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Polarized Ketene Dithioacetals-Versatile Synthons for Different Heterocycles

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The reactivity of polarized ketene dithioacetals to develop a variety of heterocycles under different conditions was studied.

Keywords polarized ketene dithioacetals, thienothiophenes, bis-benzoxazolyl/benzothiazolyl/benzimidazolyl-pyrazolidine diones/isoxazolidinediones/pyrimidinetriones/thioxopyrimidinediones, cyclocondensation

Introduction

Heterocyclic chemistry has attracted a lot of interest during recent years as many useful drugs have emerged in this branch. Ketene dithioacetals are versatile synthons for the development of a wide variety of heterocyclic systems.[1-5] In fact, nitroketene *S*,*S*-acetals have been used as intermediates for the synthesis of pyrroles with diverse functionalities.[6,7] The highly regioselective cyclocondensation of α-oxoketene *N*,*S*-acetals with arylhydrazines produced substituted pyrazoles.[8-11] The cyclocondensation of α-oxo/α-nitro ketene *N*,*S*-acylacetals either with Vilsmier reagent[12] or in the presence of $POCl_3$ in acetonitrile led to substituted quinoxaline derivatives.[13] Ring closer reactions involving a nitrile group have also been studied. When dicyano dithiolate was treated with *p*-bromophenacyl bromide instead of an *S*,*S*′-bis(bromophenacyl) derivative an aminothiophene was formed.[14] Besides, ketene dithiolates generated *in situ* from active methylene compounds and carbon disulfide in the presence of base and α-haloesters cyclized to thienothiophene derivatives.[15] Recently, we have studied the reactivity of ketene *S*,*S*-acetals having gem diester and gem cyanoester functionalities towards the development of biologically potent heterocycles, pyrazoline, isoxazoline, pyrimidine and their derivatives.[16]

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1∶3, *V*/*V*). The microwave irradiation was carried out by using scientific microwave system CATA-2R operating at power levels from 140 W to 700 W. Built-in magnetic stirring (Teflon-coated stirring bar) was used in all operations. The temperature was measured throughout the reaction by flexible probe. The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6 on a Brucker-400 spectrometer (400 MHz). The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Brucker spectrometer operating at 100 MHz. All chemical shifts are reported in δ using TMS as an internal standard. The mass spectra were recorded on Jeol JMS-D 300 and Finnigan Mat 1210 B at 70 eV with an emission current of 100 μA. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The compounds 2-(chloromethyl)benzoxazole (**1**), 2-(chloromethyl)-benzothiazole (**2**) and 2-(chloromethyl)-1*H*-benzimidazole (**3**) were prepared by the literature procedure.[18-20]

Typical procedure for the preparation of diethyl 2-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)-malonate (4)/diethyl 2-(bis((benzo[*d*]thiazol-2'-yl)-methylthio)methylene)malonate (5)/diethyl 2-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)malonate (6)

To a solution of dried potassium carbonate (1.38 g, 0.01 mol) in DMF (2 mL), diethyl malonate (1.60 g, 0.01 mol) in DMF (1 mL) followed by carbon disulfide (1.14 g, 0.015 mol) were added dropwise under vigorous stirring. After 30 min, the reaction mixture was cooled to 0 ℃ and to this 2-(chloromethyl)benzoxazole (**1**)/2-(chloromethyl) benzothiazole (**2**)/2-(chloromethyl)-1*H*-benzimidazole (**3**) (0.02 mol) in DMF (5 mL) was added in 20—30 min. The reaction mixture was then stirred for 1 h at room temperature and poured

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into cold water. The precipitate was collected, dried and recrystallized from aqueous methanol.

Diethyl 2-(bis((benzo[*d*]oxazol-2'-yl)methylthio)-methylene)malonate (4) Yield 71%, m.p. 157—159 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.36 (t, J=7.06 Hz, 6H, CH_2CH_3), 4.22 (q, J=6.56 Hz, 4H, CH_2CH_3), 4.42 (s, 4H, CH_2), 7.17—7.48 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.5 (CH_2CH_3), 30.8 (CH_2-S), 61.3 (CH_2CH_3), 104.7 (=*C*-CO), 161.5 (C-2'), 165.3 (C=*C*S(S)), 174.8 (C=O), 117.1, 120.6, 122.2, 124.6, 138.7, 148.9 (aromatic carbons); IR (KBr) v: 1715 (CO), 1620 (C=C), 1610 (C=N) cm^{-1}; MS (70 eV) *m/z*: 498.31 ($M^{+\bullet}$). Anal. calcd for $C_{24}H_{22}N_2O_6S_2$: C 57.82, H 4.45, N 5.62; found C 57.65, H 4.61, N 5.49.

Diethyl 2-(bis((benzo[*d*]thiazol-2'-yl)methylthio)-methylene)malonate (5) Yield 76%, m.p. 165—167 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.31 (t, J=7.05 Hz, 6H, CH_2CH_3), 4.25 (q, J=7.05 Hz, 4H, CH_2CH_3), 4.45 (s, 4H, CH_2), 7.46—8.01 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 13.8 (CH_2CH_3), 31.2 (CH_2-S), 62.5 (CH_2CH_3), 102.8 (=*C*-CO), 169.5 (C-2'), 167.8 (C=*C*S(S)), 175.4 (C=O), 120.4, 121.8, 124.3, 126.1, 135.7, 149.8 (aromatic carbons); IR (KBr) v: 1728 (CO), 1630 (C=C), 1605 (C=N) cm^{-1}; MS (70 eV) *m/z*: 530.48 ($M^{+\bullet}$). Anal. calcd for $C_{24}H_{22}N_2O_4S_4$: C 54.32, H 4.18, N 5.28; found C 54.55, H 4.03, N 5.43.

Diethyl 2-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methyl-thio)methylene)malonate (6) Yield 78%, m.p. 174—176 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.28 (t, J= 6.92 Hz, 6H, CH_2CH_3), 4.21 (q, J = 6.92 Hz, 4H, CH_2CH_3), 4.38 (s, 4H, CH_2), 7.28—7.53 (m, 8H, Ar-H), 12.89 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.2 (CH_2CH_3), 30.1 (CH_2-S), 63.2 (CH_2CH_3), 103.1 (=*C*-CO), 151.3 (C-2'), 166.2 (C=*C*S(S)), 173.8 (C=O), 119.1, 121.4, 122.6, 127.9, 132.5, 138.8 (aromatic carbons); IR (KBr) v: 3323 (NH), 1720 (CO), 1625 (C=C), 1615 (C=N) cm^{-1}; MS (70 eV) *m/z*: 496.17 ($M^{+\bullet}$). Anal. calcd for $C_{24}H_{24}N_4O_4S_2$: C 58.05, H 4.87, N 11.28; found C 58.32, H 4.62, N 11.41.

Typical procedure for the preparation of 2,5-di-(benzo[*d*]oxazol-2'-yl)thieno[2,3-*b*]thiophene-3,4-(2*H*,5*H*)-dione (7)/2,5-di(benzo[*d*]thiazol-2'-yl)-thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (8)/2,5-di(1′*H*-benzo[*d*]imidazol-2'-yl)thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (9)

Method A To a solution of dried potassium carbonate (1.38 g, 0.01 mol) in DMF (2 mL), **4/5/6** (0.005 mol) was added and refluxed for 1 h and poured into cold water. The precipitate was collected, dried and recrystallized from 2-propanol.

Method B To a solution of dried potassium carbonate (4.14 g, 0.03 mol) in DMF (2 mL), diethyl malonate (1.60 g, 0.01 mol) in DMF (1 mL) followed by carbon disulfide (1.14 g, 0.015 mol) were added dropwise under vigorous stirring. After 30 min, the reaction mixture was cooled to 0 ℃ and to this 2-(chloromethyl)benzoxazole (**1**)/2-(chloromethyl)-benzothiazole (**2**)/2-(chloromethyl)-1*H*-benzimidazole (**3**) (0.02 mol) in DMF (5 mL) was added in 20—30 min. The reaction mixture was then refluxed for 2 h and poured into cold water. The precipitate was collected, dried and recrystallized from 2-propanol.

2,5-Di(benzo[*d*]oxazol-2'-yl)thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (7) Yield 76% (method A), 69% (method B), m.p. 188—190 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.59 (s, 2H, C^2-H & C^5-H), 7.20—7.35 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 60.1 (C-2 & C-5), 116.7 (=*C*-CO), 161.3 (C-2'), 172.7 (C=*C*S(S)), 182.1 (C=O), 117.1, 120.6, 122.2, 124.6, 138.5, 147.4 (aromatic carbons); IR (KBr) v: 1734 (CO), 1636 (C=C), 1615 (C=N) cm^{-1}; MS (70 eV) *m/z*: 406.16 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{10}N_2O_4S_2$: C 59.10, H 2.48, N 6.89; found C 59.31, H 2.54, N 6.93.

2,5-Di(benzo[*d*]thiazol-2'-yl)thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (8) Yield 78% (method A), 70% (method B), m.p. 207—209 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.61 (s, 2H, C^2-H & C^5-H), 7.48—8.11 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 60.7 (C-2 & C-5), 117.4 (=*C*-CO), 168.3 (C-2'), 172.1 (C=*C*S(S)), 182.9 (C=O), 120.6, 122.2, 124.6, 125.4, 135.5, 151.1 (aromatic carbons); IR (KBr) v: 1740 (CO), 1630 (C=C), 1610 (C=N) cm^{-1}; MS (70 eV) *m/z*: 438.21 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{10}N_2O_2S_4$: C 54.77, H 2.30, N 6.39; found C 54.52, H 2.41, N 6.54.

2,5-Di(1'*H*-benzo[*d*]imidazol-2'-yl)thieno[2,3-*b*]-thiophene-3,4(2*H*,5*H*)-dione (9) Yield 75% (method A), 68% (method B), m.p. 220—222 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.54 (s, 2H, C^2-H & C^5-H), 7.23—7.62 (m, 8H, Ar-H), 12.80 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 59.4 (C-2 & C-5), 117.0 (=*C*-CO), 152.0 (C-2'), 171.2 (C=*C*S(S)), 183.7 (C=O), 118.9, 122.2, 123.6, 123.9, 133.2, 142.1 (aromatic carbons); IR (KBr) v: 3335 (NH), 1731 (CO), 1638 (C=C), 1612 (C=N) cm^{-1}; MS (70 eV) *m/z*: 404.14 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{12}N_4O_2S_2$: C 59.39, H 2.99, N 13.85; found C 59.63, H 2.87, N 13.68.

Typical procedure for the preparation of 4-(bis-((benzo[*d*]oxazol-2'-yl)methylthio)methylene)pyrazo-lidine-3,5-dione (10)/4-(bis((benzo[*d*]thiazol-2'-yl)-methylthio)methylene)pyrazolidine-3,5-dione (11)/4-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methyl-ene)pyrazolidine-3,5-dione (12)

A solution of **4/5/6** (0.005 mol), hydrazine hydrate (0.0075 mol) and piperidine (3 mL) in ethanol (10 mL) was refluxed for 6—8 h. After completion of the reaction, it was cooled and poured into ice-cold water containing conc. HCl. The solid obtained was filtered on a Buchner funnel, dried and recrystallized from 2-propanol.

4-(Bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)-pyrazolidine-3,5-dione (10) Yield 75%, m.p. 180—182 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.43 (s, 4H, CH_2), 7.26—7.36 (m, 8H, Ar-H), 9.12 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 31.4 (CH_2-S), 102.5 (C-4), 162.3 (C-2'), 168.1 (C=*C*S(S)), 174.9 (C-3 & C-5), 117.1, 120.6, 122.2, 124.6, 139.4,

148.3 (aromatic carbons); IR (KBr) *v*: 3420 (NH), 1690 (CO), 1622 (C=C), 1613 (C=N) cm^{-1}; MS (70 eV) *m/z*: 438.25 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{14}N_4O_4S_2$: C 54.78, H 3.22, N 12.78; found C 54.96, H 3.10, N 12.92.

4-(Bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)pyrazolidine-3,5-dione (11) Yield 78%, m.p. 193—195 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.41 (s, 4H, CH_2), 7.32—7.79 (m, 8H, Ar-H), 9.10 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.7 (CH_2-S), 103.8 (C-4), 169.1 (C-2'), 167.2 (C=*C*S(S)), 173.6 (C-3 & C-5), 119.2, 122.7, 124.1, 126.2, 135.7, 151.4 (aromatic carbons); IR (KBr) *v*: 3431 (NH), 1687 (CO), 1618 (C=C), 1609 (C=N) cm^{-1}; MS (70 eV) *m/z*: 470.38 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{14}N_4O_2S_4$: C 51.04, H 3.00, N 11.91; found C 51.29, H 3.13, N 11.79.

4-(Bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)pyrazolidine-3,5-dione (12) Yield 80%, m.p. 202—204 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.37 (s, 4H, CH_2), 7.54—7.97 (m, 8H, Ar-H), 9.14 (br s, 2H, CO-NH), 12.86 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 31.6 (CH_2-S), 103.2 (C-4), 151.7 (C-2'), 168.7 (C=*C*S(S)), 174.4 (C-3 & C-5), 120.5, 122.2, 125.7, 127.1, 131.5, 137.9 (aromatic carbons); IR (KBr) *v*: 3392 (NH), 1675 (CO), 1620 (C=C), 1613 (C=N) cm^{-1}; MS (70 eV) *m/z*: 436.16 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{16}N_6O_2S_2$: C 55.03, H 3.69, N 19.25; found C 55.31, H 3.78, N 19.37.

Typical procedure for the preparation of 4-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (13)/4-(bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (14)/4-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (15)

A mixture of **4/5/6** (0.005 mol), hydroxylamine hydrochloride (0.42 g, 0.006 mol), piperidine (5 mL) in ethanol (10 mL) was refluxed for 5—7 h. It was cooled and poured into ice-cold water containing conc. HCl. The solid separated was collected on a Buchner funnel, dried and recrystallized from 2-propanol.

4-(Bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)-isoxazolidine-3,5-dione (13) Yield 75%, m.p. 175—177 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.39 (s, 4H, CH_2), 7.14—7.70 (m, 8H, Ar-H), 10.14 (br s, 1H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.8 (CH_2-S), 101.6 (C-4), 161.8 (C-2'), 167.5 (C=*C*S(S)), 172.5 (C-3), 178.3 (C-5), 122.2, 125.7, 127.1, 128.2, 141.0, 149.9 (aromatic carbons); IR (KBr) *v*: 3420 (NH), 1729 (*CO*-O), 1685 (*CO*-NH), 1622 (C=C), 1614 (C=N) cm^{-1}; MS (70 eV) *m/z*: 439.13 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{13}N_3O_5S_2$: C 54.66, H 2.98, N 9.56; found C 54.89, H 2.86, N 9.73.

4-(Bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)-isoxazolidine-3,5-dione (14) Yield 70%, m.p. 187—189 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.37 (s, 4H, CH_2), 7.27—7.89 (m, 8H, Ar-H), 10.15 (br s, 1H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.5 (CH_2-S), 103.7 (C-4), 166.4 (C=*C*S(S)), 168.9 (C-2'), 173.7 (C-3), 179.4 (C-5), 121.3, 123.9, 124.6, 126.5, 136.2, 150.1 (aromatic carbons); IR (KBr) *v*: 3431 (NH), 1732 (*CO*-O), 1687 (*CO*-NH), 1618 (C=C), 1609 (C=N) cm^{-1}; MS (70 eV) *m/z*: 471.6 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{13}N_3O_3S_4$: C 50.94, H 2.78, N 8.91; found C 50.73, H 2.89, N 8.79.

4-(Bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)-methylene)isoxazolidine-3,5-dione (15) Yield 78%, m.p. 196—198 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.40 (s, 4H, CH_2), 7.36—7.78 (m, 8H, Ar-H), 10.08 (br s, 1H, CO-NH), 12.88 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.0 (CH_2-S), 102.8 (C-4), 151.7 (C-2'), 167.9 (C=*C*S(S)), 172.8 (C-3), 178.6 (C-5), 124.2, 125.1, 126.2, 128.2, 132.4, 139.7 (aromatic carbons); IR (KBr) *v*: 3416 (NH), 1725 (*CO*-O), 1672 (*CO*-NH), 1628 (C=C), 1605 (C=N) cm^{-1}; MS (70 eV) *m/z*: 437.07 ($M^{+\bullet}$). Anal. calcd for $C_{20}H_{15}N_5O_3S_2$: C 54.91, H 3.46, N 16.01; found C 54.65, H 3.58, N 16.17.

Typical procedure for the preparation of 5-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (16)/5-(bis((benzo[*d*]-thiazol-2'-yl)methylthio)methylene)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (17)/5-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione (18)

Method A The compound **4/5/6** (0.005 mol), urea (0.60 g, 0.01 mol), piperidine (4 mL) and ethanol (10 mL) were refluxed for 8—10 h. The contents of the flask were cooled and poured into ice-cold water containing conc. HCl. The solid separated was filtered, dried and purified by recrystallization from 2-propanol.

Method B To a well stirred solution of barbituric acid (0.64 g, 0.005 mol) in dimethyl sulfoxide (5 mL), triethylamine (1.01 g, 0.01 mol) and carbon disulfide (0.38 g, 0.005 mol) were added in succession. The mixture was stirred for 1 h at room temperature and then **1/2/3** (0.01 mol) in dimethyl sulfoxide (5 mL) was added. The stirring was continued for another 4—5 h at room temperature and poured into ice water. The solid separated was filtered, dried and recrystallized from 2-propanol.

5-(Bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (16) Yield 72% (method A), 76% (method B), m.p. 222—224 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.42 (s, 4H, CH_2), 7.12—7.64 (m, 8H, Ar-H), 10.06 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.7 (CH_2-S), 103.1 (C-5), 152.5 (C-2), 161.5 (C-2'), 166.6 (C=*C*S(S)), 168.6 (C-4 & C-6), 120.9, 122.7, 124.1, 126.2, 139.2, 151.1 (aromatic carbons); IR (KBr) *v*: 3281 (NH), 1675 (CO), 1620 (C=C), 1605 (C=N) cm^{-1}; MS (70 eV) *m/z*: 466.22 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{14}N_4O_5S_2$: C 54.07, H 3.02, N 12.01; found C 54.35, H 3.14, N 11.86.

5-(Bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (17) Yield 70% (method A), 77% (method B), m.p. 236—238 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.47 (s, 4H, CH_2), 7.34—7.84 (m, 8H, Ar-H), 9.98 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.8 (CH_2-S), 102.7

(C-5), 152.2 (C-2), 167.2 (C=*C*S(S)), 169.1 (C-2'), 169.4 (C-4 & C-6), 122.7, 124.1, 125.2, 127.0, 136.3, 150.4 (aromatic carbons); IR (KBr) *v*: 3290 (NH), 1684 (CO), 1622 (C=C), 1612 (C=N) cm^{-1}; MS (70 eV) *m/z*: 498.16 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{14}N_4O_3S_4$: C 50.58, H 2.83, N 11.24; found C 50.79, H 2.94, N 11.13.

5-(Bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)-methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (18) Yield 69% (method A), 74% (method B), m.p. 240—242 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.39 (s, 4H, CH_2), 7.45—8.21 (m, 8H, Ar-H), 9.91 (br s, 2H, CO-NH), 12.82 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.2 (CH_2-S), 103.5 (C-5), 151.1 (C-2'), 153.7 (C-2), 165.9 (C=*C*S(S)), 169.6 (C-4 & C-6), 121.4, 123.5, 126.8, 127.4, 131.1, 137.9 (aromatic carbons) cm^{-1}; IR (KBr) *v*: 3310 (NH), 1692 (CO), 1618 (C=C), 1615 (C=N); MS (70 eV) *m/z*: 464.24 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{16}N_6O_3S_2$: C 54.30, H 3.47, N 18.09; found C 54.13, H 3.58, N 18.23.

Typical procedure for the preparation of 5-(bis-((benzo[*d*]oxazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (19)/5-(bis-((benzo[*d*]thiazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (20)/5-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (21)

Method A A mixture of **4/5/6** (0.005 mol), thiourea (0.57 g, 0.0075 mol), piperidine (4 mL) and ethanol (10 mL) was refluxed for 9—11 h. The reaction mixture was cooled and poured into ice-cold water containing conc. HCl. The solid separated was filtered on a Buchner funnel, dried and recrystallized from 2-propanol.

Method B To a well stirred solution of thiobarbituric acid (0.72 g, 0.005 mol) in dimethyl sulfoxide (5 mL), triethylamine (1.01 g, 0.01 mol) and carbon disulfide (0.38 g, 0.005 mol) were added in succession. The mixture was stirred for 1 h at room temperature and then **1/2/3** (0.01 mol) in dimethyl sulfoxide (5 mL) was added. The stirring was continued for another 5—6 h at room temperature and poured into ice water. The solid separated was filtered, dried and recrystallized from 2-propanol.

5-(Bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (19) Yield 72% (method A), 78% (method B), m.p. 206—208 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.45 (s, 4H, CH_2), 7.10—7.77 (m, 8H, Ar-H), 9.96 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.4 (CH_2-S), 102.7 (C-5), 162.1 (C-2'), 166.8 (C=*C*S(S)), 168.9 (C-4 & C-6), 172.2 (C-2), 120.2, 122.4, 125.3, 126.8, 138.7, 150.3 (aromatic carbons); IR (KBr) *v*: 3350 (NH), 1689 (CO), 1621 (C=C), 1605 (C=N), 1492 (C=S) cm^{-1}; MS (70 eV) *m/z*: 482.37 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{14}N_4O_4S_3$: C 52.27, H 2.92, N 11.61; found C 52.43, H 2.83, N 11.73.

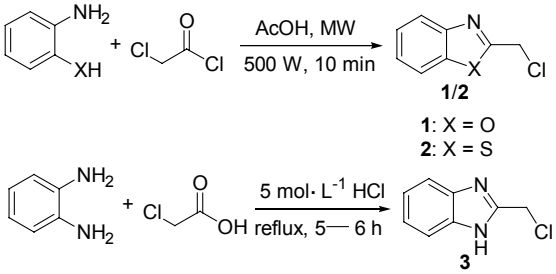
5-(Bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (20) Yield 68% (method A), 75% (method B), m.p. 220—222 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.40 (s, 4H, CH_2), 7.37—7.88 (m, 8H, Ar-H), 10.12 (br s, 2H, CO-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 32.6 (CH_2-S), 101.5 (C-5), 165.5 (C=*C*S(S)), 168.3 (C-2'), 167.6 (C-4 & C-6), 175.4 (C-2), 122.5, 124.7, 126.4, 127.0, 135.1, 151.3 (aromatic carbons); IR (KBr) *v*: 3339 (NH), 1694 (CO), 1618 (C=C), 1612 (C=N), 1495 (C=S) cm^{-1}; MS (70 eV) *m/z*: 514.46 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{14}N_4O_2S_5$: C 49.01, H 2.74, N 10.89; found C 49.23, H 2.63, N 10.97.

5-(Bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)-methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (21) Yield 74% (method A), 79% (method B), m.p. 228—230 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 4.42 (s, 4H, CH_2), 7.29—7.84 (m, 8H, Ar-H), 9.95 (br s, 2H, CO-NH), 12.80 (br s, 2H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 33.2 (CH_2-S), 103.4 (C-5), 152.5 (C-2'), 167.3 (C=*C*S(S)), 169.4 (C-4 & C-6), 174.7 (C-2), 119.4, 122.2, 125.6, 127.7, 132.5, 139.3 (aromatic carbons); IR (KBr) *v*: 3369 (NH), 1676 (CO), 1620 (C=C), 1608 (C=N), 1490 (C=S) cm^{-1}; MS (70 eV) *m/z*: 480.08 ($M^{+\bullet}$). Anal. calcd for $C_{21}H_{16}N_6O_2S_3$: C 52.48, H 3.36, N 17.49; found C 52.75, H 3.22, N 17.61.

Results and Discussion

In continuation of our interest to study the reactivity of ketene dithiolates towards the development of a new class of heterocycles,[17] the following work has been taken up. The reactive intermediates, 2-(chloromethyl)-benzoxazole (**1**) and 2-(chloromethyl)benzothiazole (**2**) were prepared by the irradiation of 2-aminophenol/2-aminothiophenol and chloroacetyl chloride for 10 min at a power of 500 W.[18] However, 2-(chloromethyl)-1*H*-benzimidazole (**3**) was obtained by treating *o*-phenylenediamine with chloroacetic acid in the presence of 5 mol•L^{-1} HCl[20] (Scheme 1).

Scheme 1

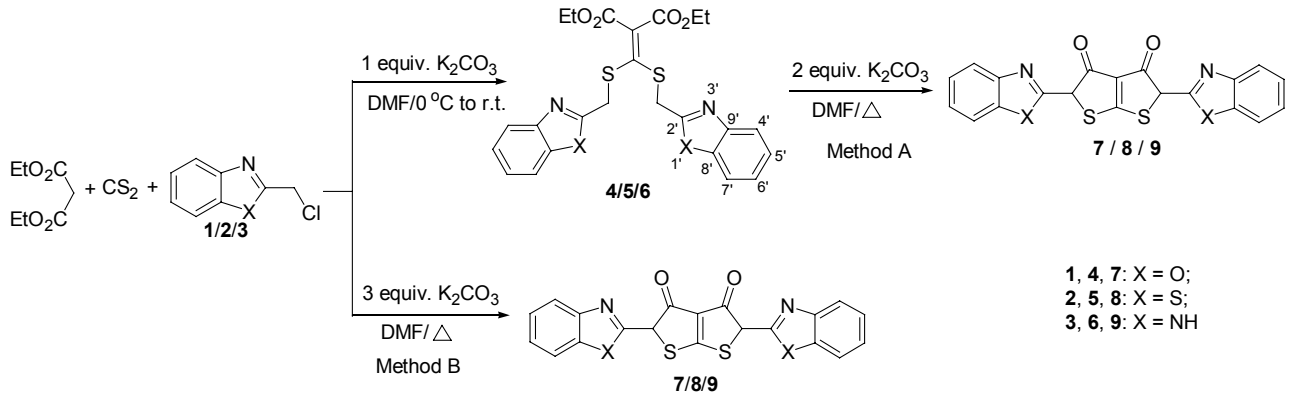


A one-pot reaction of diethyl malonate, carbon disulfide and **1/2/3** in the presence of K_2CO_3 in DMF led to *gem* difunctionalized synthetic intermediates, diethyl 2-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)-malonate (**4**), diethyl 2-(bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)malonate (**5**) and diethyl 2-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)-malonate (**6**) (Scheme 2). The ^{1}H NMR spectra of **4**, **5** and **6** displayed a singlet at δ 4.42, 4.45, 4.38 for me-

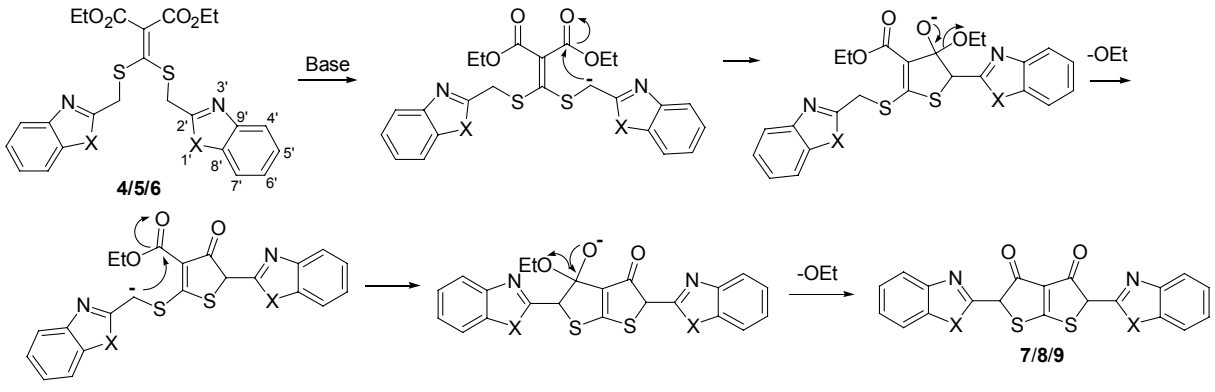
thylene protons, a triplet and a quartet at δ 1.36, 1.31, 1.28 and 4.22, 4.25, 4.21 for carboethoxy protons, respectively. In addition to these, compound **6** displayed a broad singlet at δ 12.89 due to NH which disappeared on deuteration. In our endeavor to exploit the *gem* diester functionality to develop different heterocycles, the compound **4** was treated with hydrazine hydrate in the presence of K_2CO_3 in DMF. Instead of the expected tris heterocyclic compound, intramolecular cyclization of **4** took place resulting in the formation of 2,5-di(benzo[*d*]oxazol-2'-yl)thieno[2,3-*b*]thiophene-3,4-(2*H*,5*H*)-dione (**7**) in low yield [28%] (Scheme 2). Later the reaction was repeated in the absence of hydrazine hydrate where the product was obtained in 78% yield. In the presence of polar aprotic solvent, the methylene group in compound **4** is readily deprotonated by K_2CO_3. It is followed by the intramolecular attack on carbonyl carbon of ester which is then transformed into **7** by the elimination of alcohol (Scheme 3). Similar cyclization took place when **5** and **6** were treated with K_2CO_3 resulting in the formation of 2,5-di(benzo[*d*]thiazol-2'-yl)thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (**8**) and 2,5-di(1'*H*-benzo-[*d*]imidazol-2'-yl)thieno[2,3-*b*]thiophene-3,4(2*H*,5*H*)-dione (**9**). On the other hand, the compounds **7**, **8** and **9** were obtained directly by the reaction of **1**, **2** and **3** with diethyl malonate and carbon disulfide in the presence of three-fold excess K_2CO_3. Though the aromaticity of **7**—**9** was possible by intramolecular H-bonding, the compounds existed as diketo tautomers which were confirmed by ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectra of **7**, **8** and **9** displayed a singlet at δ 4.59, 4.61, 4.54 for methine protons whereas in ^{13}C NMR spectra a singlet was observed at 60.1, 60.7, 59.4 for methine carbon, respectively. The 70 eV mass spectra of **7**, **8** and **9** displayed $M^{+\bullet}$ peak at *m*/*z* 406.1, 437.9 and 404.1, respectively.

However when the reaction was repeated by adding **4**/**5**/**6** in ethanol dropwise into a solution of hydrazine hydrate in piperidine and ethanol, 4-(bis((benzo[*d*]-oxazol-2'-yl)methylthio)methylene)pyrazolidine-3,5-dione (**10**), 4-(bis((benzo[*d*]thiazol-2'-yl)methylthio)-methylene)pyrazolidine-3,5-dione (**11**) and 4-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)pyrazolidine-3,5-dione (**12**) were obtained (Scheme 4). Similarly, 4-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (**13**), 4-(bis((benzo[*d*]-thiazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (**14**) and 4-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)isoxazolidine-3,5-dione (**15**) were prepared by the reaction of **4**/**5**/**6** with hydroxylamine hydrochloride. Likewise, the reaction of **4**/**5**/**6** with urea produced 5-(bis((benzo[*d*]oxazol-2'-yl)methylthio)methyene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**16**), 5-(bis((benzo[*d*]thiazol-2'-yl)methylthio)-methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**17**) and 5-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)methylthio)methylene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**18**). Adopting similar methodology, 5-(bis((benzo[*d*]oxazol-2'-yl)-

Scheme 2



Scheme 3



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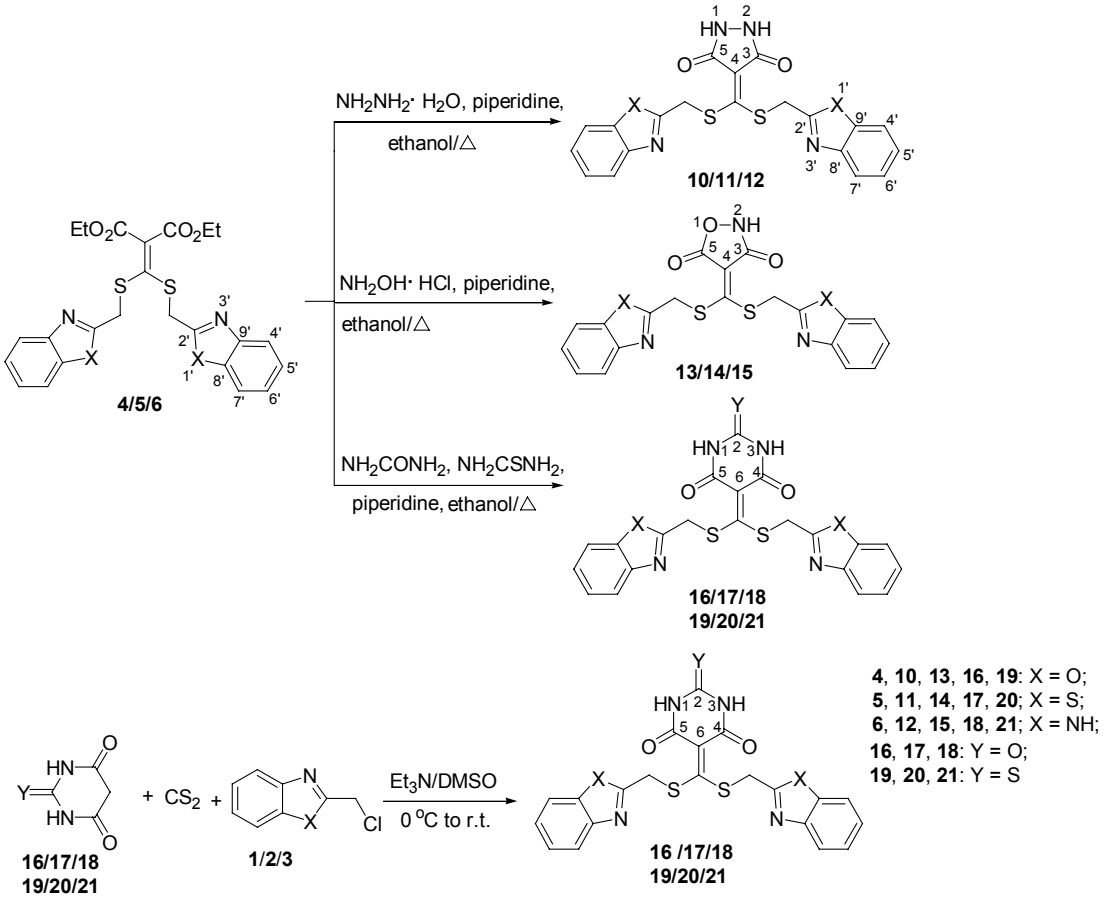
Scheme 4



methylthio)methylene)dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione (**19**), 5-(bis((benzo[*d*]thiazol-2'-yl)methylthio)methylene)dihydro-2-thioxopyrimidine-4,6(1*H*,5*H*)-dione (**20**) and 5-(bis((1'*H*-benzo[*d*]imidazol-2'-yl)-methylthio)methylene)dihydro-2-thioxopyrimidine-4,6-(1*H*,5*H*)-dione (**21**) were prepared by treating **4**/**5**/**6** with thiourea (Scheme 4). The compounds **16**, **17** and **18** were also prepared in a one pot reaction of barbituric acid with carbon disulfide and **1**/**2**/**3** in the presence of triethylamine in DMSO. Similarly, **19**, **20** and **21** were obtained by the reaction of thiobarbituric acid with carbon disulfide and **1**/**2**/**3** (Scheme 4). The absence of signals corresponding to carboethoxy protons in the ^{1}H NMR spectra of **10**—**21** indicated their formation. The structures of these compounds were further established by IR, ^{13}C NMR and mass spectra.

Conclusions

The reactivity of polarized ketene dithioacetals was exploited to develop a new class of heterocycles. In the presence of K_2CO_3, self condensation of ketene dithiolates took place with the formation of substituted thienothiophene derivatives. However in the presence of piperidine and appropriate nucleophiles, tris-heterocyclic compounds, bis-benzoxazolyl/benzothiazolyl/benzimidazolylmethylthiomethylenepyrazolidinediones/isoxazolidinediones/pyrimidinetriones/thioxopyrimidinediones were obtained. The structures of the compounds were established by spectral parameters.

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