s, 1H, NH); 12.23 (s, 1H, NH); (*m*/*z* 276); Found: C, 69.35; H, 4.53; N, 20.39%; Calcd. for C₁₆H₁₂N₄O: C, 69.57; H, 4.35; N, 20.29%.

5b: White; m.p., 250–251°C; from methanol; yield, 82%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3445, 3310 (NH); 2199 (CN); 1656 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 6.87–7.63 (m, 8H, 2C₆H₄); 9.15 (s, 1H, NH); 10.43 (s, 1H, NH); 12.35 (s, 1H, NH); (*m*/*z* 310); Found: C, 61.66; H, 3.63; N, 18.22%; Calcd. for C₁₆H₁₁ClN₄O: C, 61.84; H, 3.54; N, 18.04%.

5c: White; m.p., 244–245°C; from ethanol; yield, 78%; ν_{max}/cm^{-1} (KBr) 3415, 3302 (NH); 2178 (CN); 1644 (CO); $\delta_{H}[(CD_{3})_{2}SO]$: 2.26 (s, 3H, CH₃); 7.06–7.56 (m, 8H, 2C₆H₄); 8.71 (s, 1H, NH); 9.00 (s, 1H, NH); 12.39 (s, 1H, NH); (*m*/*z* 290); Found: C, 70.47; H, 4.81; N, 19.49%; Calcd. for C₁₇H₁₄N₄O: C, 70.35; H, 4.83; N, 19.31%.

5d: White; m.p., 254–256°C; from ethanol; yield, 72%; ν_{max}/cm^{-1} (KBr) 3400, 3250 (NH); 2190 (CN); 1654 (CO); $\delta_{H}[(CD_{3})_{2}SO]$: 3.95 (s, 3H, OCH₃), 7.00–7.54 (m, 8H, 2C₆H₄); 9.00 (s, 1H, NH); 10.12 (s, 1H, NH); 12.09 (s, 1H, NH); (*m*/*z* 306); Found: C, 66.81; H, 4.51; N, 18.20%; Calcd. for C₁₇H₁₄N₄O₂: C, 66.67; H, 4.58; N, 18.30%.

5e: White; m.p., 256–258°C; from ethanol; yield, 74%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3427, 3318 (NH); 2193 (CN); 1644 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 7.00–7.80 (m, 9H, C₆H₅ and C₆H₄); 9.20 (s, 1H, NH); 10.30 (s, 1H, NH); (*m*/*z* 277); Found: C, 69.54; H, 3.88; N, 15.31%; Calcd. for C₁₆H₁₁N₃O₂: C, 69.31; H, 4.00; N, 15.16%.

5f: White; m.p., 245–247°C; from isopropanol; yield, 76%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3440, 3316 (NH); 2198 (CN); 1652 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 7.38–7.63 (m, 8H, 2C₆H₄); 8.86 (s, 1H, NH); 10.42 (s, 1H, NH); (*m*/z 311); Found: C, 61.84; H, 3.32; N, 13.60%; Calcd. for C₁₆H₁₀ClN₃O₂: C, 61.64; H, 3.21; N, 13.48%.

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5g: White; m.p., 235–236°C; from ethanol; yield, 70%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3414, 3309 (NH); 2182 (CN); 1648 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 2.23 (s, 3H, CH₃); 7.09–7.44 (m, 8H, 2C₆H₄); 8.79 (s, 1H, NH); 10.11 (s, 1H, NH); (*m*/*z* 288); Found: C, 70.23; H, 4.61; N, 14.34%; Calcd. for C₁₇H₁₃N₃O₂: C, 70.10; H, 4.47; N, 14.43%.

5h: White; m.p., 240–242°C; from ethanol; yield, 72%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3412, 3256 (NH); 2192 (CN); 1656 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 4.09 (s, 3H, OCH₃), 7.15–7.88 (m, 8H, 2C₆H₄); 9.56 (s, 1H, NH); 11.50 (s, 1H, NH); (*m*/*z* 307); Found: C, 66.24; H, 4.38; N, 13.86%; Calcd. for C₁₇H₁₃N₃O₃ (307): C, 66.45; H, 4.24; N, 13.68%.

5i: Yellow; m.p., 226–227°C; from ethanol; yield, 73%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3416, 3166 (NH); 2198 (CN); 1678 (CO); $\delta_{\text{H}}[(\text{CD}_3)_2\text{SO}]$: 7.22–7.89 (m, 9H, C₆H₅ and C₆H₄); 9.45 (s, 1H, NH); 10.56 (s, 1H, NH); (*m*/*z* 293); Found: C, 65.34; H, 3.83; N, 14.45%; Calcd. for C₁₆H₁₁N₃OS: C, 65.53; H, 3.75; N, 14.34%.

5j: Yellow; m.p., 236–238°C; from ethanol; yield, 76%; ν_{max}/cm^{-1} (KBr) 3420, 3160 (NH); 2195 (CN); 1670 (CO); $\delta_{H}[(CD_{3})_{2}SO]$: 7.07–8.01 (m, 8H, 2C₆H₄); 9.38 (s, 1H, NH); 12.91 (s, 1H, NH); (*m*/*z* 327); Found: C, 58.41; H, 3.02; N, 13.00%; Calcd. for C₁₆H₁₀ClN₃OS: C, 58.63; H, 3.05; N, 12.82%.

5k: Yellow; m.p., 224–226°C; from ethanol; yield, 77%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3414, 3159 (NH); 2189 (CN); 1648 (CO); δ_{H} [(CD₃)₂SO]: 2.28 (s, 3H, CH₃); 7.09–7.95 (m, 8H, 2C₆H₄); 9.20 (s, 1H, NH); 12.90 (s, 1H, NH); (*m*/*z* 307); Found: C, 66.57; H, 4.30; N, 13.89%; Calcd. for C₁₇H₁₃N₃OS: C, 66.45; H, 4.24; N, 13.68%.

51: Yellow; m.p., 220–222°C; from ethanol; yield, 70%; $\nu_{\text{max}}/\text{cm}^{-1}$ (KBr) 3434, 3163 (NH); 2190 (CN); 1665 (CO); δ_{H} [(CD₃)₂SO]: 4.12 (s, 3H, OCH₃), 6.88–7.70 (m, 8H, 2C₆H₄); 9.67 (s, 1H, NH); 10.90 (s, 1H, NH); (m/z 323); Found: C, 63.02; H, 4.01; N, 13.08%; Calcd. for C₁₇H₁₃N₃O₂S: C, 63.16; H, 4.03; N, 13.00%.

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