The Reactivity of Dimethyl Acetylenedicarboxylate and Heterocyclization of Hydrazinecarbothioamides to 1,3-Thiazolidin-4-ones

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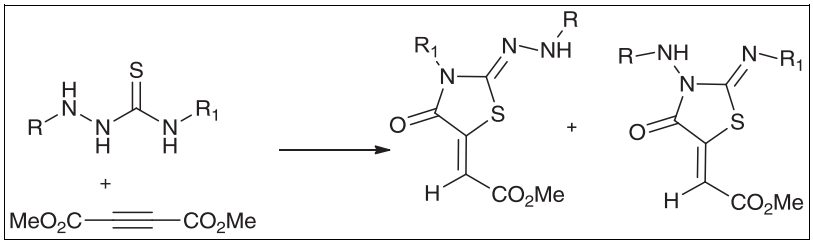

2-Substituted hydrazinecarbothioamides and *N*,2-disubstituted hydrazinecarbothioamides react, in high yields with dimethyl acetylenedicarboxylate to give 4-oxo-*Z*-(thiazolidin-5-ylidene)acetate derivatives. Several mechanistic options involving interaction are presented. The structures of thiazolidin-4-ones have been unambiguously confirmed by single crystal X-ray crystallography.

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INTRODUCTION

The reaction of hydrazinecarbothioamides with electron deficient compounds is a convenient method for the synthesis of various heterocyclic compounds, such as pyrazolo[1,2-c]-1,3,4-thiadiazoles [1], spiro(indolone-3,2′-[1,3,3]thiadiazole)-2-ones [2], indazoles [3], and thiadiazines [3].

Thiazoles are synthetic intermediates and common substructures in numerous other biologically active compounds [4–9]. Owing to the various physiological activities of thiazolidinones, many thiazolidinone derivatives have been prepared, and several new methods for the preparation of substituted thiazolidin-4-ones have been reported [9,10].

Thiazolidin-4-one compounds display antimicrobial [11,12], antimycobacterial [13,14], anti-HIV [15,16], anti-inflammatory [17], and anticancer [18,19]. Moreover, they have been studied extensively because of their ready accessibility, diverse chemical reactivity, and broad spectrum of pharmacological activities [20]. Furthermore, 2-iminothiazolidin-4-ones have been found to have antifungal activity [21].

Methyl [3-aryl-4-oxo-1-(phenylthiocarbamoyl)-4,5-dihydro-pyrazol-5-ylidene]ethanoates were formed from the reaction of arenealdehyde 4-phenylthiosemi-carbazones with dimethyl acetylenedicarboxylate (DMAD, **2**) [22], whereas 1,2,4-triazepine-3-thiones **4a–c** and **5a–d** were formed *via* conventional and microwave irradiation of 4-substituted thiosemicarbazides **1a–c** and 2,4-disubstituted thiosemicarbazides **3a–d** with DMAD, **2** (Scheme 1) [23].

RESULTS AND DISCUSSION

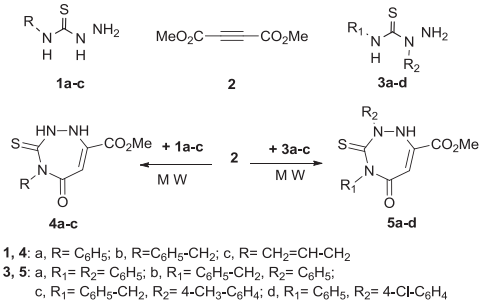
We report here the results of our investigations on the reaction of hydrazinecarbothioamides **6a–e** with **2**. These results are compared with those obtained in Scheme 1 [23]. As shown in Scheme 2, the synthesis of thiazolidin-4-ones **7** and **8** was simply affected by the nucleophilic active centers in hydrazinecarbothioamides **6a–e** and an electrophilic acetylenic ester (DMAD, **2**). The reaction proceeds smoothly, without using catalyst, by treatment of **6a–e** with one molar equivalent of DMAD (**2**) in ethanol at reflux temperature to give the products **7a,b** and **8a–c** in 78–89% yields (Scheme 2).

Elemental analyses and mass spectra clearly revealed that the products were formed by the addition of equimolar amounts of DMAD (**2**) and **6a–e** with the elimination of one molecule of methanol. There are different possibilities for the formation of various isomers, which would behave spectroscopically very similar. Hydrazinecarbothioamides, N^1, N^2, N^3, and sulfur atom are the nucleophilic sites in compounds **6a–e**. Thus, several options for the interaction between **6a–e** and **2** may be envisaged. It is probable that all the products observed are formed from one of the five labile (1:1) adducts (**A–E**) (Fig. 1).

To elucidate the tautomeric states and structure of the products as well as to characterize the products, we use IR, ^{1}H NMR, and ^{13}C NMR as well as mass spectrometry. Rigorous structure proof comes from the single crystal X-ray structural analyses of **7b** (Fig. 2) and **8b** (Fig. 3).

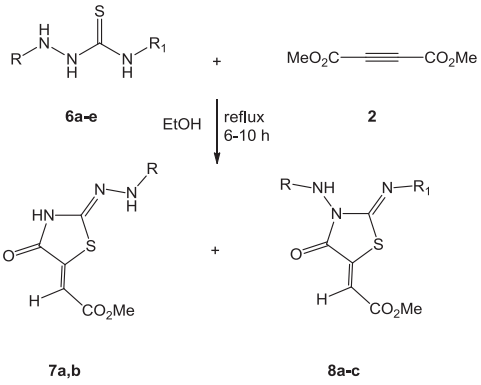
To illustrate the structure elucidation of compounds **7a, b**, we choose **7b** as an example. Thus, IR spectrum showed

Scheme 1. Reactions of hydrazinecarbothioamides **1a–c** and **3a–d** with dimethyl acetylenedicarboxylate **2.**



1, 4: a, R= C_6H_5; b, R=C_6H_5-CH_2; c, R= CH_2=CH-CH_2
3, 5: a, R_1= R_2= C_6H_5; b, R_1= C_6H_5-CH_2, R_2= C_6H_5;
c, R_1= C_6H_5-CH_2, R_2= 4-CH_3-C_6H_4; d, R_1= C_6H_5, R_2= 4-Cl-C_6H_4

Scheme 2. Reaction of hydrazinecarbothioamides **6a–e** with dimethyl acetylenedicarboxylate.



6: **a**, R = C_6H_5, R_1 = H; **b**, R = O_2S-(C$_6$H$_4$)-CH_3 , R_1 = H;
c, R = R_1= C_6H_5; **d**, R = C_6H_5, R_1 = C_2H_5;
e, R = C_6H_5, R_1 = CH_2=CH-CH_2
7: **a**, R = C_6H_5, R_1 = H; **b**, R = O_2S-(C$_6$H$_4$)-CH_3 , R_1= H;
8: **a**, R = R_1 = C_6H_5; **b**, R = C_6H_5,R_1 = C_2H_5;
c, R = C_6H_5, R_1 = CH_2=CH-CH_2

two carbonyl absorption bands at 1745, 1685 (C=O) and a band at 1615 cm^{-1} that assigned to C=N vibration. Broad bands at 3310 and 3160 cm^{-1} are due to NH-groups.

The ^{1}H NMR spectrum of **7b** showed one methoxy group at δ_H = 3.86, methyl group at δ_H = 2.24 ppm, one phenyl group in the range of δ_H = 6.85–7.24, one vinylic

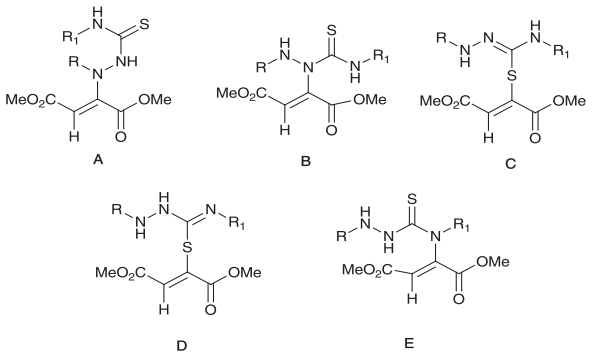


Figure 1. Expected adducts (1:1) (**A–E**) through interactions between **6a–e** and **2.**

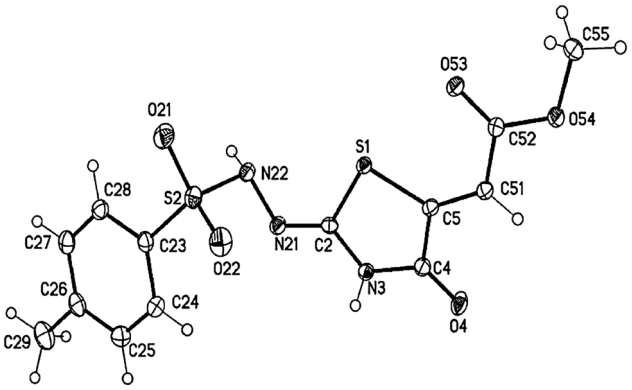


Figure 2. Molecular structure of **7b** in the crystal (displacement parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

proton at δ_H = 6.85 and NH at δ_H = 8.27. In addition its ^{13}C NMR spectrum showed five downfield lines at 168.12, 166.64, 145.94, 140.22, and 115.73 ppm, because of (C=O, ester), (C-4), (C=N), (C-5) and vinyl-CH, respectively. Full ^{1}H NMR and ^{13}C NMR data are given in the experimental part.

Moreover, the structure of *Z*-methyl-2-[(*Z*)-4-oxo-2-(2-tosylhydrazono)-thiazolidin-5-ylidene]acetate **7b** has been unambiguously confirmed by a single crystal X-ray structure analysis (Fig. 2 and Tables S1–7 in the supplementary data), which confirms a *cisoid* geometry with respect to C=C and C=N double bonds. Also, the vinyl-CH is in *cis* form with the cyclic C=O. The thiazolidine moiety is planar.

On the other hand, refluxing a solution of equimolar amounts of **6c–d** and **2** in absolute EtOH (25 mL) for 6–8 h furnished the new thiazolidine-4-ones **8a–c**, as the only reaction product. The structures of **8a–c** were confirmed for the reaction products on the basis of their elemental and spectral data. Their IR spectra showed two carbonyl absorption bands about 1690–1725 cm^{-1}, and an absorption

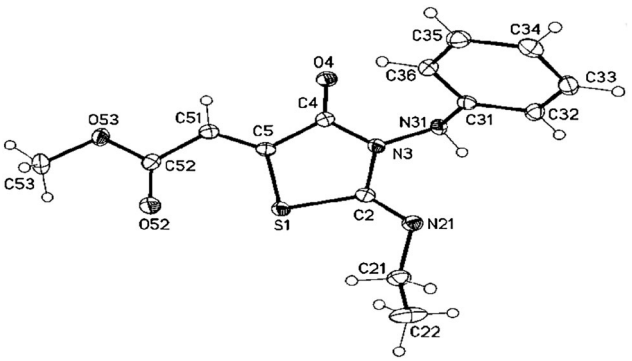


Figure 3. Molecular structure of **8b** in the crystal (displacement parameters are drawn at 50% probability level). The crystallographic numbering does not reflect the systematic IUPAC numbering.

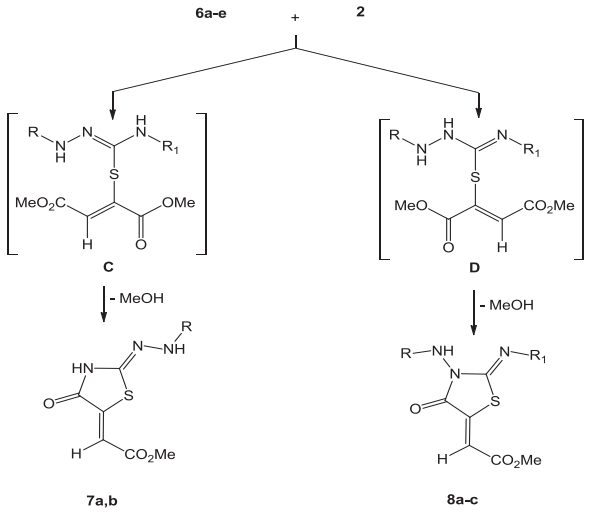
band between 1635 and 1655 cm^{-1} that was assigned to a C=N vibration. A broad band at 3295–3320 cm^{-1} is due to NH group. ^{1}H NMR revealed a vinyl-CH singlet between 6.50–6.65 ppm, and a methoxy singlet at about 3.85–3.90 ppm. In all cases, the IR and ^{13}C NMR confirmed the disappearance of a thione group. ^{13}C NMR showed signals at 166.28–166.64 (C=O, ester), 162.24–162.99 (C-4), 145.46–145.77 (C=N), 138.78–140.51 (thiazolidine-C-5) and 115.05–115.36 (vinyl-CH), in addition to the aromatic carbons.

The ^{1}H-NMR spectrum of **8c** clearly indicated the presence of an allyl group, which appeared as three multiplets centered at 4.15, 5.12, and 5.92 ppm due to (allyl-CH_2N), (allyl-CH_2=), and (allyl-CH=), respectively. The presence of the allyl group was also proved by the ^{13}C-DEPT-NMR spectrum, exhibiting positive signals at 133.72 (allyl-CH=) and negative signal at 45.24 and 117.15 due to (allyl-CH_2N) and (allyl-CH_2=), respectively.

Unambiguous support for products **8a–c** came from the X-ray structure analysis of (*Z*)-methyl-2-[(*Z*)-2-(ethylimino)-4-oxo-3-(phenylamino)thiazolidin-5-ylidene)]acetate **8b** (Fig. 3 and Tables S8–14, in the supplementary data). A *cisoid* geometry with respect to C=C and C=N double bonds and the thiazolidine moiety is planar.

A rationale for the formation of products **7a,b** and **8a–c** is depicted in (Scheme 3). Nucleophilic attack of SH of **6a–e** on the triple bond of **2** through the intermediate (**C**), followed by intramolecular nucleophilic attack of the NH_2 of **6a,b** at α-ester carbonyl group, the products **7a,b** would be isolated, where *via* the intermediate (**D**) and nucleophilic attack of SH on the triple bond of **2** with elimination of one molecule of MeOH during the attack of *N*-hydrazinecarbothioamide at the carbonyl ester, the thiazolidin-4-ones **8a–c** would be formed.

Scheme 3. The mechanism for the formation of products **7a,b** and **8a–c.**



CONCLUSION

Reaction of 2-substituted hydrazinecarbothioamides **6a,b** and *N*,2-disubstituted hydrazinecarbothioamides **6c-e** with DMAD (**2**) can involve possible competition between nucleophilic addition of several sites (N^1, N^2, N^3, and SH of hydrazinecarbothioamide group) to the triple bond of activated acetylenic ester. Thioheterocyclic N-C-S + C2 mode of cyclization is favored.

EXPERIMENTAL

All melting points were determined using open capillaries on a Gallenkamp melting point apparatus. The IR spectra were recorded with a Shimadzu 408 instrument using potassium bromide. The 400 MHz ^{1}H NMR and 100 MHz ^{13}C NMR spectra were observed on a Bruker AM 400 spectrometer with tetramethylsilane as the internal standard, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The ^{13}C NMR signals were assigned on the basis of DEPT 135/90 spectra. The mass spectra (70 eV, electron impact mode) were recorded on Finnigan MAT instrument. Elemental analyses are carried out at the Microanalytical Center, Cairo University, Egypt. 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 eluted with acetone.

Starting materials. 2-Substituted hydrazinecarbothioamides **6a,b** and *N*,2-disubstituted hydrazinecarbothioamides **6c–e** were prepared according to the literature: **6a** [24], **6b** [25], **6c** [26], **6d** [26], and **6e** [27]. DMAD (**2**) was bought from Fluka.

Reaction of substituted hydrazinecarbothioamides 6a–e with dimethyl acetylenedicarboxylate (2). A mixture of substituted hydrazinecarbothioamides **6a–e** (1 mmol) and DMAD (**2**) (0.142 g, 1 mmol) in absolute ethanol (30 mL) was refluxed for 6–10 h and was cooled to room temperature. Yellow crystals from **7a,b** were precipitated, filtered, and washed with a small amount of cold ethanol and recrystallized from listed solvents. The reaction mixture between **6c–e** and **2** was preconcentrated, applied to chromatographic plates, and developed using toluene/ethyl acetate (Qr = 10:1) to give only one zone containing compounds **8a–c**. The products so obtained were recrystallized.

(Z)-Methyl-2-[(Z)-4-oxo-2-(2-phenylhydrazno)-thiazolidin-5-ylidene]acetate (7a). Yellow crystals (0.246 g, 89%), mp 222–224°C (acetonitrile); IR (KBr) ν = 3288, 3252 (NH), 1692, 1668 (CO), 1640 (C=N), 1605 cm^{-1} (Ar–C=C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 3.85 (s, 3H, OCH_3), 6.85 (m, 2H, Ar-H and vinyl-CH), 7.24 (m, 4H, Ar-H), 8.27 (br, 1H, NH), 11.27 (br, s, 1H, thiazolidine-NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ_C = 52.71 (OCH_3), 116.12 (vinyl-CH), 122.81, 127.19, 129.67 (Ar-CH), 140.12 (thiazolidine-C5), 142.88 (Ar-C), 146.12 (thiazolidine-C2), 166.73 (thiazolidine-C4), 168.19 (CO-ester); MS (70 eV): *m/z* = 277 (M^+, 100), 246 (12), 218 (19), 145 (22), 105 (39), 92 (54), 77 (62), 65 (42), 59 (21). *Anal.* Calcd. for $C_{12}H_{11}N_3O_3S$ (277.05): C, 51.98; H, 4.00; N, 15.15; S, 11.56. Found: C, 52.11; H, 3.88; N, 15.06; S, 11.74.

(Z)-Methyl 2-[(Z-4-oxo-2-(2-tosylhydrazono)thiazolidin-5-ylidene] acetate (7b). Yellow crystals (0.290 g, 82%), mp

234–236°C (acetonitrile); IR (KBr) $\nu = 3310$, 3160 (NH), 1745, 1685 (CO), 1615 (C=N), 1590 cm^{-1} (Ar–C=C); ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 2.24$ (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 6.80 (s, 1H, vinyl-CH), 6.90–7.00 (m, 2H, Ar-H), 7.28 (m, 2H, Ar-H), 8.45 (br, 1H, NH), 11.16 (br, 1H, thiazolidine-NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 22.16$ (CH_3), 52.75 (OCH_3), 115.73 (vinyl-CH), 129.29, 129.53 (Ar-CH), 138.12 (Ar-C), 140.22 (thiazolidine-C5), 143.42 (Ar-C), 145.94 (thiazolidine-C2), 166.64 (thiazolidine-C4), 168.12 (CO-ester); MS (70 eV): $m/z = 355$ (M^+, 21), 324 (12), 200 (100), 155 (11), 117 (23), 91 (37). *Anal.* Calcd. for $C_{13}H_{13}N_3O_5S_2$ (355.04): C, 43.93; H, 3.69; N, 11.82; S, 18.04. Found: C, 44.14; H, 3.78; N, 11.67; S, 17.91.

(Z)-Methyl-2-[(Z)-4-oxo-3-(phenylamino)-2-(phenyl-imino) thiazolidin-5-ylidene]acetate (8a). Yellow crystals (0.286 g, 81%), mp 183–185°C (acetone); IR (KBr) $\nu = 3295$ (NH), 1690, 1710 (CO), 1635 (C=N), 1595, 1605 cm^{-1} (Ar–C=C); ^1H NMR (400, MHz, $CDCl_3$): $\delta_H = 3.90$ (OCH_3), 6.65 (vinyl-CH), 6.85 (m, 3H, Ar-H), 7.28 (m, 3H, Ar-H, and NH), 7.50 (m, 5H, Ar-H); ^{13}C NMR (100 Hz, $CDCl_3$): $\delta_C = 52.67$ (OCH_3), 115.13 (vinyl-CH), 121.03, 126.90, 127.61, 128.74, 129.52 (Ar-CH), 133.99 (Ar-C), 140.23 (thiazolidine-C5), 142.33 (Ar-C), 145.46 (thiazolidine-C2), 162.99 (thiazolidine-C4), 166.64 (CO-ester); MS (70 eV): $m/z = 353$ (M^+, 100), 322 (12), 135 (81), 92 (28). *Anal.* Calcd. For $C_{18}H_{15}N_3O_3S$ (353.08): C, 61.18; H, 4.28; N, 11.89; S, 9.07. Found: C, 61.29, H, 4.19; N, 12.02; S, 8.92.

(Z)-Methyl-2-[(Z)-2-(ethylimino)-4-oxo-3-(phenylamino)-thiazolidin-5-ylidene]acetate (8b). Yellow crystals (0.256 g, 84%), mp 151°C (acetone); IR (KBr): $\nu = 3310$ (NH), 1695, 1725 (CO), 1655 (C=N), 1615 (Ar–C=C) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 1.15$ (t, 3H, $J = 7.6$ Hz, CH_3), 3.40 (m, 2H, CH_2) 3.85 (s, 3H, OCH_3), 6.50 (s, 1H, vinyl-CH), 6.73 (m, 2H, Ar-H), 6.92 (m, 2H, Ar-H), 7.20 (m, 2H, Ar-H and NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 15.67$ (CH_3), 47.21 (CH_2), 52.65 (OCH_3), 115.05 (vinyl-CH), 116.82, 122.82, 129.23 (Ar-CH), 138.78 (thiazolidine-C5), 145.16 (Ar-C), 145.77 (thiazolidine-C2), 162.24 (thiazolidine-C4), 166.28 (CO-ester); MS (70 eV): $m/z = 305$ (M^+, 100), 290 (11), 274 (18), 247 (11), 134 (38), 106 (21), 92 (16). *Anal.* Calcd. For $C_{14}H_{15}N_3O_3S$ (305.08): C, 55.07; H, 4.95; N, 13.76; S, 10.50. Found: C, 54.97; H, 5.02; N, 13.85; S, 10.39.

(Z)-Methyl-2-[(Z)-2-(allyimino)-4-oxo-3-(phenylamino)-thiazolidin-5-ylidene]acetate (8c). Yellow crystals (0.247 g, 78%), mp 129°C (acetone); IR (KBr): v = 3320 (NH), 1710, 1695 (CO), 1650 (C=N), 1605 cm^{-1} (Ar–C=C); ^1H NMR (400 MHz, $CDCl_3$) $\delta_H = 3.88$ (s, 3H, OCH_3), 4.15 (m, 2H, allyl-CH_2), 5.12 (m, 2H, allyl-CH_2=), 5.92 (m, 1H, allyl-CH=), 6.60 (s, 1H, vinyl-CH), 6.85 (m, 1H, Ar-H), 7.0 (m, 2H, Ar-H), 7.3 (m, 2H, Ar-H and NH); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta_C = 45.24$ (allyl-CH_2N), 52.61(OCH_3), 115.36 (vinyl-CH), 117.15 (allyl-CH_2=), 122.85, 129.26, 129.26 (Ar-CH), 133.72 (allyl-CH=), 140.51 (thiazolidine-C5), 141.46 (Ar-C), 145.61 (thiazolidine-C2), 162.92 (thiazolidine-C4), 166.56 (CO-ester); MS (70 eV): $m/z = 317$ (M^+, 100), 286 (13), 258 (9), 225 (14), 92 (33). *Anal.* Calcd. For $C_{15}H_{15}N_3O_3S$ (317.08): C, 56.77; H, 4.76; N, 13.24; S, 10.10. Found: C, 56.89, H, 4.68; N, 13.12; S, 10.24.

Single crystal X-ray structure determination of 7b and **8b**. Suitable crystals were obtained by recrystallization from acetonitrile. The single crystal X-ray diffraction study was carried out on a Bruker-Nonius ApexII diffractometer at 123 (2) K (**7b**) or a Bruker Apex Duo at 120(2) K (**8b**) using MoKα radiation ($\lambda = 0.71073$ Å). Direct methods (SHELXS-97) [28] were used for structure solution, and refinement was carried out using SHELX-97 [28], (full-matrix least-squares on F2). Hydrogen atoms were localized by difference electron density determination and refined using a riding model (H(N) free). An extinction correction was applied for **7b** and a semi-empirical absorption correction was applied for **8b**.

Compound 7b. $C_{13}H_{13}N_3O_5S_2$, $M = 355.38$ $gmol^{-1}$, yellow crystals, crystal size $0.50 \times 0.45 \times 0.40$ mm, orthorhombic, space group Pbca (No. 61), $a = 13.8883(3)$Å, $b = 12.8134(4)$ Å, $c = 16.8953(5)$ Å, $V = 3006.63(14)$ $Å^3$, $Z = 8$, $D_{calcd} = 1.570$ Mgm^{-3}, $\mu = 0.384$ mm^{-1}, $T = 123(2)$ K, 14529 reflection, 3424 unique [$R_{int} = 0.019$], $2\theta_{max} = 55^o$, 217 parameters, two restraints, R_1 [for 3198 $I > 2\sigma$ (I)] = 0.028, wR2 (all data) = 0.074, S = 1.12, largest diff. peak and hole = 0.385/ −0.347 e A^{-3}.

Compound 8b. $C_{14}H_{15}N_3O_3S$, Mr = 305.35 $gmol^{-1}$, yellow crystal, crystal size $0.50 \times 0.30 \times 0.20$ mm, monoclinic, space group P21/n (no. 14), a = 7.3170(2) Å, $b = 10.8893(3)$ Å, $c = 17.6717(5)$ Å, $\beta = 96.992(1)$ Å, $V = 1397.56(7)$ A^{-3}, $Z = 4$, $D_{calcd} = 1.451$ Mgm^{-3}, $\mu = 0.246$ mm^{-1}, $T = 120(2)$ K, 11545 reflection, 3144 unique [$R_{int} = 0.012$], $2\theta_{max} = 55^o$, 194 parameters, one restraint, R_1 [for 2967 $I > 2\sigma$ (I)] = 0.028 WR2(all data) = 0.072, S = 1.04, largest diff. peak and hole = 0.370/−0.232 e A^{-3}.

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