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Novel Cyanoketene *N,S*-Acetals and Pyrazole Derivatives using Potassium 2-Cyanoethylene-1-thiolates

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Abstract: Novel ketene *N,S*-acetals **3** were readily prepared by the reaction of cyanoacetamide or cyanothioacetamide with phenylisothiocyanate in the presence of potassium hydroxide, followed by alkylation of the produced salts with methyl iodide. The reaction of compounds **3** with hydrazines afforded different substituted pyrazoles **6**.

Keywords: activated nitriles, cyanoacetamide, cyano ketene *N,S*-acetals, cyanothioacetamide, phenylisothiocyanate, pyrazoles

Ketene dithioacetals bearing the cyano, amide, thioamide, or alkoxycarbonyl group at the α-position are extremely interesting electrophilic reagents for the introduction of three or two carbon units into the ring of heterocyclic compounds.[1,2] We have recently reported different successful approaches for synthesis of new classes of novel antimetabolites utilizing ketene *S,S*- and *N,S*-acetals as starting materials.[3] In an extension of this

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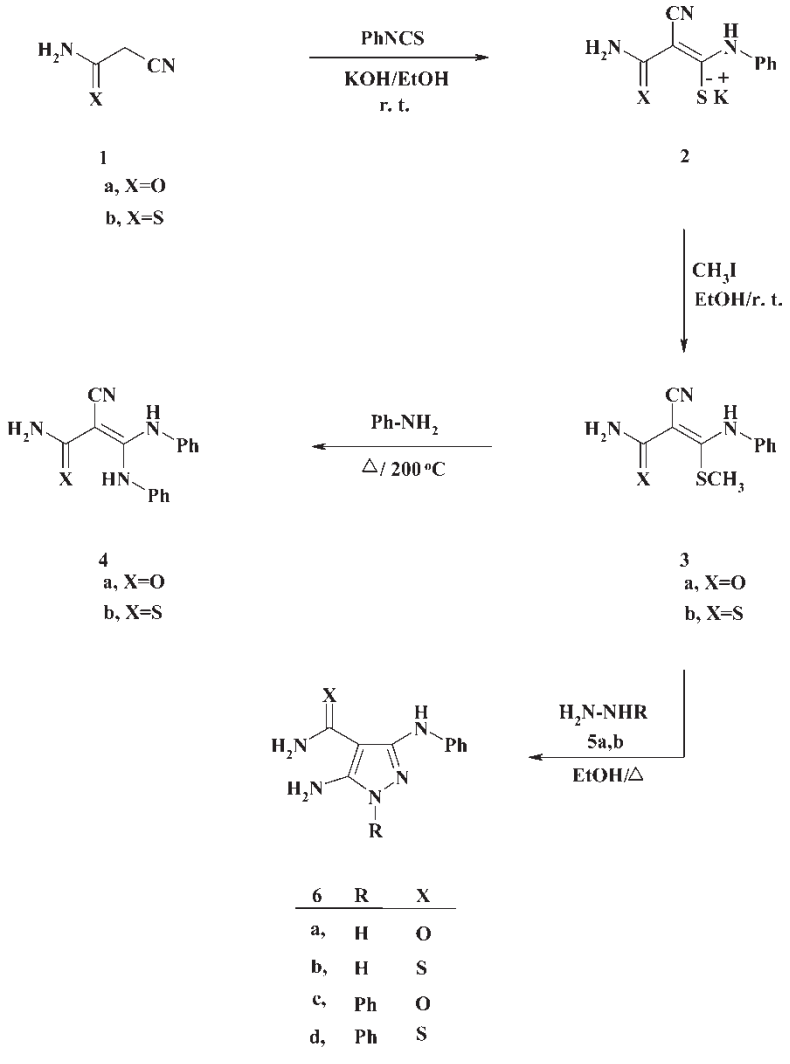
work, we now report a synthesis of some novel ketene *N,S*-acetals and their use in the synthesis of functionalized pyrazole derivatives. Thus, it has been found that reaction of cyanoacetamide **1a** and cyanothioacetamide **1b** with phenylisothiocyanate in KOH-EtOH at room temperature gives the corresponding potassium 2-cyanoethylene-1-thiolate derivatives **2** in high yield. Alkylation of the latter with methyl iodide gives the corresponding novel ketene *N,S*-acetals **3**. The structures of **3** were established on the basis of their elemental analysis and spectral data (MS, IR, and ^{1}H NMR). Reaction of ketene *N,S*-acetals **3** with aniline afforded the corresponding ketene *N,N*-acetals **4**. When compounds **3** were treated with substituted hydrazines **5**, the 5-anilinopyrazoles **6** were obtained. The structures of compounds **6** were established on the basis of their elemental analyses and spectral data. To investigate the scope of this reaction further, we studied the reaction of ethyl cyanoacetate **7** with phenylisothiocyanate in KOH-EtOH at room temperature to give the corresponding potassium salt of addition product **8**. Alkylation of the latter with methyl iodide afforded the methylated product **9**. Compound **9** reacted with thiourea and hydrazines **5a**,**b** to form the corresponding novel pyrimidine-2-thiones **12** and 5-aminopyrazols **10**, respectively. Reaction of the ketene *N,S*-acetal **9** with aniline afforded the corresponding ketene *N,N*-acetal **11**. Phenylthiosemicarbazide **13** reacted with phenylisothiocyanate under analogous conditions to yield the potassium salt of pyrazole ketene *N,S*-acetal **15** and not the expected potassium salt of 2-cyanoethylene-1-thiolate derivative **14**. The formation of **15** is assumed to proceed via intermediacy of **14**, which cyclized via addition to the cyano group to yield **15**. On alkylation with methyl iodide in ethanol, compound **15** afforded the novel pyrazole ketene *N,S*-acetal **16**. The structure of **16** was established on the basis of its elemental analysis and spectral data (MS, IR, and ^{1}H NMR) (Schemes 1–3).

In summary, we have achieved a regiospecific synthesis of interesting ketene *N,S*- and *N,N*-acetals and their conversions to several substituted pyrazole derivatives.

EXPERIMENTAL

All melting points are uncorrected on a Gallenkamp melting-point apparatus. The IR spectra were recorded (KBr disk) on a Perkin Elmer 1650 FT-IR instrument. The ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solution $(CD_3)_2SO$ using $Si(CH_3)_4$ 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.



1
a, X=O
b, X=S

2

3
a, X=O
b, X=S

4
a, X=O
b, X=S

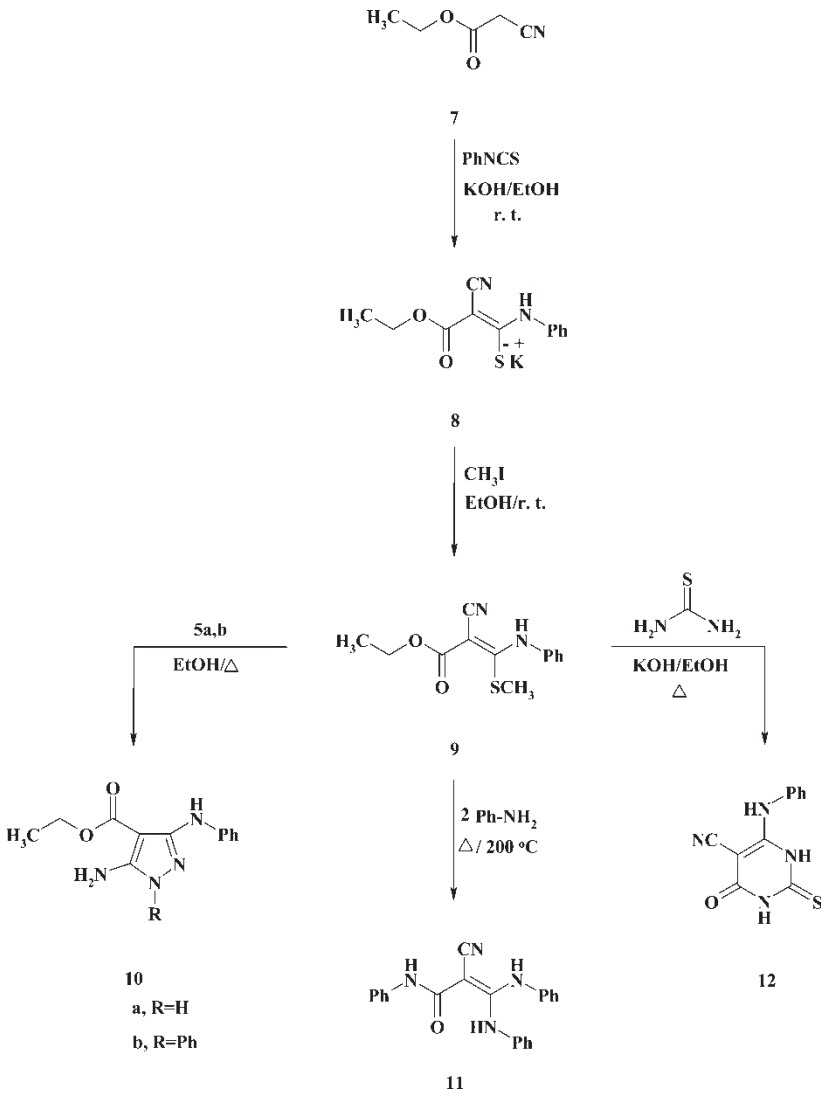
6	R	X
a,	H	O
b,	H	S
c,	Ph	O
d,	Ph	S

Scheme 1.

Ketene *N*,*S*-acetals (3,9)

General Procedure

A mixture of cyanoacetamide, cyanothioacetamide **1a**,**b**, or ethyl cyanoacetate **7** (0.01 mol) and phenylisothiocyanate (0.01 mol, 1.19 mL) was stirred at room temperature for 30 min in the presence of potassium hydroxide (0.01 mol, 0.56 g) in ethanol (30 mL). Methyl iodide (0.01 mol, 0.62 mL) was then added to the reaction mixture, and stirring is continued until a

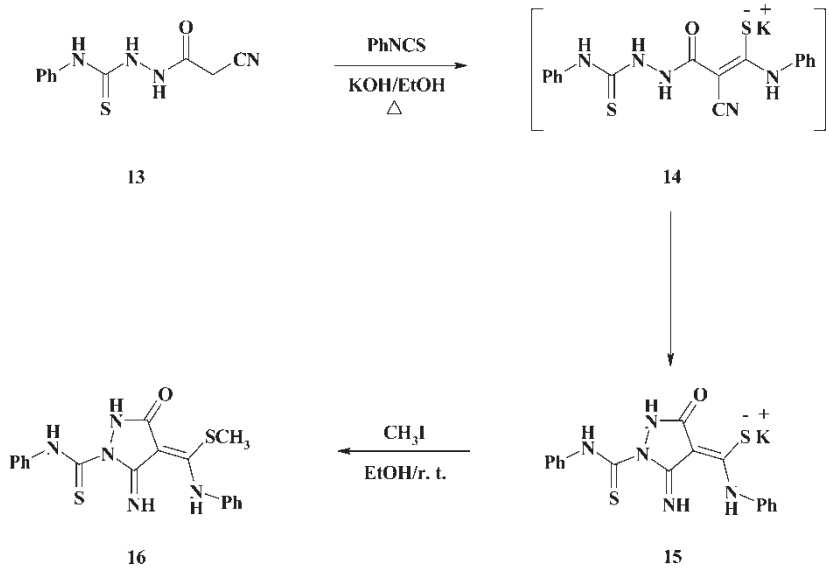


Scheme 2.

solid product is formed. The precipitated solid product was filtrated off and recrystallized from the appropriate solvent.

Data

3a: White; mp 163°C; from ethanol; yield 83%; ν_{max}/cm^{-1} (KBr) 3422, 3331 (NH, NH_2), 2190 (CN), 1642 (CO); $\delta_H[(CD_3)_2SO]$: 2.52 (s, 3H,



Scheme 3.

SCH_3), 6.98 (s, 2H, NH_2), 7.25–7.49 (m, 5H, C_6H_5), 8.67 (s, 1H, NH); m/z (233); found: C, 56.50; H, 4.62; N, 18.12%; calcd. for $C_{11}H_{11}N_3OS$ (233): C, 56.65; H, 4.72; N, 18.03%. **3b**: Yellow; mp 217°C; from ethanol; yield, 78%; ν_{max}/cm^{-1} (KBr) 3447, 3326 (NH, NH_2), 2177 (CN); $\delta_H[(CD_3)_2SO]$: 2.56 (s, 3H, SCH_3), 5.40 (s, 2H, NH_2), 7.18–7.45 (m, 5H, C_6H_5); 10.73 (s, 1H, NH); m/z (248); found: C, 53.25; H, 4.35; N, 16.98%; calcd. for $C_{11}H_{11}N_3S_2$ (249): C, 53.01; H, 4.42; N, 16.87%. **9**: White; mp 82°C; from ethanol; yield 86%; ν_{max}/cm^{-1} (KBr) 3472 (NH), 2204 (CN), 1659 (CO); $\delta_H[(CD_3)_2SO]$: 1.33–1.38 (t, 3H, CH_3); 2.25 (s, 3H, SCH_3); 4.23–4.30 (q, 2H, CH_2); 7.27–7.43 (m, 5H, C_6H_5); 11.51 (s, 1H, NH); m/z (262); found: C, 59.71; H, 5.40; N, 10.78%; calcd. for $C_{13}H_{14}N_2O_2S$ (262): C, 59.54; H, 5.34; N, 10.69%.

Ketene *N,N*-Acetals (4,11)

General Procedure

A mixture of compounds **3a**,**b** or **9** (0.01 mol) and aniline (0.02 mol, 1.96 mL or 0.01 mol, 0.98 mL) was heated for 2–3 h at 200°C in an oil bath, and then the reaction mixture was diluted with ethanol. The resulting solid product was filtered off and recrystallized from the appropriate solvent.

Data

4a: Pale brown; mp 238°C; from ethanol; yield 75%; ν_{max}/cm^{-1} (KBr) 3469 (NH); 1649 (CO); $\delta_H[(CD_3)_2SO]$: 6.00 (s, 2H, NH_2), 6.95–7.48 (m, 10H, $2C_6H_5$), 8.66 (s, 1H, NH), 9.89 (s, 1H, NH); found: C, 69.30; H, 5.12; N, 19.98%; calcd. for $C_{16}H_{14}N_4O$ (278): C, 69.07; H, 5.04; N, 20.14%. **4b**: Pale brown; mp 240°C; from ethanol; yield 75%; ν_{max}/cm^{-1} (KBr) 3290 (NH); found: C, 65.17; H, 4.71; N, 19.25%, calcd. for $C_{16}H_{14}N_4S$ (294): C, 65.31; H, 4.76; N, 19.05%. **11**: Pale brown; mp 243°C; from ethanol; yield 78%; ν_{max}/cm^{-1} (KBr) 3327, 3196 (NH); 1650 (CO); $\delta_H[(CD_3)_2SO]$: 6.93–7.46 (m, 15H, $3C_6H_5$), 8.62 (s, 1H, NH), 9.99 (s, 1H, NH), 10.42 (s, 1H, NH); m/z (343); found: C, 74.41; H, 5.02; N, 15.95%; calcd. for $C_{22}H_{18}N_4O$ (354): C, 74.58; H, 5.09; N, 15.82%.

5-Amino-3-anilino-4-substituted Pyrazoles (6,10)

General Procedure

A mixture of compounds **3a**,**b** or **9** (0.01 mol) and hydrazine derivatives **5a**,**b** (0.01 mol) was refluxed for 3–4 h in ethanol (30 mL). The solution mixture was poured over ice water and acidified with drops of dilute hydrochloric acid. The solid product was collected by filtration and recrystallized from the appropriate solvent.

Data

6a: White; mp 178°C; from ethanol; yield 76%; ν_{max}/cm^{-1} (KBr) 3423, 3325 (NH, NH_2); 1646 (CO); $\delta_H[(CD_3)_2SO]$: 5.58 (s, 2H, NH_2), 6.70 (s, 2H, NH_2), 7.15–7.54 (m, 5H, C_6H_5), 8.25 (s, 1H, NH), 10.58 (s, 1H, NH); m/z (219); found: C, 55.43; H, 5.15; N, 32.37%; calcd. for $C_{10}H_{11}N_5O$ (217): C, 55.30; H, 5.07; N, 32.26%. **6b**: White; mp 285°C; from ethanol; yield 72%; ν_{max}/cm^{-1} (KBr) 3453, 3310 (NH, NH_2); m/z (233); found: C, 51.33; H, 4.77; N, 30.21%; calcd. for $C_{10}H_{11}N_5S$ (233): C, 51.50; H, 4.72; N, 30.04%. **6c**: White; mp $>$ 300°C; from ethanol; yield 69%; ν_{max}/cm^{-1} (KBr) 3432, 3315 (NH, NH_2), 1659 (CO); found: C, 65.66; H, 5.20; N, 23.76%; calcd. for $C_{16}H_{15}N_5O$ (293): C, 65.53; H, 5.12; N, 23.89%. **6d**: White; mp $>$ 300°C; from ethanol; yield 66%; ν_{max}/cm^{-1} (KBr) 3435, 3354 (NH, NH_2); found: C, 61.99; H, 4.76; N, 22.82%; calcd. for $C_{16}H_{15}N_5S$ (309): C, 62.14; H, 4.85; N, 22.65%. **10a**: White; mp 168°C; from ethanol; yield 80%; ν_{max}/cm^{-1} (KBr) 3473, 3380 (NH, NH_2), 1642 (CO); $\delta_H[(CD_3)_2SO]$: 1.29–1.36 (t, 3H, CH_3), 4.22–4.32 (q, 2H, CH_2), 6.05 (s, 2H, NH_2), 6.80–7.59 (m, 5H, C_6H_5), 8.06 (s, 1N, NH), 11.10 (s, 1H, NH); m/z (246); found: C, 58.43; H, 5.73; N, 22.57%; calcd. for $C_{12}H_{14}N_4O_2$ (246): C, 58.54; H, 5.69; N,

22.76%. **10b**: White; mp > 300°C; from ethanol; yield 62%; ν_{max}/cm^{-1} (KBr) 3423, 3353, 3280 (NH, NH_2), 1654 (CO); found: C, 67.23; H, 5.54; N, 17.60%; calcd. for $C_{18}H_{18}N_4O_2$ (322): C, 67.08; H, 5.59; N, 17.39%.

4-Anilino-5-cyano-6-oxopyrimidine-2-thione (12)

Procedure

A mixture of compound **9** (0.01 mol, 2.62 g) and thiourea (0.01 mol, 0.76 g) was heated for 3 h in ethanol (25 mL) containing an equivalent amount of potassium hydroxide (0.01 mol, 0.56 g). The reaction mixture was poured over ice water and acidified with drops of dilute hydrochloric acid. The solid product was filtered off and recrystallized from ethanol.

Data

12: White; mp 276°C; from ethanol; yield 75%; ν_{max}/cm^{-1} (KBr) 3420, 3310 (NH); 2212 (CN); 1647 (CO); $\delta_H[(CD_3)_2SO]$: 7.27–7.46 (m, 5H, C_6H_5), 9.42 (s, 1H, NH), 12.51 (s, 1H, SH); m/z (244); found: C, 54.23; H, 5.17; N, 23.07%; calcd. for $C_{11}H_8N_4OS$ (244): C, 54.10; H, 3.28; N, 22.95%.

(4*Z*)-4-[Anilino(methylthio)methylene]-5-imino-3-oxo-*N*-phenylpyrazolidine-1-carbothioamide (16)

Procedure

A mixture of 1-cyanoacetyl-4-phenylthiosemicarbazide **13** (0.01 mol, 2.34 g) and phenylisothiocyanate (0.01 mol, 1.19 mL) was heated for 20 min in ethanol (25 mL) containing potassium hydroxide (0.01 mol, 0.56 g). After cooling, methyl iodide (0.01 mol, 0.62 mL) was added, and the mixture was stirred until a solid product was formed. The precipitated solid product was collected by filtration and recrystallized from 30 ml of ethanol.

Data

16: Yellow; mp 219°C; from ethanol; yield 77%; ν_{max}/cm^{-1} (KBr) 3450, 3375 (NH); 1642 (CO); $\delta_H[(CD_3)_2SO]$: 2.10 (s, 3H, SCH_3), 7.25–7.58 (m, 10H, $2C_6H_5$), 10.82 (s, 1H, NH), 12.31 (s, 1H, NH), 12.52 (s, 1H, NH), 12.97 (s, 1H, NH), m/z (383); found: C, 56.24; H, 4.52; N, 18.13%; calcd. for $C_{18}H_{17}N_5OS_2$ (383): C, 56.40; H, 4.44; N, 18.28%.

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