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KETENE S,S-ACETALS IN THE SYNTHESIS OF SOME NEW FUSED PYRIMIDINE DERIVATIVES

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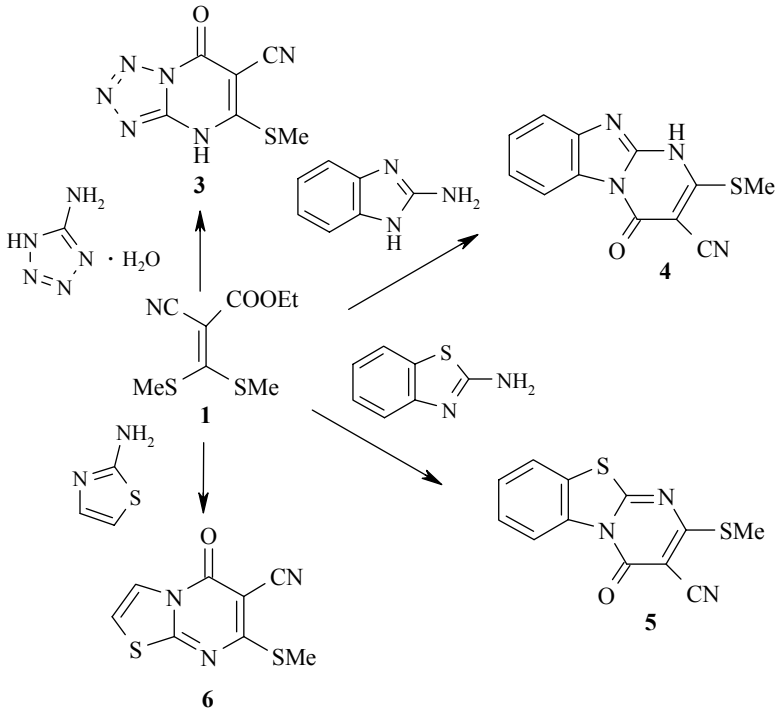
Condensation of ketene dithioacetal derivatives with some aminoazoles (5-aminotetrazole monohydrate, 2-aminobenzimidazole, 2-aminobenzothiazole, and 2-aminothiazole) in the presence or absence of triethylamine gave the corresponding tetrazolopyrimidines, benzimidazopyrimidines, benzothiazolo-pyrimidines, and thiazolopyrimidines.

Keywords: aminoazoles, ketene dithioacetals, pyrimidines.

Ketene S,S-acetals are attractive building blocks for the synthesis of heterocyclic compounds [1-21]. In particular, pyrimidine derivatives have been the subject of chemical and biological studies due to their interesting pharmacological activity, including antipyretic, analgesic, anti-inflammatory potential as well as herbicide, fungicide, and leishmanicide properties [2, 22-24]. This work aimed to synthesize some pyrimidine derivatives with the hope of obtaining interesting biological activities.

Scheme 1



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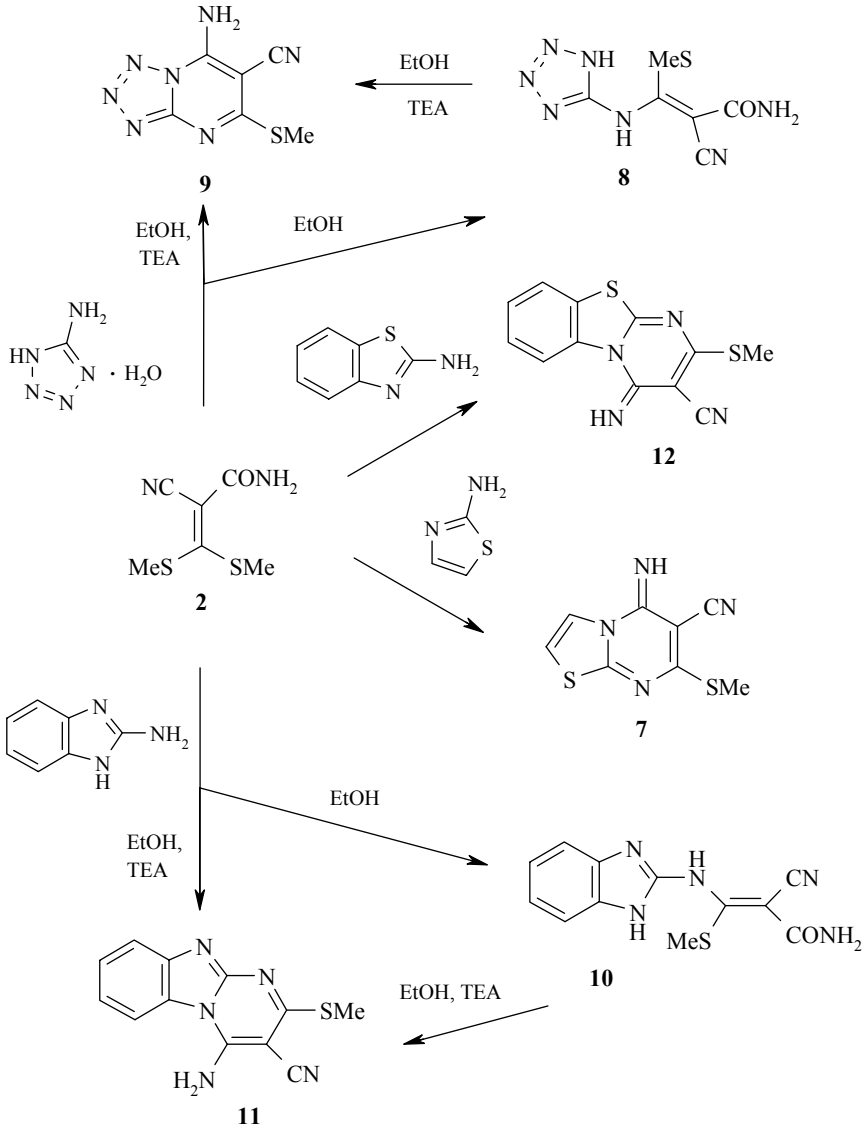
Due to the great interest in this class of pharmacologically active compounds, we report the preparation of novel functionalized azolopyrimidine derivatives by the reaction of ketene S,S-acetal derivatives **1** (Scheme 1) and **2** (Scheme 2) with some aminoazoles in the presence (or absence) of triethylamine.

Scheme 2



The treatment of ethyl 2-cyano-3,3-bis(methylthio)acrylate (**1**) [25] with 5-aminotetrazole monohydrate in absolute ethanol allowed the isolation of a compound which possessed elemental analysis and spectral data concordant with the formation of the tetrazolopyrimidine **3** (Scheme 1). The IR spectrum is characterized by the presence of strong absorption bands of NH group at 3200, cyano group at 2207, and carbonyl group at 1669 cm^{-1}. The ^1H NMR spectrum showed a singlet signal at δ 2.60 corresponding to the SCH_3 protons and a singlet at δ 7.75 ppm due to NH proton.

Compound **1** was allowed to react with 2-aminobenzimidazole in absolute ethanol for 5 h to give 3-cyano-2-methylthio-4-oxo-1,4-dihydrobenzimidazo[1,2-*a*]pyrimidine (**4**) in 82% yield. Assignment of product **4** was based on its elemental analysis, IR, ^1H NMR, and MS spectral data.

The reaction of 2-aminobenzothiazole with ethyl 2-cyano-3,3-bis(methylthio)acrylate (**1**) gave the corresponding benzothiazolopyrimidine derivative **5**. The structure of the latter was confirmed by its elemental analysis and spectral data.

Thiazolo[3,2-*a*]pyrimidine derivatives **6** and **12** were synthesized by the treatment of 2-aminothiazole with ketene S,S-acetals **1** and **2**, respectively. The synthesis of **6** and **7** proceeded successfully in ethanol containing a catalytic amount of triethylamine. The structures of thiazolo[3,2-*a*]pyrimidines **6** and **7** were elucidated by their elemental analysis and spectral data.

Condensation of 2-cyano-3,3-bis(methylthio)acrylamide (**2**) [26] with 5-aminotetrazole monohydrate in absolute ethanol afforded the enamine derivative **8** (Scheme 2). Compound **8** underwent cyclization upon boiling in ethanol and triethylamine to give the tetrazolopyrimidine ring system **9**. An alternative preparation of **9** was carried out by the treatment of ketene S,S-acetal **2** with 5-aminotetrazole monohydrate in absolute ethanol and triethylamine. The elemental analyses and spectral measurements are compatible with the assigned structures of products **8** and **9**.

Compound **2** reacts readily with 2-aminobenzimidazole in absolute ethanol to give the corresponding enamine derivative **10**. However, when the reaction mixture was refluxed in ethanol and triethylamine, the pyrimidobenzimidazole derivative **11** was isolated directly. The structures of products **10** and **11** were established by their elemental analyses and spectral data.

Compound **2** reacts readily with 2-aminobenzothiazole in absolute ethanol and triethylamine, the pyrimidobenzothiazole derivative **12** was isolated directly. The structure of product **12** was established by its of elemental analysis and spectral data. The IR spectrum of **12** revealed the absence of amide group and the presence of imino function at 3109 in addition to the cyano function at 2208 cm^{-1}. The ^1H NMR spectrum showed a singlet for SCH_3 protons at δ 2.60, a multiplet for aromatic protons at δ 6.90-7.40, and a singlet at δ 9.60 ppm for NH.

EXPERIMENTAL

All melting points (uncorrected) were determined on a Gallenkamp electric melting point apparatus. Elemental analyses were carried out in the microanalytical center of Cairo University. IR spectra were recorded (KBr pellets) on a Mattson 5000 FTIR spectrometer (not all frequencies are reported). ^1H NMR spectra were measured on a Brucker WP-300 (300 MHz) spectrometer using TMS as an internal standard. Mass spectra (EI, 70 eV) were recorded on a Finnigan MAT 212 instrument.

5-Methylsulfanyl-7-oxo-4,7-dihydrotetrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**3**). A mixture of **1** (5 mmol) and 5-aminotetrazole monohydrate (5 mmol) in absolute ethanol (30 ml) was boiled under reflux for 10 h, left to stand at room temperature overnight, poured into crushed ice, and neutralized with diluted hydrochloric acid. The solid product separated was filtered off, dried, and crystallized from ethanol to give yellow crystals of **3.** Yield 56%, mp 144-145°C. IR spectrum, ν, cm^{-1}: 3200 (NH), 2207 (CN), 1669 (CO). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 2.60 (3H, s, SCH_3); 7.25 (1H, s, NH). MS, *m/z* (I_{rel}, %): 208 [M^+] (70), 187 (5), 125 (8), 97 (15), 83 (23), 69 (40), 55 (100). Found, %: C 34.65; H 1.83; N 40.44. $C_6H_4N_6OS$ (M 208.20). Calculated, %: C 34.61; H 1.94; N 40.37.

2-Methylsulfanyl-4-oxo-1,4-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**4**). A mixture of **1** (2 mmol) and 2-aminobenzimidazole (2 mmol) in absolute ethanol (20 ml) was refluxed for 10 h. The white precipitate formed was filtered off and crystallized from EtOH–DMF, 2:1, to give compound **4.** Yield 89%, mp >300°C. IR spectrum, ν, cm^{-1}: 3293 (NH), 2209 (CN), 1659 (CO). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 (3H, s, SCH_3); 7.15-7.60 (4H, m, Ar–H); 8.40 (1H, s, NH). MS, *m/z* (I_{rel}, %): 256 [M^+] (100), 201 (12), 195 (14), 181 (24), 160 (30), 133 (10), 102 (8), 90 (22). Found, %: C 56.33; H 3.27; N 21.80. $C_{12}H_8N_4OS$ (M 256.28). Calculated, %: C 56.24; H 3.15; N 21.86.

2-Methylsulfanyl-4-oxo-4H-pyrimido[2,1-*b*]benzothiazole-3-carbonitrile (**5**). A mixture of **1** (2 mmol) and 2-aminobenzothiazole (2 mmol) in absolute ethanol (20 ml) was refluxed for 10 h. The yellow precipitate formed was filtered off and recrystallized from EtOH–acetone mixture, 1:1, to give colorless crystals of compound **5**. Yield 64%, mp 200-201°C. IR spectrum, ν, cm^{-1}: 2211 (CN), 1669 (CO). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.60 (3H, s, CH_3); 7.40-7.80 (4H, m, Ar–H). MS, *m/z* (I_{rel}, %): 273 [M^+] (100), 240 (30), 212 (25), 198 (65), 134 (25), 108 (16). Found, %: C 52.88; H 2.64; N 15.21. $C_{12}H_7N_3OS_2$ (M 273.33). Calculated, %: C 52.73; H 2.58; N 15.37.

Thiazolo[3,2-*a*]pyrimidines 6 and 7 (General procedure). A mixture of **1** or **2** (3 mmol), 2-aminothiazole (3 mmol), and a few drops of triethylamine in absolute ethanol (20 ml) were refluxed for 5 h, poured into crushed ice, and neutralized with diluted acetic acid. The solid product separated was filtered off, dried, and crystallized from ethanol to give compound **6** or **7** as buff crystals.

7-Methylsulfanyl-5-oxo-5H-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**6**). Yield 62%, mp 226-228°C. IR spectrum, ν, cm^{-1}: 2220 (CN), 1680 (CO). ^{1}H NMR (DMSO) spectrum, δ, ppm (*J*, Hz): 2.60 (3H, s, SCH_3); 7.60 (1H, d, *J* ~3, C-2); 8.10 (1H, d, *J* ~3, C-3). MS, *m/z* (I_{rel}, %): 223 [M^+] (100), 190 (25), 176 (28), 148 (43), 127 (23), 104 (15), 82 (19), 70 (26), 58 (80). Found, %: C 43.15; H 2.37; N 18.67. $C_8H_5N_3OS_2$ (M 223.27). Calculated, %: C 43.03; H 2.26; N 18.82.

5-Imino-7-methylsulfanyl-5H-thiazolo[3,2-*a*]pyrimidine-6-carbonitrile (**7**). Yield 68%, mp 190-191°C. IR spectrum, ν, cm^{-1}: 3318 (NH), 2206 (CN), 1640 (C=N). Found, %: C 43.34; H 2.87; N 25.17. $C_8H_6N_4S_2$ (M 222.29). Calculated, %: C 43.23; H 2.72; N 25.20.

2-Cyano-3-methylsulfanyl-3-(1H-tetrazol-5-ylamino)acrylamide (**8**). A mixture of **2** (5 mmol) and 5-aminotetrazole monohydrate (5 mmol) in absolute ethanol (30 ml) was refluxed for 6 h and poured into crushed ice. The solid product separated was filtered off and recrystallized from ethanol to give pale yellow crystals of **8**. Yield 80%, mp 135-136°C. IR spectrum, ν, cm^{-1}: 3369, 3418 (NH and NH_2), 2206 (CN), 1698 (CO). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.61 (3H, s, SCH_3); 6.34 (1H, s, NH); 7.54 (1H, s, NH); 7.67 (2H, s, NH_2). MS, *m/z* (100%): 225 [M^+] (5), 207 (5), 188 (20), 173 (68), 143 (22), 127 (37), 98 (75), 83 (60), 75 (32), 46 (100). Found, %: C 32.05; H 3.32; N 43.67. $C_6H_7N_7OS$ (M 225.23). Calculated, %: C 32.00; H 3.13; N 43.53.

7-Amino-5-methylsulfanyltetrazolo[1,5-*a*]pyrimidine-6-carbonitrile (**9**). A mixture of **2** (5 mmol) and 5-aminotetrazole monohydrate (5 mmol) was refluxed for 10 h in 30 ml absolute ethanol containing 1 ml of triethylamine. The yellow precipitate formed was filtered off and recrystallized from ethanol to give **9**. Yield: 62%, mp 212-213°C. IR spectrum, ν, cm^{-1}: 3402, 3200 (NH_2), 2203 (CN), 1638 (C=N). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.60 (3H, s, SCH_3), 6.51 (2H, br. s, NH_2). Found, %: C 34.91; H 2.52; N 47.35%. $C_8H_{10}N_6O_2S$ (M 207.22). Calculated, %: C 34.78; H 2.43; N 47.32.

3-(1H-Benzimidazol-2-ylamino)-2-cyano-3-methylsulfanylacrylamide (**10**). A mixture of **2** (2 mmol) and 2-aminobenzimidazole (2 mmol) in absolute ethanol (20 ml) was refluxed for 10 h and poured into crushed ice. The solid product separated was filtered off and recrystallized from ethanol to give compound **10** as yellow crystals. Yield 66%, mp 178-179°C. IR spectrum, ν, cm^{-1}: 3300, 3130 (NH, NH_2), 2204 (CN), 1701 (CO), 1639 (C=N). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.55 (3H, s, SCH_3); 6.40 (1H, s, NH); 7.05-7.60 (4H, m, Ar–H); 7.90 (2H, s, NH_2); 8.40 (1H, s, NH). Found, %: C 52.82; H 4.22; N 25.7. $C_{12}H_{11}N_5OS$ (M 273.31). Calculated, %: C 52.73; H 4.04; N 25.62.

4-Amino-2-methylsufanylpyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**11**). A mixture of **2** (2 mmol), 2-aminobenzimidazole (2 mmol) and about 0.5 ml triethylamine in absolute ethanol (20 ml) was refluxed for 10 h, poured into crushed ice, and neutralized with diluted acetic acid. The solid product separated was filtered off, dried, and recrystallized from EtOH–DMF, 1:1, to give yellowish brown crystals of compound **11**. Yield 72%, mp > 300°C. IR spectrum, ν, cm^{-1}: 3412, 3111 (NH_2), 2213 (CN), 1640 (C=N). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.60 (3H, s, SCH_3); 6.60 (1H, s, NH_2), 7.10-7.70 (4H, m, Ar–H). Found, %: C 56.40; H 3.45; N 27.34. $C_{12}H_9N_5S$ (M 255.30). Calculated, %: C 56.45; H 3.55; N 27.43.

4-Imino-2-methylsulfanyl-4H-pyrimido[2,1-*b*]benzothiazole-3-carbonitrile (**12**). Compound **12** was prepared similarly to pyrimido[1,2-*a*]benzimidazole derivative **11** using 2-aminobenzo- thiazole instead of 2-aminobenzimidazole. Yield 55%, mp >300°C. IR spectrum, ν, cm^{-1}: 3109, (NH), 2208 (CN). ^1H NMR (DMSO), δ, ppm: 2.60 (3H, s, SCH_3); 6.90-7.40 (4H, m, Ar–H); 9.60 (1H, s, NH). MS, *m/z* ($I_{rel.}$, %): 273 [M^+ + 1] (15), 273 (M^+ + 2, 27), 218 (17), 213 (15), 150 (100), 134 (23), 123 (18), 109 (22), 96 (32), 69 (29). Found, %: C 52.98; H 2.87; N 20.66. $C_{12}H_8N_4S_2$. (M 272.35). Calculated. C 52.92; H 2.96; N 20.57.

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