1,3-Dipolar cycloaddition reactions in heterocyclic synthesis. Synthesis of [1-[4-(thiazolyl/imidazothiazolyl/triazolyl)phenyl]-1*H*-pyrazole-3,4-dicarboxylate esters from 3-(4-acetylphenyl)sydnone

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Cycloaddition of 3-(4-acetylphenyl)sydnone (**1**) with DMAD gave dimethyl 1-(4-acetylphenyl)-1*H*-pyrazole-3,4-dicarboxylate (**2**), which on bromination yielded the corresponding monobromoacetyl (**3**) and dibromoacetyl (**4**) derivatives. Both compounds **3** and **4** on reaction with thiourea and thioacetamide afforded the 2-amino- (**5**) and the 2-methyl- (**6**) thiazole derivatives respectively, while compound **3** on reaction with 2-aminothiazole gave the imidazothiazole **7**. Compound **3** was converted into its azide (**8**), which on 1,3-dipolar cycloaddition with DMAD afforded the 1,2,3-triazole-4,5-dicarboxylate (**9**).

Keywords: sydnones, 1,2,3-triazoles, pyrazoles, fused imidazoles, fused thiazoles, 1,3-dipolar cycloaddition, DMAD

The ability of sydnones to undergo 1,3-dipolar cycloaddition reactions has been extensively used in heterocyclic ring construction.[1] It provides a facile and convenient means of synthesising a variety of five-membered ring nitrogen heterocycles. A number of examples of the reaction of DMAD with some 3-arylsydnones, leading to the formation of pyrazole-3,4-dicarboxylates, has been reported from our laboratory.[2a,b] Such pyrazoledicarboxylates have been obtained by a cumbersome method from the reaction of α-halogenated phenylhydrazines with β-ketoesters and β–diketones,[3] but are obtained in a single step from sydnones in excellent yield (~90–98 %) and purity. Hence, this route provides a convenient and simple method using easily accessible and inexpensive chemicals. In view of this, we thought of extending this reaction to a functionalised sydnone – 3-(4-acetylphenyl)sydnone[4] (**1**) – wherein the acetyl group could be utilised for the construction of heterocycles, while the sydnone ring would be used as a synthon to obtain pyrazole-3,4-dicarboxylates.

The ring conversion of 3-(4-acetylphenyl)sydnone (**1**) into dimethyl 1-(4-acetylphenyl)-1*H*-pyrazole-3,4-dicarboxylate (**2**) by reaction with DMAD was reported earlier from our laboratory.[4] The present work involves the acetyl group of this compound, which was converted into its bromoacetyl derivative (**3**) by reaction with one molar ratio of bromine. With two molar equivalents of bromine the dibromoacetyl (**4**) was the major product. The formation of the dibromo compound was evidenced by the deshielded signal at δ 6.66 which integrated for a single proton ($COCHBr_2$). Both the brominated acetyl compounds on reaction with thiourea and thioacetamide yielded the 2-amino- (**5**) and 2-methyl-thiazoles (**6**) respectively. The formation of these compounds from the dibromoacetyl compound (**4**) shows that reductive debromination occurs in the reaction.[5] The imidazothiazole derivative **7** was obtained only from the monobromoacetyl compound **3** by reaction with 2-aminothiazole.

In an extension of this work, the monobromoacetyl compound (**3**) was converted into its azidoacetyl derivative (**8**) by reaction with NaN_3. This compound showed a typical sharp band of the N_3 stretching frequency at 2109 cm^{-1}. The ^{13}C NMR chemical shifts of this compound are shown in Fig. 1.

Next, the azide group of compound (**8**) with DMAD underwent 1,3-dipolar cycloaddition to afford the 1,2,3-triazole-4,5-dimethyldicarboxylate (**9**) (Scheme 1). The IR spectrum of this compound showed the absence of the azide band. The ^{13}C NMR (Fig. 2) and the analytical data were consistent with the assigned structure.

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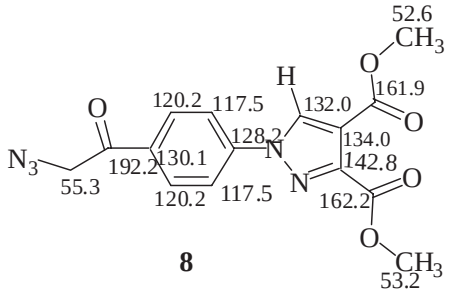

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Fig. 1

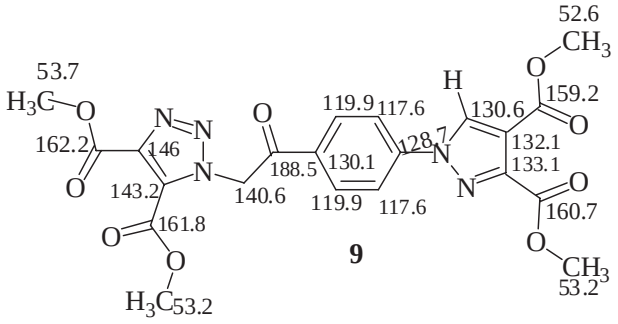

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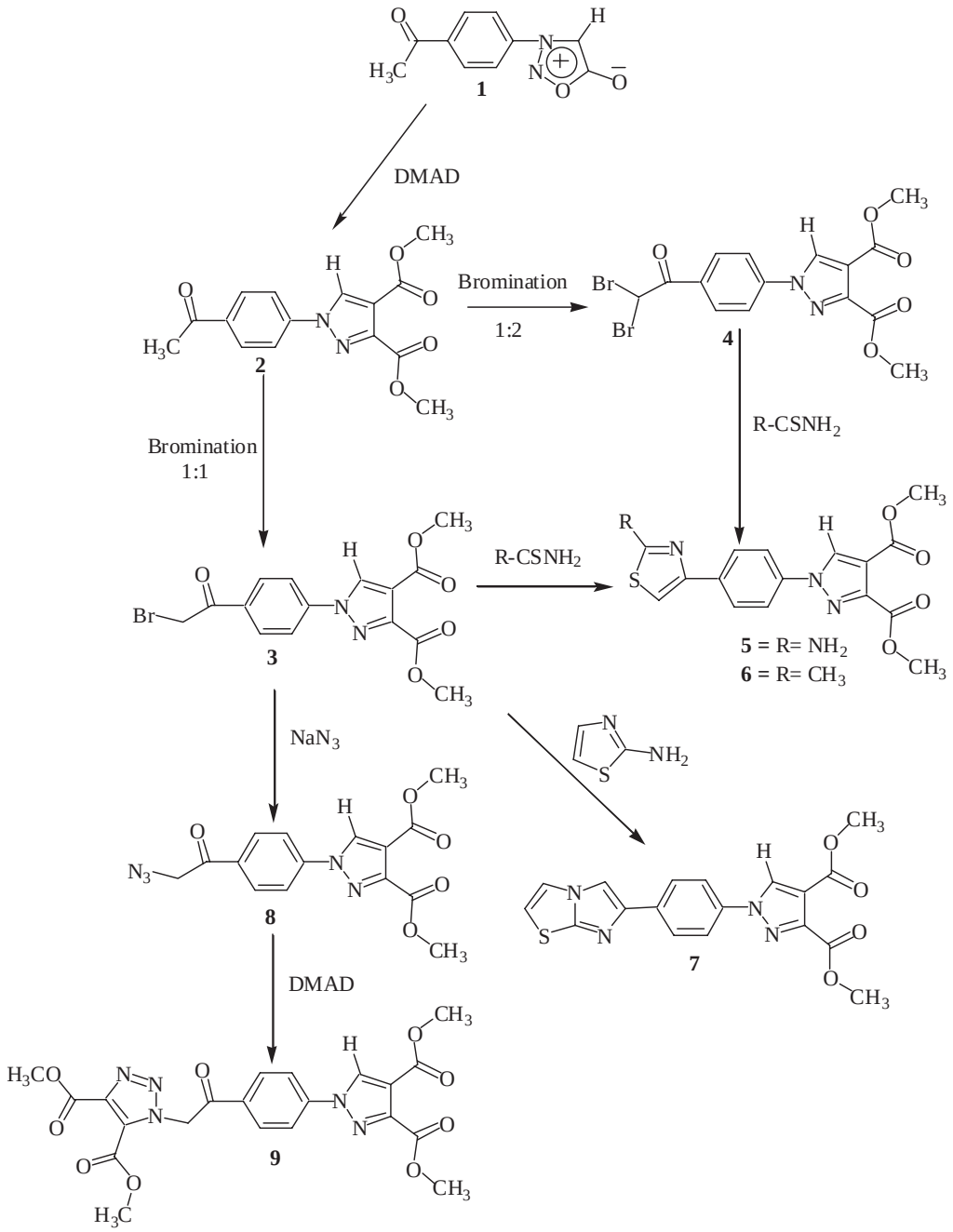
Fig. 2

Experimental

The IR spectra were recorded on Nicolet Impact 410 FT IR spectrophotometer using KBr pellets. ^1H and ^{13}C NMR were recorded on a Bruker-300MHz FT NMR spectrometer in $CDCl_3$ with TMS as an internal standard. The mass spectrum was measured using a M.I. ver. 14 on UIC 002002. Elemental analysis was carried out using a Heraus CHN rapid analyzer.

Dimethyl 1-[4-(2-bromoacetyl)phenyl]-1H-pyrazole-3,4-dicarboxylate (**3**): Compound (**2**)[4] (1 mmol) was suspended in 30 ml of chloroform and bromine (1 mmol) in chloroform (10 ml) was added under irradiation of visible light (40 W bulb) with constant stirring. After 15 min the colour of the bromine had faded. The solvent was removed and the residue was recrystallised from ethanol, forming yellow crystals (yield 72%), m.p.170–172 °C. IR (KBr): ν/cm^{-1} 3136, 1725, 1705 and 1694. ^1H NMR ($CDCl_3$): δ 3.92 (s, 3H, C-4 ester CH_3), 4.03 (s, 3H, C-3 ester CH_3), 4.47 (s, 2H, $COCH_2$), 7.92 (d, 2H, *J* = 9 Hz, ArH), 8.16 (d, 2H, *J* = 9 Hz, ArH) and 8.51 (s, 1H, pyrazole). Anal: Calcd. for $C_{15}H_{13}BrN_2O_5$: C, 47.26; H, 3.44; N, 7.32. Found: C, 47.23; H, 3.40; N, 7.32 %.

Dimethyl 1-[4-(2,2-dibromoacetyl)phenyl]-1H-pyrazole-3,4-dicarboxylate (**4**): Compound (**2**) (1 mmol) was suspended in 30 ml of chloroform and bromine (2 mmol) in chloroform (10 ml) was added under irradiation of visible light (40 W bulb) with constant stirring. After 15 min the colour of the bromine was lost. The solvent was removed to dryness and the residue was recrystallised from benzene/



Scheme 1

pet. ether, forming brown crystals (yield 65%), m.p. 167–169 °C. IR (KBr): ν/cm^{-1} 3123, 1744, 1722. ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H, C-4 ester CH_3), 4.02 (s, 3H, C-3 ester CH_3), 6.66 (s, 1H, $CHBr_2$), 7.91 (d, 2H, *J* = 9 Hz, Ar–H), 8.28 (d, 2H, *J* = 9 Hz, Ar–H), 8.52 (s, 1H, pyrazole). Anal: calcd. for $C_{15}H_{12}Br_2N_2O_5$: C, 39.16; H, 2.63; N, 6.09. Found: C, 39.12; H, 2.60; N, 6.00 %.

Dimethyl1-[4-(2-amino-/2-methyl-thiazol-4-yl)-phenyl]-1H-pyrazole -3,4-dicarboxylates (**5**, **6**): To a solution of compound (**3**) (1 mmol) in (20ml) of ethanol was added thiourea or thioacetamide (1 mmol) and the reaction mixture was stirred for 3 h. The precipitate was collected by filtration and dissolved in aqueous ethanol (1:1) and the solution was neutralised with sodium hydrogen carbonate.

Amino compound **5**: Yellow crystals from ethanol (yield 69 %), m.p. 155–157 °C. IR (KBr): ν/cm^{-1} 3448, 1727,1698. ^{1}H NMR ($CDCl_3$): δ 3.91 (s, 3H, C-4 ester CH_3), 4.02 (s, 3H, C-3 ester CH_3), 5.06 (s, 2H, NH_2), 6.82 (s, 1H, thiazole), 7.76 (d, 2H, *J* = 8.8 Hz, ArH), 7.93 (d, 2H, *J* = 8.8 Hz, ArH), 8.49 (s, 1H, pyrazole). Anal: calcd. for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.94; N, 15.63. Found: C, 53.60; H, 3.90; N, 15.60 %.

Methyl compound **6**: Pale yellow crystals (yield 70%) from methanol, m.p. 160–162 °C. IR (KBr): ν/cm^{-1} 344, 1720, 1678; ^{1}H NMR ($CDCl_3$): δ 2.82 (s, 3H, thiazole CH_3), 3.94 (s, 3H, C-4 ester CH_3), 4.05 (s, 3H, C-3 ester CH_3), 6.78 (s, 1H, thiazole), 7.56 (d, 2H, *J* = 8.8 Hz, ArH), 7.73 (d, 2H, *J* = 8.8 Hz, ArH), 8.89 (s, 1H, pyrazole). Anal: calcd. for $C_{17}H_{15}N_3O_4S$: C,57.13; H, 4.20; N, 11.73. Found: C, 57.10; H, 4.23; N, 11.76 %.

Dimethyl 1-[4-(imidazo[2,1-b]thiazol-6-yl)phenyl]-1H-pyrazole-3,4-dicarboxylate (**7**): To compound 3 (1 mmol) in ethanol (20 ml) was added 2-aminothiazole (1 mmol) and the reaction mixture was stirred for 3 h. The precipitate was collected by filtration and dissolved in aqueous ethanol (1:1) and the solution was neutralised with sodium hydrogen carbonate, forming compound **6** as white crystals (yield 68%) from ethanol, m.p. 166–168 °C. IR (KBr): ν/cm^{-1} 1756,1712; ^{1}H NMR ($CDCl_3$): δ 3.93 (s, 3H, C-4 ester CH_3), 4.05 (s, 3H, C-3 ester CH_3), 6.87–7.72 (m, 7H, phenyl, imidazothiazole), 8.48 (s, 1H, pyrazole). Anal: calcd. for $C_{18}H_{14}N_4O_4S$: C, 56.54; H, 3.69; N, 14.65. Found: C, 56.52; H, 3.65; N, 14.63 %.

Dimethyl 1-[4-(2-azidoacetyl)phenyl]-1H-pyrazole-3,4-dicarboxylate (**8**): Compound **3** (1 mmol) was dissolved in acetone (20 ml) and to this sodium azide (12 mmol) in water (3 ml) was added dropwise with stirring. Stirring was continued for 5 h. The separated solid was filtered and washed with water. White crystals (yield 72%)

from benzene, m.p. 170–172 °C. IR (KBr): ν/cm^{-1} 2109, 1739, 1713, 1677. ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H, C-4 ester CH_3), 4.03 (s, 3H, C-3 ester CH_3), 4.60 (s, 2H, $COCH_2$), 7.90 (d, 2H, *J* = 9.1 Hz, ArH), 8.09 (d, 4H, *J* = 9.1 Hz, ArH), 8.51 (s, 1H, pyrazole). ^{13}C NMR: 52.6, 53.2, 55.3, 128.2, 130.4, 132.0, 134.1, 142.8, 162.2, 192.0. Anal: calcd. for $C_{15}H_{13}N_5O_5$: C, 52.48; H, 3.82; N, 7.32. Found: C, 52.45; H, 3.80; N, 7.32 %.

Dimethyl 1-[2-[4-(3,4-bismethoxycarbonylpyrazol-1-yl)phenyl]-2-oxoethyl]-1H-1,2,3-triazole-4,5-dicarboxylate (**9**): To a solution of **8** (1 mmol) in dry xylene (4 ml) dimethyl acetylenedicarboxylate (1 mmol) was added and the reaction mixture heated at 120 ºC under reflux for *ca.* 1 h. The solvent was removed under reduced pressure and the residue was triturated with petroleum ether (60–80 °C). The solid obtained was recrystallised from ethanol as white crystals (yield 67%), m.p. 145–147 °C. IR (KBr): ν/cm^{-1} 1747, 1694; ^{1}H NMR ($CDCl_3$): δ 3.92 (s, 3H, pyrazole C-4 ester CH_3), 4.02 (s, 3H, pyrazole C-3 ester CH_3), 3.94 (s, 3H, triazole C-4 ester CH_3), 4.03 (s, 3H, triazole C-3 ester CH_3), 6.22 (s, 2H, CH_2CO), 7.96 (d, 2H, *J* = 8.7 Hz, ArH), 8.16 (d, 2H, *J* = 8.7 Hz, ArH), 8.54 (s, 1H, pyrazole). ^{13}C NMR ($CDCl_3$): 52.6, 53.2, 53.7, 117.6, 119.9, 130.6, 132.1, 133.1, 140.3, 143.2, 146.5, 159.2, 160.7, 161.8, 162.1, 188.0. EI-MS: *m/z* 485 (M^+, 10), 454 (48), 426 (15), 287 (100). Anal: calcd. for $C_{21}H_{19}N_5O_9$: C, 51.96; H, 3.95; N, 14.43. Found: C, 51.85; H, 4.00; N, 14.38 %.

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