Synthesis of imidazo- and pyrazolothiadiazoles from dithiobiureas and dimethyl ethynedicarboxylate

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Microwave irradiation of 1-substituted-2, 5-dithiobiureas and 1, 6-disubstituted-2, 5-dithiobiureas with dimethyl ethynedicarboxylate gave methyl 2-{6-oxo-2-(substituted amino)imidazo-[2, 1-*b*][1, 3, 5]thiadiazol-5(6*H*)-ylidene} acetate and methyl 7-oxo-1, 3-bis(substituted imino)-3, 7-dihydro-1*H*-pyrazolo[1, 2-*c*][1, 3, 4]thiadiazole-5-carboxylate. Rationales for these transformations are presented.

Keywords: 2, 5-dithiobiurea, dimethyl ethynedicarboxylate, (imidazo[2, 1-*b*][1, 3, 5]thiadiazolylidene)acetate

Acetylenecarboxylic acid derivatives are classified as electrophilic reagents whose reactions with thioamides were used for the synthesis of various heterocyclic systems over the last century.[1-5] The reactions of acetylenecarboxylic acid derivatives with unsubstituted thioureas,[6,7] *N*-mono-substituted thioureas,[8-10] *N, N*-disubstituted thioureas,[11] *N*, *N*′-disubstituted thioureas,[12] as well as substituted thiosemicarbazides were reported.[13-18] Unlike thioureas, the molecule of thiosemicarbazide contains four nucleophilic centres; therefore hydrazinothiazolidinone was obtained by heating unsubstituted thiosemicarbazide with dimethyl ethynedicarboxylate in methanol.[19] On the other hand, microwave (MW) irradiation or refluxing in acetic acid equimolar amounts of 4-substituted-thiosemicarbazides **1a–c** and dimethyl ethynedicarboxylate (**2**) in DMF afforded the formation of 5-oxo-3-thioxo-1, 2, 4-triazepine-7-carboxylic acid methyl ester derivatives **3a–c** and **4a–c** (Scheme 1).[20]

In addition, microwave (MW) heating has been employed for the rapid synthesis of a wide variety of organic substances,[21] where chemical reactions are accelerated because of selective absorption of MW energy by polar molecules.

The application of MW irradiation provides enhanced reaction rates, higher yields, greater selectivity, and the ease of manipulation.

Unfortunately, no reactions between diester **2** and 1-substituted-2, 5-dithiobiureas **5a–c** or 1, 6-disubstituted-2, 5-dithiobiureas **5d–f** have been published so far. The heterocyclisation of dithiobiureas **5a–f** using ethenetetra-carbonitrile (TCNE) gave pyrazole,[22] thiadiazepine,[22] thiadiazole[22] and imidazothiadiazole derivatives.[23]

Compound **2** offers the C/C triple bond and the elecrtophilic carbonyl carbon atoms for attack by nucleophiles, and compounds **5a–f** may react at least with their sulfur atom, N-3, N-4 and N-6 as nucleophilic sites. Thus several options for interactions between **5a–f** and **2** may be envisaged as will be outlined later. In the light of the abovementioned findings, we undertook to investigate the reaction of dithiobiureas **5a–f** with dimethyl ethynedicarboxylate (**2**) (Scheme 2).

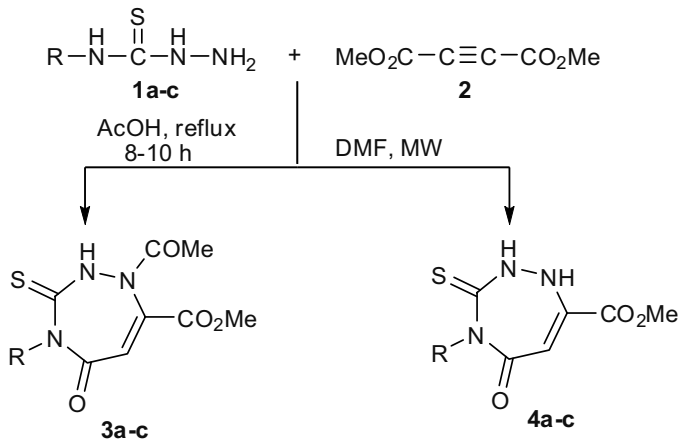
Results and discussion

In methanol at reflux temperature or by using microwave irradiation, the dithiobiureas **5a–f** reacted with dimethyl ethynedicarboxylate to give methyl 2-{6-oxo-2-(substituted amino)imidazo[2,1-*b*][1,3,4]thiadiazol-5(6*H*)-ylidene}acetate **6a–c** and methyl 7-oxo-1, 3-bis(substituted imino)-3, 7-dihydro-1*H*-pyrazolo[1, 2-*c*][1, 3, 4]thiadiazol-5-carboxylate **7a–c** (Scheme 2).

The structure of compounds **6a–c** and **7a–c** is in accord with their IR, ^{1}H NMR, ^{13}C NMR and mass spectral data in addition to elemental analyses.

Compounds **6a–c**

From elemental analyses and the mass spectra a net release of H_2S and MeOH (M.Wt 66) has occurred; the weak noticeable $M^{\bullet+}$ peak in the mass spectra which also showed the following three fragments common to all products [M^+-31], [M^+-RNCS] and [M^+-28]. In the IR spectra (see also table 1) two carbonyl bands were seen in the ranges 1720–1715 cm^{-1} and 1695–1690 cm^{-1}, and a band between 1615 and 1630 cm^{-1}



Scheme 1

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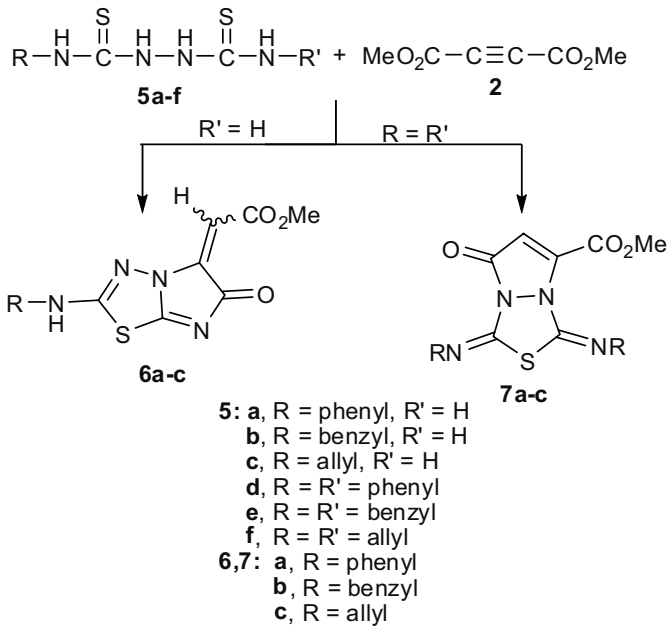


Scheme 2

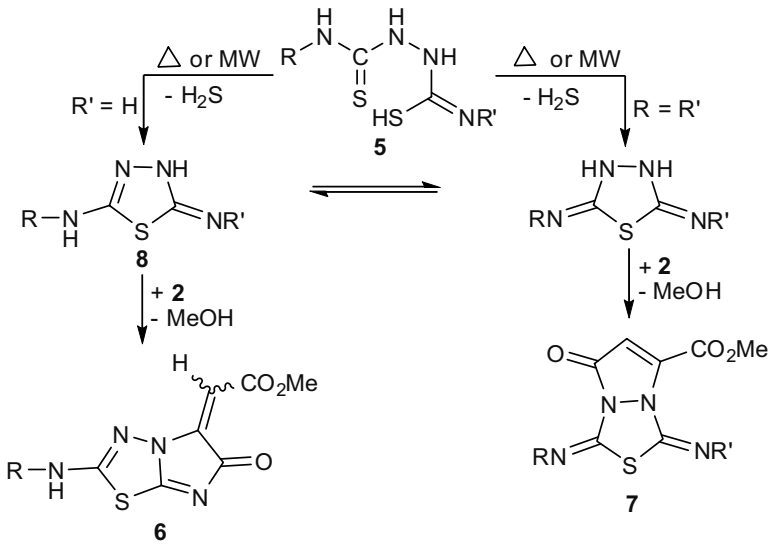
was assigned to C=N vibration, in addition to another band between 3310 and 3295 due to NH group.

The ^{1}H NMR of **6c** did reveal a vinylic-CH at 6.51 ppm; while a low field NH attached to allyl group resonated at 7.89 ppm,[24] the expected signals for the allyl group at 4.27 (allyl-CH_2N), 5.26–5.34 (allyl-CH_2=) and 6.03–6.12 (allyl-CH=) were observed. The ^{13}C NMR spectrum of **6c** showing signals at 165.83 (ring-*C*=*O*), 170.00 (ester-*C*=*O*), 154.96 (*C*-2), 154.72 (*C*-7a), 139.12 (*C*-5), 110.02 (vinyl-*C*H) ppm. One ester group was converted into a ring carbonyl, and the hydrazinecarbothioamide groups had taken part in heterocyclisation.

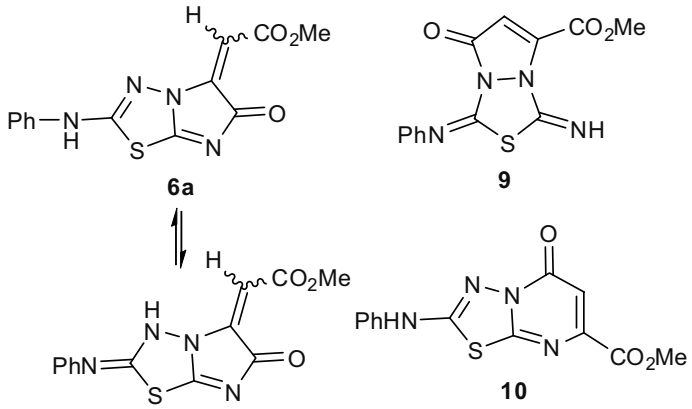
Since **2** can offer only electrophilic sites for attack, N-3, N-4, N-6, C-2 and C-5 of **5a–c** have to act as a nucleophile. Taking all the restrictions from above into account, a total of four alternative products structures (Scheme 4) may be expected from the following reactions which involving cyclisation of compounds **5a–c** *via* intermolecular nucleophilic attacks on either of the thiocarbonyl groups.

Nucleophilic attack on the triple bond of **2** by exocyclic or endocyclic NH of thiadiazole **8** or its tautomer on either the α- or β-ester group followed by elimination a molecule of MeOH giving rise to structures **6** or the isomeric products **9** and **10** (Scheme 4).

Structure **9** could be ruled out on the basis of ^{1}H NMR and the absence of an exocyclic-NH group, whereas the presence of NH attached to phenyl (δ_H = 9.96 ppm), benzyl (δ_H = 8.75 ppm) and allyl (δ_H = 7.89 ppm). There is no way so far to experimentally discriminate between compounds **6** and **10**. As can be seen easily, structure **6**, however, accommodates all spectral data listed above, especially the ^{13}C chemical shifts for the ring carbonyl C-atom (C-5), see Table 1 for comparison with all relevant spectral data with literature data of suitable model substances for **6** and its alternative **10**. For the latter alternative structural type in every case expected ring carbonyl ^{13}C resonances are considerably upfield to these which have been observed, and the IR frequencies (1695–1690 cm^{-1}) to be expected are typical for such α, β-unsaturated esters (1750–1725).[25] The ring C=O frequencies



Scheme 3



Scheme 4

(1720–1715 cm^{-1})[26] observed rule out structures **10a–c** (1667-1648 cm^{-1})[27-29] while they are agreeable for structures **6a–c**. The values found for ester C=O ^{13}C resonances do not allow an assignment beyond doubt (see Table 1). A rationale for the formation of **6a–c** is given in Scheme 3.

Finally, the question whether the products **6a–c** has an *E*- or *Z*-configuration, has to be left unanswered at present.

Compounds **7a–c**

The molecular ions in their EI-mass spectra confirm the molecular masses and the gross compositions. Further, the following common features of fragmentation patterns lend support to the assigned structures: Loss of 31 amu (representing methoxy group). The resulting acylium fragment ions undergo loss of RNCS followed by loss of 28 amu (may be dinitrogen or CO). The spectroscopic data found for isolated products fit best for structure **7**.

The ^{13}C chemical shifts for the ring carbons resonated at 164.21–164.08 ppm, due to lactam-C=O[33] (Table 1). Also, the IR absorption for pyrazol-3-ones comparable to **7a–c** resonate at (1710–1735 cm^{-1}).[34] Pyrazolone-proton 4-H showed in DMSO-d_6 a strong singlet between 6.95 and 6.92 ppm, for all compounds.

As shown in Table 2 the application of MW irradiation provided higher yields in comparison with yields obtained by application of a direct heating process.

Conclusion

The reactions and products presented here provide insight into the spontaneous reactions between mono- and disubstituted dithiobiureas **5a–f** and dimethyl ethynedicarboxylate (**2**), followed by heterocyclisation. Although, we have thiaheterocycles neither the S–C–N + C–2 nor N–C(S)–N + C-2 mode of cyclisation is found in this study, a novel

Table 1 ^{13}C NMR data for C=O groups (ring and ester)[a] in products **6a–c** and **7a–c** and literature data[26-34] of compounds comparable to **6**,**7** and structural alternatives.

Structures	^{13}C of ring C=O	^{13}C of ester C=O
Products **6a–c**	165.64–165.87[a]	169.74–170.0
Products **7a–c**	164.08–164.21	169.75–169.83
Pyrimidin-4-ones comparable to **6a–c**	158.6[27], 160[28]	164.7–165[27]
Imidazol-5-ones comparable to **6a–c**	164.6–166.1[26] 165.2–165.7[30] 168[31], 163.6–165.5[32]	170.1[26]
Pyrazol-3-ones comparable to **7a–c**	160.3–163.4[33]	164.9,166.04,166.5[34]

Table 2 Conventional heating under reflux (A) and MW irradiation (B) of dithiobiureas **5a–f** and dimethyl ethynedicarboxylate (**2**)

Starting materials (Conditions)	Products	Yield/%	
		A	B
5a + **2**			
(A: Reflux in MeOH, 3 h)	**6a**	51	78
(B: MW, 3 min, power 70%)	**6a**		
5b + **2**			
(A: Reflux in MeOH, 5 h)	**6b**	47	75
(B: MW, 5 min, power 100 %)	**6b**		
5c + **2**			
(A: Reflux in MeOH, 6 h)	**6c**	43	71
(B: MW, 6 min, power 100 %)	**6c**		
5d + **2**			
(A: Reflux in MeOH, 5 h)	**7a**	58	79
(B: MW, 4 min, power 100 %)	**7a**		
5e + **2**			
(A: Reflux in MeOH, 7 h)	**7b**	53	79
(B: MW, 6 min, power 100 %)	**7b**		
5f + **2**			
(A: Reflux in MeOH, 8 h)	**7c**	51	76
(B: MW, 7 min, power 100 %)	**7c**		

N–C–N + C-2 mode is observed due to dibithiourea reactivity. The results reported here supplement the rich chemistry of dimethyl ethynedicarboxylate and dithiobiureas.

Experimental

All the melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorected. The IR spectra were recorded with a Shimadzu 408 using potassium bromide pellets. 500 MHz ^{1}H and 125 MHz ^{13}C NMR spectra were recorded from DMSO-d_6 solution on a Bruker Avance DRX 500 spectrometer. Chemical shifts are expressed as δ [ppm] with reference to tetramethylsilane as an internal standard, s = singlet, d = doublet, dd = doublet of doublet and b = broad. ^{13}C assignments were made with the aid of distortionless enhancement by polarisation transfer (DEPT) 135/90 spectra. Mass spectra were recorded on a Varian MAT CH-7 instrument in EI mode at 70 eV ionisation energy. A Somsung MX 45 microwave oven was used at its full power 1400 W, 100% and 700% power level for the experiments recorded for this study. Preparative layer chromatography (PLC) used air dried 1.0 mm thick layers of slurry applied silica gel Merck Pf_{254} on 48 cm wide and 20 cm high glass plates using the solvents listed. Zones were detected by quenching of indicator fluorescence upon exposure to 254 nm light and were extracted with acetone.

Starting materials: 1-Substituted-2, 5-dithiobiureas **5a–c** and 1, 6-disubstituted-2, 5-dithiobiureas **5d–f** were prepared according to published procedures as were 1-phenyl-2, 5-dithiobiurea (**5a**),[35] 1-benzyl-2, 5-dithiobiurea (**5b**),[35,36] 1-allyl-2, 5-dithiobiurea (**5c**),[35] 1, 6-diphenyl-2, 5-dithiobiurea (**5d**),[37] 1, 6-dibenzyl-2, 5-dithiobiurea (**5e**),[38] 1, 6-diallyl-2, 5-dithiobiurea (**5f**).[39] Dimethyl ethynedicarboxylate (**2**) was bought from Fluka.

Reactions of **5a–f** *with dimethyl ethynedicarboxylate* (**2**)
Method (A): Conventional heating under refluxing in methanol: Into a 250 cm^3 two-necked flask containing **2** (284 mg, 2.0 mmol) in methanol (10 mL), a solution of 2 mmol of **5a–f** in methanol (50 mL) was added dropwise with stirring. The mixture was gently refluxed with stirring for 3–8 h. The resulting yellow precipitate was filtered off, washed with methanol, and recrystallised from a suitable solvent to give pure crystals of **6a–c** and **7a–c**.

Method (B): Heterocyclisation by microwave irradiation: Equimolar amounts of **5a–f** (2 mmol) and **2** (284 mg, 1 mmol) were well-mixed in methanol (10 mL). The mixture was irradiated in a microwave oven in an open glass tube (the time of irradiation as monitored in Table 2. After completion of the reaction as monitored by TLC, the residue was separated as reported above. Comparison of the yields from compounds **2** and **5a–f** is given in Table 2.

Methyl 2-{6-oxo-2-(phenylamino)imidazo[2, 1-b][1, 3, 4]thiadiazol-5 (6H)-ylidene}acetate **(6a):** Yellow crystals, m.p. 261–263 °C (acetonitrile). IR (KBr): 3310 (NH), 1720 (CO), 1695 (COO), 1620 (C=N), 1600 (Ar-C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.81 (s, 3H, CH_3), 6.48 (s, 1H, methylene-H), 7.28–7.40 (m, 5H, phenyl-H), 9.96 ppm (br, 1H, Ph-NH). ^{13}C NMR (DMSO-d_6): δ = 53.63 (O*C*H$_3$), 109.93 (methylene-*C*H), 127.57, 127.98, 128.44 (Ph-*C*H), 137.73 (Ph-*C*), 138.96 (*C*-5), 154.67 (*C*-7a), 155.11 (*C*-2), 165.87 (*C*-6), 169.74 ppm (ester-*C*O). MS (*m/z*,%): 302 [M$^+$] (17), 271 (41), 167 (38), 139 (51), 135 (64), 91 (62), 77 (100), 66 (69). Anal. Calcd for $C_{13}H_{10}N_4O_3S$ (302.31): C, 51.65; H, 3.33; N, 18.53; S, 10.61. Found: C, 51.79; H, 3.41; N, 18.37; S, 10.75%.

Methyl 2-{6-oxo-2-(benzylamino)imidazo[2, 1-b][1, 3, 4]thiadiazol-5 (6H)-ylidene}acetate **(6b)**: Yellow crystals, m.p. 276–278 °C (methanol). IR (KBr): 3295 (NH), 1715 (CO), 1690 (COO), 1630 (C=N), 1595 (Ar-C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.79 (s, 3H, CH_3), 4.59 (s, 2H, Ph-CH_2), 6.45 (s, 1H, methylene-H), 7.26–7.37 (m, 5H, phenyl-H), 8.75 ppm (br, 1H, PhCH_2-NH). ^{13}C NMR (DMSO-d_6): δ = 46.91 (*C*H$_2$Ph), 53.47 (O*C*H$_3$), 109.74 (methylene-*C*H), 127.42, 127.93, 128.36 (Ph-*C*H), 137.84 (Ph-*C*), 138.73 (*C*-5), 154.56 (*C*-7a), 155.31 (*C*-2), 165.64 (*C*-6), 169.83 ppm (ester-*C*O). MS (*m/z*,%): 316 [M$^+$] (11), 285 (26), 167 (37), 149 (76), 91 (100), 77 (62), 66 (51). Anal. Calcd for $C_{14}H_{12}N_4O_3S$ (316.34): C, 53.16; H, 3.82; N, 17.71; S, 10.14. Found: C, 52.93; H, 3.91; N, 17.58; S, 9.97%.

Methyl 2-{6-oxo-2-(allylamino)imidazo[2, 1-b][1, 3, 4]thiadiazol-5(6H)-ylidene}acetate **(6c):** Yellow crystals, m.p. 218–220 °C (ethanol). IR (KBr): 3305 (NH), 2990 (Ali-H), 1715 (CO), 1695 (COO), 1620 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.80 (s, 3H, CH_3), 4.27 (br, 2H, allyl-CH_2N), 5.26–5.34 (m, 2H, allyl-CH_2 =), 6.03–6.12 (m, 1H, allyl-CH=), 6.51 (s, 1H, methylene-H), 7.89 ppm (br, 1H, allyl-NH). ^{13}C NMR (DMSO-d_6): δ = 43.67 (allyl-*C*H$_2$N), 53.59 (O*C*H$_3$), 110.12 (methylene-*C*H), 116.06 (allyl-*C*H$_2$=), 153.14 (allyl-*CH*=), 139.12 (*C*-5), 154.72 (*C*-7a), 154.96 (*C*-2), 165.83 (*C*-6), 170.00 ppm (ester-*C*O). MS (*m/z*,%): 266 [M$^+$] (21), 235 (12), 136 (41), 108 (42), 99 (23), 66 (36), 41 (100). Anal. Calcd for $C_{10}H_{10}N_4O_3S$ (266.28): C, 45.11; H, 3.79; N, 21.04; S, 12.04. Found: C, 44.89; H, 3.92; N, 20.88; S, 11.94%.

Methyl 7-oxo-1, 3-bis(phenylimino)-3, 7-dihydro-1H-pyrazolo[1, 2-c] [1, 3, 4]thiadiazol-5-carboxylate **(7a)**: Yellow crystals, m.p. 282–284 °C (acetonitrile). IR (KBr): 1720 (CO), 1697 (COO), 1625 (C=N), 1605 (Ar-C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.76 (s, 3H, CH_3), 6.95 (s, 1H, pyrazole-H), 7.11–7.51 ppm (m, 10H, Ph-H). ^{13}C NMR (DMSO-d_6): δ = 52.86 (O*C*H$_3$), 87.12 (pyrazole-*C*H), 126.28, 127.56, 129.47 (Ph-*C*H), 147.76 (Ph-*C*), 153.37 (*C*-5), 157.55 (*C*-1, 3), 164.12 (pyrazole-*C*O), 169.75 ppm (ester-*C*O). MS (*m/z*,%): 378 [M$^+$] (14), 347 (26), 212 (41), 184 (22), 135 (36), 103 (16), 91 (56), 77 (100), 65 (68). Anal. Calcd for $C_{19}H_{14}N_4O_3S$ (378.40): C, 60.31; H, 3.73; N, 14.81; S, 8.47. Found: C, 60.47; H, 3.61; N, 15.02; S, 8.32%.

Methyl 7-oxo-1, 3-bis(benzylimino)-3, 7-dihydro-1H-pyrazolo[1, 2-c] [1, 3, 4]thiadiazol-5-carboxylate **(7b):** This compound was obtained as pale yellow crystals, m.p. 303–305 °C (acetonitrile). IR (KBr): 1715 (CO), 1695 (COO), 1630 (C=N), 1595 (Ar-C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.78 (s, 3H, CH_3), 4.56 (s, 2H, Ph-CH_2), 6.92 (s, 1H, pyrazole-H), 7.18–7.56 ppm (m, 10H, Ph-H). ^{13}C NMR (DMSO-d_6): δ = 47.18 (*C*H$_2$Ph), 52.82 (O*C*H$_3$), 87.98 (pyrazole-*C*H), 126.19, 127.45, 129.45 (Ph-*C*H), 137.67 (Ph-*C*), 153.24 (*C*-5), 157.49 (*C*-1, 3), 164.21 (pyrazole-*C*O), 169.83 ppm (ester-*C*O). MS (*m/z*,%): 406 [M$^+$] (19), 375 (38), 226 (32), 198 (45), 127 (18), 91 (100), 77 (55). $C_{21}H_{18}N_4O_3S$ (406.46): Anal. Calcd for C, 62.05; H, 4.46; N, 13.78; S, 7.89. Found: C, 61.88; H, 4.32; N, 13.93; S, 8.03%.

Methyl 7-oxo-1, 3-bis(allylimino)-3, 7-dihydro-1H-pyrazolo[1, 2-c] [1, 3, 4]thiadiazol-5-carboxylate **(7c):** Pale yellow crystals, m.p. 246–248 °C (acetonitrile). IR (KBr): 2995 (Ali-H), 1715 (CO), 1700 (COO), 1625 (C=N) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 3.75 (s, 3H, CH_3), 4.19 (br, 2H, allyl-CH_2N), 5.28–5.33 (m, –2H, allyl-CH_2=), 5.96–6.05 (m, 1H, allyl-CH=), 6.95 ppm (s, 1H, pyrazole-H). ^{13}C NMR (DMSO-d_6): δ = 43.56 (allyl-*C*H$_2$N), 52.90 (O*C*H$_3$), 87.05 (pyrazole-*C*H), 115.94 (allyl-*C*H$_2$=), 135.21 (allyl-*CH*=), 153.28 (*C*-5), 157.62 (*C*-1, 3), 164.08 (pyrazole-*C*O), 169.80 ppm (ester-*C*O). MS (*m/z*,%): 306 [M$^+$] (16), 275 (29), 176 (37), 148 (7), 99 (27), 55 (17), 41 (100). Anal. Calcd for $C_{13}H_{14}N_4O_3S$ (306.34): C, 50.97; H, 4.61; N, 18.29; S, 10.47. Found: C, 51.14; H, 4.49; N, 18.11; S, 10.61%.

Received 14 June; accepted 17 August 2009
Paper 09/0640 doi: 10.3184/030823409X12510192920270
Published online: 8 October 2009

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