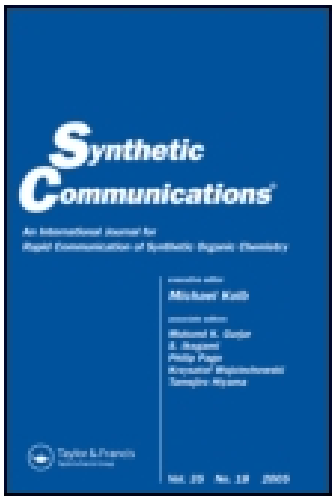

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Synthesis of Benzimidazole Ketene *N,S*-Acetals and Their Reactions with Nucleophiles

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ABSTRACT

The novel ketene thioacetal **4** and ketene *N,S*-acetal **5** were readily prepared by the reaction of 2-cyanomethylbenzimidazole with either carbon disulfide or phenyl isothiocyanate in the presence of a base, followed by alkylation of the produced salts with methyl iodide. The reaction of compounds **4** and **5** with hydrazines afforded different benzimidazolyl substituted pyrazoles.

Key Words: Benzimidazole ketene *N,S*-acetals; Nucleophiles; Phenyl isothiocyanate; Pyrazoles; Benzimidazole derivatives.

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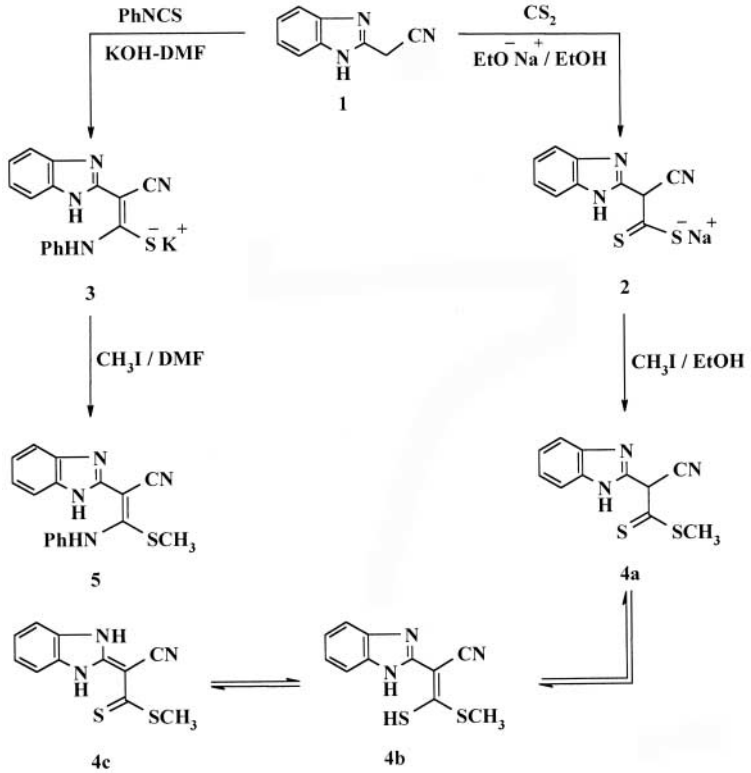
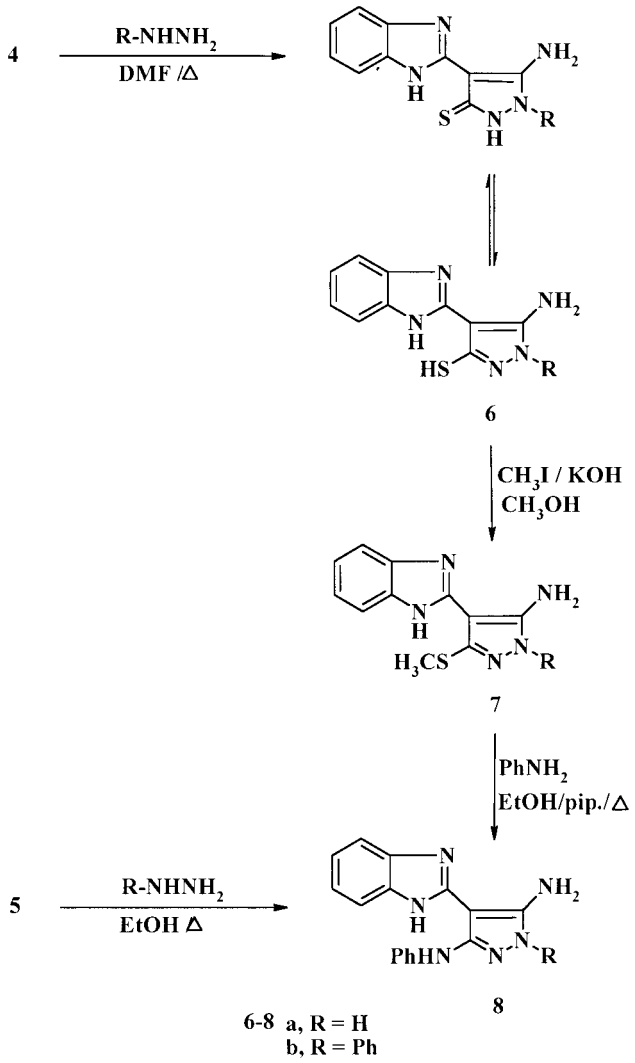
Heterocyclic ketene dithioacetals are versatile starting materials for the synthesis of a wide variety of fused heterocyles.[1–3] Although their synthesis and reactions have received much attention,[4] the synthesis and reactions of their corresponding *S*,*N*- and *S*,*O*-acetals have only been studied in a few cases.[5] Recently, the synthesis and some reactions of heterocyclic ketene *S*,*S*- and *N*,*S*-acetals have been reported by us.[6] Here, we describe the synthesis of benzimidazole ketene *N*,*S*-acetals and their reactions with nucleophiles. Using the latter reactions, several benzimidazolyl substituted pyrazole derivatives can be synthesized. Thus, it has been found that 2-cyanomethylbenzimidazole **1**[7] reacted with carbon disulfide in the presence of sodium ethoxide to give the corresponding sodium monothiolate derivative **2** in high yields. The latter on treatment with 1 eqv. of methyl iodide gives the novel thioester **4**. The structure of **4** (Sch. 1) has been established on the basis of its elemental



Scheme 1.

analysis and spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS). Thus, structure **4** is supported by its mass spectrum which showed a molecular formula $C_{11}H_9N_3S_2$ ($M^+ = 247$). Compound **4** can potentially exist in three tautomeric forms **4a–c**. Spectral studies, however, indicated the presence of the thione tautomer **4a** in solutions. Thus, the ^{13}C NMR signal at 200.25 ppm indicated the presence of a thione carbon rather than =C–SH. No significant amounts of the alternative tautomers **4b** and **4c** could be detected. ^{1}H NMR revealed a singlet band at $\delta =$ 2.49 ppm assignable to a methylsulfanyl group and another multiplet at $\delta = 7.34$–7.69 ppm assignable to aromatic protons. Another broad singlet appeared at $\delta = 13.61$ ppm assignable to NH group. The course of the reaction between **1** and carbon disulfide prompted us to investigate this reaction between **1** and phenyl isothiocyanate under a basic reaction condition. Thus, in a typical experiment, 2-cyanomethylbenzimidazole **1** reacted with phenyl isothiocyanate in DMF–KOH to give the corresponding stable potassium salt **3**. The latter on alkylation with methyl iodide in methanol afforded the novel benzimidazole ketene *N,S*-acetal **5**. The structure of **5** was established on the basis of elemental analysis and spectral data (IR, MS and ^{1}H NMR). The analytical data for **5** revealed a molecular formula $C_{17}H_{14}N_4S$ ($M^- = 306$). The ^{1}H NMR spectrum revealed a multiplet at $\delta =$ 7.17–7.62 ppm assigned to the aromatic protons and two broad singlets at $\delta = 12.49$ and 12.57 ppm assignable for two NH groups. Reaction of compound **4** with substituted hydrazines in a molar ratio 1:1 in refluxing DMF containing a catalytic amount of piperidine gave the corresponding 4-benzimidazolyl-5-aminopyrazole derivatives **6**. The structures of **6** (Sch. 2) were established on the basis of their elemental analysis and spectral data (IR, MS, ^{1}H NMR and ^{13}C NMR). Thus, structure **6** is supported by its mass spectrum which showed a molecular formula $C_{10}H_9N_5S$ ($M^- = 231$). Compound **6** can potentially exist in two tautomeric forms, 5-aminopyrazolin-3-thione and 5-amino-3-mercaptopyrazole. The mercapto form would be expected to be more stable, because of the weakened basicity of the ring *N* atom at the 2-position, in turn arising from the adjacent heteroatom and the sulfur atom at the 3-position. Spectral studies proved the mercapto form and indicated the presence of the SH tautomer in solution (e.g., the ^{13}C NMR signal at 150 ppm indicates a =C–SH rather than a thione carbon). Similarly, the benzimidazole ketene *N,S*-acetal **5** reacted with substituted hydrazines in refluxing ethanol containing a catalytic amount of piperidine to give the corresponding pyrazole derivatives **8** in good yields (method a). Structure **8a** was supported by its mass ($M^- = 290$), which agrees with its molecular formula $C_{16}H_{14}N_6$; its ^{1}H NMR spectrum displayed signals at $\delta =$ 7.16–7.50 ppm related to the aromatic protons,



Scheme 2.

a broad signal at $\delta =$ 7.92 ppm corresponding to the NH_2 group and another three singlets at $\delta = 7.99$, 9.63 and 10.46 ppm assignable to the three NH groups. Compounds **8** could also be prepared by alkylation of the pyrazole derivatives **6** with methyl iodide followed by reaction with aniline (Method B).

In summary, we have achieved a highly regioselective synthesis of interesting benzimidazole ketene *N,S*-acetals and their conversions to several benzimidazolyl substituted pyrazole derivatives. The compounds obtained seem promising as high potential antimetabolite agents.

EXPERIMENTAL

All melting points are uncorrected on a Gallenkamp melting point apparatus. The IR spectra were recorded (KBr disk) on a Perkin Elmer 11650 FT-IR instrument. The ^{1}H NMR spectra were measured on a Varian 400 MHz spectrometer for solutions in $(CD_3)_2SO$ 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.

Sodium Thiolate Derivative (2)

A mixture of 2-cyanomethylbenzimidazole **1** (0.01 mol) and sodium ethoxide (0.02 mol) in ethanol (50 mL) was gently heated at 40–50°C for 20 min. After the solution has become cold, carbon disulfide (0.01 mol) was added gradually and the reaction mixture was then refluxed for 15 min. The solvent was concentrated by evaporation over water bath. The performed sodium salt was separated by filtration and recrystallized from ethanol.

2: Yellow; m.p. >300°C; yield, 58%; ν_{max}/cm^{-1} (KBr) 3323, 3199 (NH); 2208 (CN); Found: C, 47.41; H, 2.01; N, 16.52%; Calcd. for $C_{10}H_6N_3S_2Na$ (255): C, 47.06; H, 2.35; N, 16.47%.

2-[(1-Cyano-2-methylsulfanyl-2-mercapto)ethylene]-(1*H*)-benzimidazole (4)

To a cold solution of compound **2** (0.01 mol) in ethanol (30 mL), methyl iodide (0.01 mol) was added dropwise and stirring was continued for 1 h. The reaction mixture was poured over ice-water mixture (50 mL). The resulting solid product was collected by filtration and recrystallized from ethanol.

4: Brown; m.p. >300°C; from ethanol; yield, 78%; ν_{max}/cm^{-1} (KBr) 3200 (NH); 2192 (CN); δ_H [$(CD_3)_2SO$] 2.49 (s, 3H, CH_3); 3.70 (s, 1H, CH); 7.34–7.69 (m, 4H, C_6H_4); 13.61 (s, 1H, NH); ^{13}C NMR: 16.88 (SCH_3);

80.51(CH), 117.81 (CN); 124.27–129.80 (aromatic carbons); 149.45 (C-2); 200.25 (C=S); *m/z* (248); Found: C, 53.02; H, 3.78; N, 16.94%; Calcd. for $C_{11}H_9N_3S_2$ (247): C, 53.44; H, 3.64; N, 17.00%.

Potassium Thiolate Derivative (3)

A solution of compound **1** (0.01 mol) and phenyl isothiocyanate (0.01 mol) in DMF (30 mL) was treated with a solution of KOH (0.01 mol in 5 mL H_2O). The mixture was stirred for 1 h and the resulting salt product was collected by filtration and recrystallized from ethanol.

3: Yellow; m.p. >300°C; yield, 91%; ν_{max}/cm^{-1} (KBr) 3340, 3195 (NH); 2206 (CN); Found: C, 58.61; H, 2.88; N, 17.26%; Calcd. for $C_{16}H_{11}N_4SK$ (330); C, 58.18; H, 3.33; N, 16.97%.

2-[(1-Cyano-2-methylthio-2-anilino)ethylene]-(1*H*)-benzimidazole (5)

Methyl iodide (0.01 mol) was added gradually to a cooled solution of the potassium salt **3** (0.01 mol) in DMF (30 mL). The reaction mixture was left under stirring overnight and the resulting product was collected by filtration and recrystallized from ethanol.

5: Brown; m.p. 219°C; yield, 88% (according to Method A); 61%; ν_{max}/cm^{-1} (KBr) 3450–3250 (NH); 2220 (CN); δ_H [$(CD_3)_2SO$] 2.21 (s, 3H, CH_3); 7.17–7.62 (m, 9H, C_6H_5, C_6H_4); 12.49 (s, br, 1H, NH), 12.57 (s, br, 1H, NH); *m/z* (304); Found: C, 66.23; H, 4.72; N, 17.96%; Calcd. for $C_{17}H_{14}N_4S$ (306): C, 66.66; H, 4.57; N, 18.30%.

4-[(1*H*)-Benzimidazolo-2-yl]-3-mercapto-5-aminopyrazoles (6a,b)

A mixture of compounds **4a**,**b** (0.01 mol) and hydrazine hydrate or phenyl hydrazine (0.01 mol) was refluxed in DMF (30 mL) containing a catalytic amount of piperidine for 4 h. The solvent was evaporated and the resulting product was collected by filtration and recrystallized from ethanol.

6a: Colorless; m.p. 230°C; yield, 65%; ν_{max}/cm^{-1} (KBr) 3214, 3460, 3370 (NH, NH_2); ^{1}H NMR: 4.56 (s, 2H, NH_2); 7.23–7.81 (m, 4H, C_6H_4), 10.49 (s, br, 1H, NH), 12.00 (s, br, 1H, SH); Found: C, 52.12;

H, 3.58; N, 30.61%; Calcd. for $C_{10}H_9N_5S$ (231): C, 51.94; H, 3.89; N, 30.30%.

6b: Yellow; m.p. 206°C; from ethanol; yield, 69%; ν_{max}/cm^{-1} (KBr) 3468–3215 (NH, NH_2); ^1H NMR: 4.99 (s, 2H, NH_2); 7.05–7.76 (m, 9H, C_6H_5, C_6H_4), 9.89 (s, br, 1H, NH); Found: C, 62.00; H, 4.61, N, 23.11%; Calcd. for $C_{16}H_{13}N_5S$ (307); C, 62.54; H, 4.23, N, 22.80%.

1-Substituted-3-methylthio-4-[(1*H*)-benzimidazolo-2-yl]-5-aminopyrazoles (7a,b)

A mixture of **6** (0.01 mol), KOH (0.01 mol) and methyl iodide (0.01 mol) in ethanol (30 mL) was refluxed for 30 min and then diluted with cold water (50 mL). The resulting solid product was collected by filtration and recrystallized from ethanol.

7a: Colorless; m.p. 258°C; yield, 48%; ν_{max}/cm^{-1} (KBr) 3124, 3186, 3435 (NH, NH_2); ^1H NMR: 2.55 (s, 3H, SCH_3), 4.89 (s, 2H, NH_2); 7.11–7.67 (m, 4H, C_6H_4), 11.00 (s, br, 1H, NH); *m/z* (245); Found: C, 53.97; H, 4.01; N, 28.33%; Calcd. for $C_{11}H_{11}N_5S$ (245): C, 53.88; H, 4.48; N, 28.57%.

7b: Yellow; m.p. 243°C; yield, 61%; ν_{max}/cm^{-1} (KBr) 3195, 3296 (NH, NH_2); *m/z* (321); Found: C, 63.97; H, 4.20; N, 21.55%; Calcd. for $C_{17}H_{15}N_5S$ (321): C, 63.55; H, 4.67; N, 21.81%.

1-Substituted-3-phenylamino-4-[2-(1*H*)benzimidazolo-yl]-5-amino-pyrazoles (8a,b)

Method A

To a mixture of **5** (0.01 mol) and hydrazine or phenylhydrazine (0.01 mol) in ethanol (50 mL), pipridine (3 drops) was added. The mixture was heated under reflux for 3–6 h. The resultant precipitate was isolated by suction and recrystallized from ethanol.

Method B

A mixture of compound **7a**,**b** (0.01 mol) and aniline (0.01 mol) was refluxed in ethanol for 6 h. The solvent was concentrated by evaporation

and the formed product was collected by filtration and recrystallized from ethanol.

8a: Yellow; m.p. >300°C; from ethanol; yield, 78%; ν_{max}/cm^{-1} (KBr)$^-$ 3480–3230 (NH, NH_2); ^{1}H NMR: 7.16–7.50 (m, 9H, C_6H_5, C_6H_4), 7.92 (s, br, 2H, NH_2), 7.99 (s, br, 1H, NH), 9.63 (s, br, 1H, NH), 10.46 (s, br, 1H, NH); *m/z* (291); Found: C, 65.97; H, 4.58; N, 28.57% Calcd. for $C_{16}H_{14}N_6$ (290); C, 66.20; H, 4.82; N, 28.96%.

8b: Yellow; m.p. 287°C; from ethanol; yield, 79%; ν_{max}/cm^{-1} (KBr) 3330, 3340, 3450 (NH, NH_2); ^{1}H NMR: 7.00–7.77 (m, 14H, $2C_6H_5$, C_6H_4), 7.92 (s, br, 2H, NH_2), 9.76 (s, br, 1H, NH), 10.34 (s, br, 1H, NH); *m/z* (291); found: C, 72.42; H, 4.68; N, 23.10%. Calcd. for $C_{22}H_{18}N_6$ (366): C, 72.13; H, 4.92; N, 22.95%

REFERENCES

1. Elgemeie, G.H.; El-Ezbawy, S.E.; Ali, H.A.; Mansour, A.K. Bull. Chem. Soc. Jpn. **1994**, *67*, 738.
2. Elgemeie, G.H.; Elghandour, A.H.; Elzanate, A.M.; Ahmed, S.A. J. Chem. Soc. Perkin Trans. 1 **1997**, 3285.
3. Tominaga, Y. J. Heterocyclic Chem. **1989**, *26*, 1167.
4. Elgemeie, G.H.; Elghandour, A.H.; Elzanate, A.M.; Hussein, A.M. J. Chem. Research (S) **1997**, 256.
5. Henriksen, L. Acta Chem. Scand. **1996**, *50*, 432.
6. Elgemeie, G.H.; Elghandour, A.H.; Elzanate, A.M.; Ahmed, S.A. J. Chem. Research (S) **1998**, 162.
7. Franke, W.; Ried, W. Industrie Chim. Belge. **1955**, *20*, 605.

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