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CuTC MEDIATED COUPLING OF 6,7-DISUBSTITUTED BENZOTHIAZOLES

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Abstract – A synthesis of the halogeno derivatives of substituted benzothiazoles (**2**-**6**) is described, and dimerization using copper in different oxidation states is examined. Dimerization of iododerivatives (**2**) and (**4**) by copper(I) thiophen-2-carboxylate (CuTC) mediated coupling afforded the corresponding *o*,*o*'-disubstituted bibenzothiazoles (**7**) and (**8**) in excellent yield.

INTRODUCTION

Benzothiazoles represent structural units frequently found in a broad range of organic compounds, including natural product, pharmaceuticals, dyes and other functional synthetic compounds.[1] Consequently, methods for functionalization and expansion of heterocyclic moiety would find application in various scientific disciplines. Due to the fact that many natural and commercial interesting molecules contain several bounded aromatic ring, aryl-aryl bond formation is one of the most important tools of modern organic synthesis.[2]

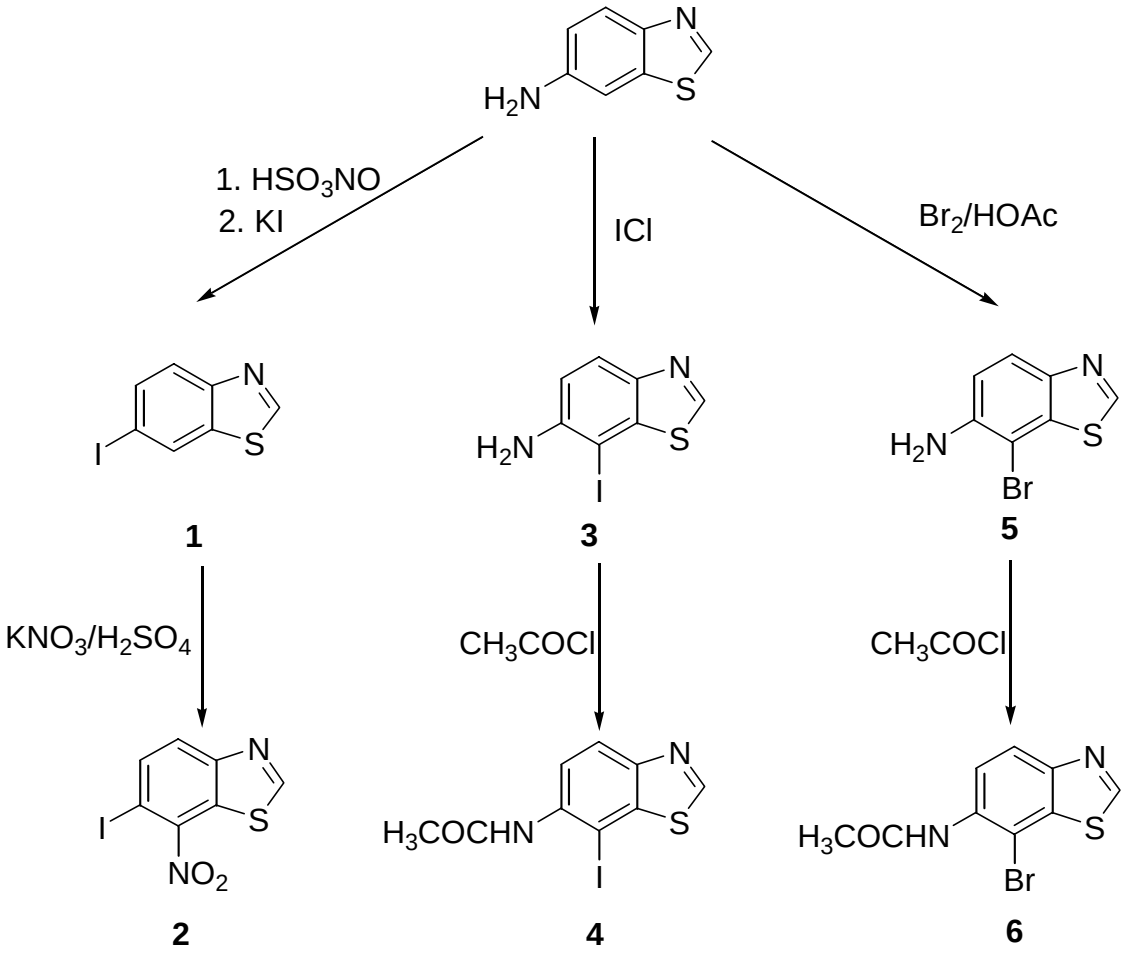
Arylation of benzothiazoles using palladium as catalyst was efficiently carried out mostly in position 2, while 6-bromo-2-methylbenzothiazole was coupled with arylzinc chloride in position 6.[3] Furthermore, direct arylation in position 2 with iodoarene was achieved with cobalt and Cu_2O as catalyst.[4]

In connection with our studies on the synthesis and properties of substituted benzothiazoles,[5] we turned our attention on the preparation and homocoupling of 6,7-disubstituted benzothiazoles, one of substituents being halogen, by copper in different oxidation states. The copper(I) thiophen-2-carboxylate (CuTC) promoted reductive homocoupling reaction was chosen because it successfully coupled aryl, heteroaryl, and alkenyl iodides and bromides bearing a coordinating *ortho*-substituent at ambient

temperature in high yield.[6] In addition CuTC can be easily prepared on multigram scale from thiophene-2-carboxilic acid and Cu_2O, and handled without any special precaution.

RESULTS AND DISCUSSION

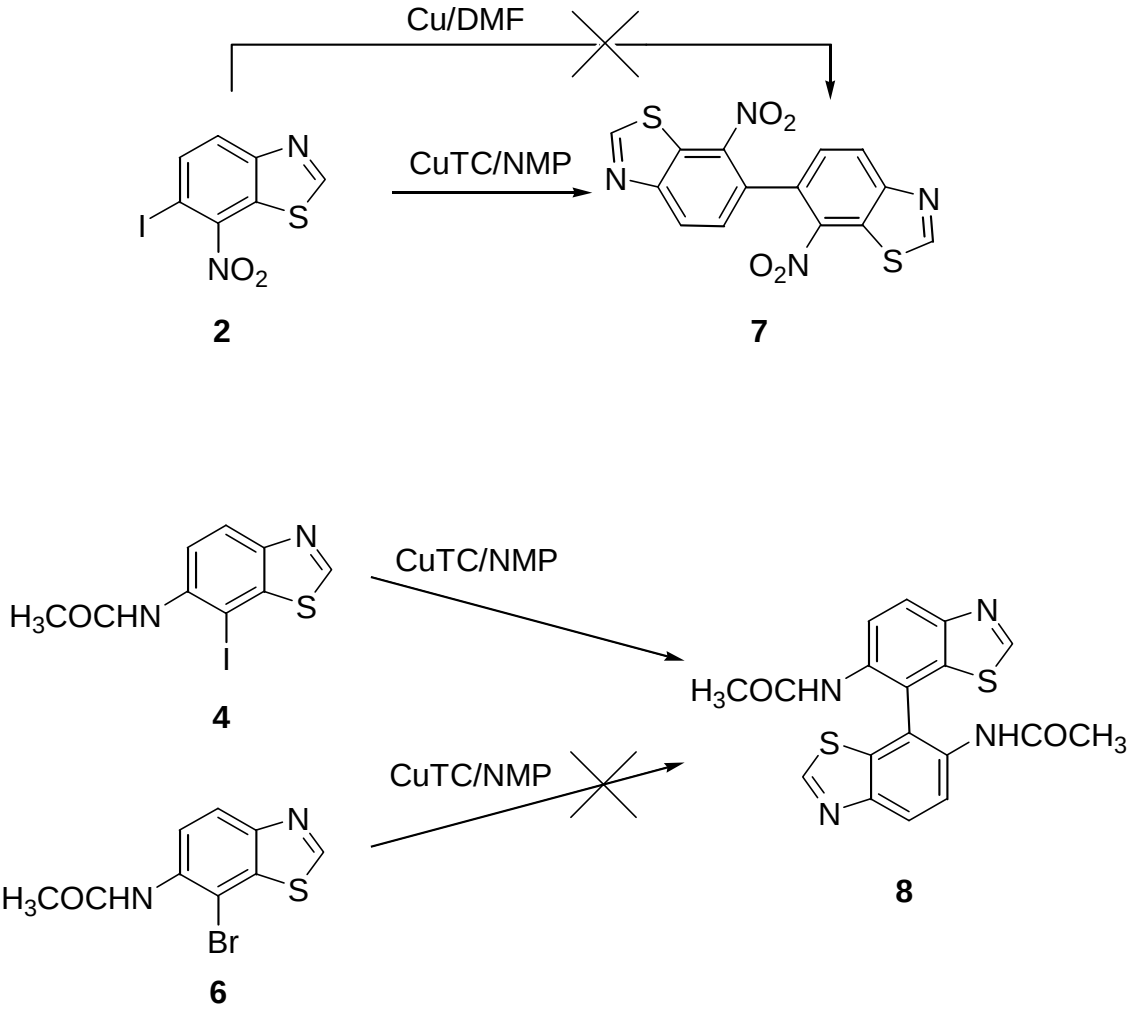
Preparation of 6,7-disubstituted benzothiazoles as starting compounds for homocoupling reaction is shown in Scheme 1.



Scheme 1

There are two ways for preparation of substituted 6- or- 7-halogenobenzothiazoles from readily accessible 6-aminobenzothiazole. Diazotization with nitrosylsulfate in acetic acid followed by Sandmeyer reaction gave 6-iodobenzothiazole (**1**) in moderate yield (54 %). Although 6-iodobenzothiazole has been previously mentioned as a reagent in one patent[7] there exist no literature data on the preparation and characterization of this compound. Therefore, the synthesis and X-Ray structure characterization of 6-iodobenzothiazole is given in this article. Nitration of **1** with KNO_3 in sulfuric acid gave 6-iodo-7-nitrobenzothiazole (**2**) in yield of 80 %. Halogenation of starting 6-aminobenzothiazole afford 6-amino-7-iodobenzothiazole (**3**) and 6-amino-7-bromobenzothiazole (**5**),[8] respectively. The yield of

compound (**3**) strongly depends on the method of preparation and purification. Thus, we found that iodination with ICl in acetic acid affords **3** in low yield (cca 30 %) opposite to iodination with ICl in diluted HCl giving good yield (70 %). Purification of compound (**3**) was performed using dry column chromatography, as not time consuming method for purification of large quantities of crude product. The amino derivatives (**3**) and (**5**) were transformed into corresponding acetyl derivatives, 6-acetylamino-7-iodobenzothiazole (**4**), and 6-acetylamino-7-bromobenzothiazole (**6**), respectively. Our approach to the homocoupling of substitueted benzothiazoles (**2**), (**4**), and (**6**) is outlined in Scheme 2.



Scheme 2

Attempt to form C-C bond between two benzothiazole using the Ullmann coupling reaction of 6-iodo-7-nitrobenzothiazole (**2**) with activated copper in DMF was unsuccessful. In analogy to oxidative homocoupling of substituted 2-aminonaphtalene,[9] we tried to couple 6-aminobenzothiazole directly using Cu(II)-salts. This method was unsuccessful, too. Homocoupling of substituted benzothiazole was successful when CuTC promoted method was used. Thus, iodo derivatives (**2**) and (**4**) were homocoupled in NMP with 2.5 eq CuTC at room temperature in very good yield (90 %). Isolation of

7,7'-dinitro-6,6'-bibenzothiazole (**7**) and 6,6'-diacetylamino-7,7'-bibenzothiazole (**8**) was quite simple. Pouring the reaction mixture in diluted ammonia provided compounds (**7**) and (**8**) in almost pure form. In spite of the fact homocoupling of bromoaryl derivative is described in literature,[6] we didn't succeed to couple the compound (**6**) with CuTC/NMP. We carried out the homocoupling at 70° C, and prolonged reaction time (5 days) but only the bromo derivative (**6**) was regenerated from reaction mixture.

The structures of new compounds were confirmed by elemental analysis, IR, ^{1}H, and ^{13}C NMR spectra, while structures of **1** and **7** were also additionally confirmed by X-Ray structure analysis on single crystals. The X-Ray molecular structures of **1** and **7** are shown in Figures 1a and 1b, respectively.

The molecule of 6-iodobenzothiazole (**1**) is planar (Figure 1a). Molecular geometry is as expected.

Nitro groups in the molecule of 7,7'-dinitro-6,6'-bibenzothiazole (**7**) are in *trans* position (Figure 1b). The molecule is not planar with the dihedral angle between planes calculated through two benzothiazole ring atoms of 70.4(1)°.

(a) (b)

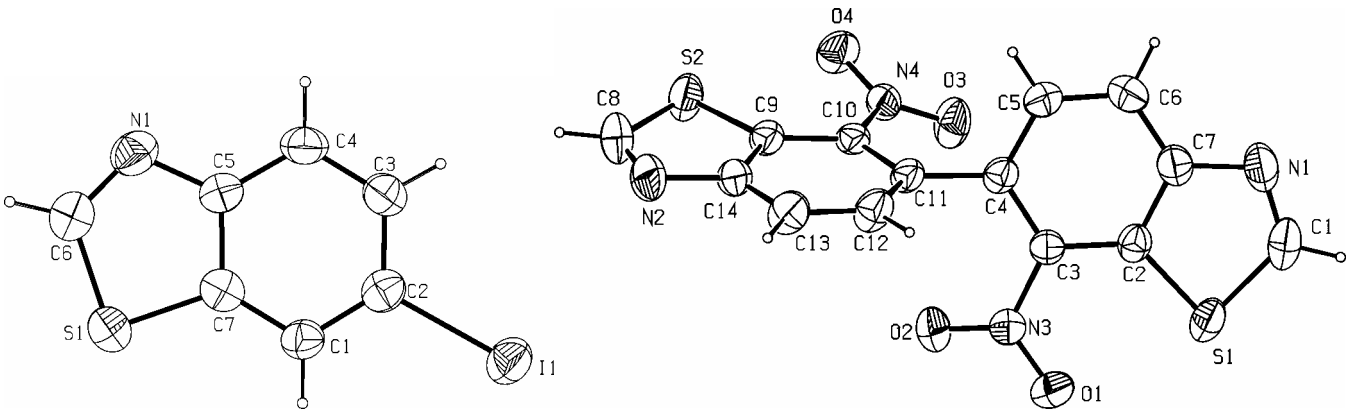


Figure 1. ORTEP drawings of molecular structures of **1** and **7**

We can conclude that successful CuTC promoted homocoupling is carried out only with iodo-substituted benzothiazoles (**2**) and (**4**) in excellente yield.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage microscope and are uncorrected. IR spectra were recorded on a Nicolet Magna 760 spectrophotometer in KBr discs. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Gemini 300 or a Brucker Avance DPX 300 spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) relative to tetramethylsilane (TMS) as an internal standard, and coupling constants (J) are given in hertz (Hz). Elemental analyses were carried out in the Microanalytical laboratory at the Rudjer Boskovic Institute. All compounds were routinely checked by TLC with Merck silica gel 60F-254 glass plates.

6-Amino-7-bromobenzothiazole (**5**) was prepared according to the literature procedure.[8]

6-Iodobenzothiazole (1) To the mixture of concd H_2SO_4 (45 mL) and $NaNO_2$ (3.04 g, 44 mmol) prepared at 70 °C, cooled to 40 °C, 6-aminobenzothiazole (6.0 g, 40 mmol) in acetic acid (80 mL) was added and stirred at rt for 30 min. The stirred solution of KI (7.32 g, 44 mmol) in water (70 mL) was heated at 70 °C, and the previously prepared diazonium salt was added. After 30 min the reaction mixture was poured on ice and the crystals of crude product were filtered off, washed with water and dissolved in $CHCl_3$. The $CHCl_3$ solution was treated with 10 % $Na_2S_2O_3$, washed with water and dried. The solvent was evaporated, and the residue was crystallized from cyclohexane. Yield of colorless crystals was 5.54 g (53.3 %), mp 79-80 °C. IR (KBr, cm^{-1}): 3043, 1578, 1427, 1386, 861, 816, 799. ^{1}H NMR (DMSO-d_6, 300 MHz) δ: 9.35 (s, 1H), 8.61 (d, 1H, J=1.6 Hz), 7.88 (d, 1H, J=8.5 Hz), 7.88 (dd, 1H, J=1.7 Hz, J=8.6 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 157.5, 152.9, 136.6, 135.3, 131.3, 125.2, 91.2. Anal. Calcd for C_7H_4NIS: C, 32.20; H, 1.54; N, 5.36. Found: C, 32.34; H, 1.58; N, 5.21.

6-Iodo-7-nitrobenzothiazole (2) The 6-iodobenzothiazole (**1**) (10.5 g, 40 mmol) was added to a stirred solution of KNO_3 (8.4 g, 83 mmol) in concd H_2SO_4 (45 mL), and stirred at rt for 4 d. Reaction mixture was poured on crushed ice, and neutralized with ammonia. The obtained crystals were filtered off, washed with water and crystallized from toluene/cyclohexane (charcoal). Yield of pale yellow crystals was 9.94 g (80.8 %), mp 188-189 °C. IR (KBr, cm^{-1}): 1587, 1508, 1325, 1301, 855. ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 9.52 (s, 1H), 8.34 (d, 1H, J=8.4 Hz), 8.13 (d, 1H, J=8.4 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 160.4, 154.4, 145.4, 140.1, 131.2, 128.8, 88.7. Anal. Calcd for $C_7H_3N_2O_2IS$: C, 27.47; H, 0.99; N, 9.15. Found: C, 27.30; H, 1.02; N, 9.32.

6-Amino-7-iodobenzothiazole (3) A solution of ICl (15.0 g, 0.1 mol) in diluted HCl (18 mL of concd HCl and 60 mL of water) was added to a solution of 6-aminobenzothiazole (12 g, 80 mmol) in diluted HCl (9 mL of concd HCl and 120 mL of water). Reaction mixture was stirred at rt for 1 h and neutralized with saturated solution of $NaHCO_3$. The crude product was purified by dry column chromatography on SiO_2 with petrolether/AcOEt 8/2 to give colorless crystals 15.9 g (72.0 %), mp 130-132 °C. IR (KBr, cm^{-1}): 3448, 3359, 3050, 1611, 1586, 1540, 1465, 1449, 1387, 868, 844, 811. ^{1}H NMR (DMSO-d_6, 300 MHz), δ: 9.01 (s, 1H), 7.76 (d, 1H, J= 8.7 Hz), 6.95 (d, 1H, J=8.7 Hz), 5.56 (s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 148.8, 148.2, 143.6, 142.8, 123.7, 114.7, 70.2. Anal. Calcd for $C_7H_5N_2IS$: C, 30.45; H, 1.38; N, 10.15. Found: C, 30.63; H, 1.46; N, 9.88.

6-Acetylamino-7-iodobenzothiazole (4) To a stirred mixture of 6-amino-7-iodobenzothiazole (**3**) (2.75 g, 10 mmol), and Et_3N (1.4 mL) in 1,2-dichlorethane, acetyl chloride (1.5 mL, 20 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h, and the crude product was filtered off, washed

with 1,2-dichlorethane and dried. The product was suspended in water, filtered off and crystallized from EtOH/ $CHCl_3$ (1/1). Yield of colorless crystals was 2.95 g (92.8 %), mp 244 °C. IR (KBr, cm^{-1}): 3265, 1658, 1526, 1462, 1377. ^1H NMR (DMSO-d_6, 300 MHz), δ: 9.74 (s, 1H), 9.47 (s, 1H), 8.06 (d, 1H, J=8.7 Hz), 7.52 (d, 1H, J=8.7 Hz), 2.10 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 168.6, 155.4, 148.0, 142.6, 138.2, 125.6, 122.6, 87.3, 23.2. Anal. Calcd for $C_9H_7N_2OIS$: C, 33.98; H, 2.22; N, 9.88. Found: C, 34.12; H, 2.38; N, 8.67.

6-Acetylamino-7-bromobenzothiazole (6) To a stirred mixture of 6-amino-7-bromobenzothiazole (**5**) (2.30 g, 10 mmol), and Et_3N (1.4 mL) in chloroform (150 mL), acetyl chloride (1.5 mL, 20 mmol) was added dropwise. The reaction mixture was stirred at rt for 1 h, and the solution was washed with water, dried and evaporated to a volume of 15 mL. After cooling overnight the obtained colorless crystals were filtered off. Yield was 2.23 g (82.4 %), mp 204 °C. IR (KBr, cm^{-1}): 3245, 1672, 1649, 1529, 1384. ^1H NMR (DMSO-d_6, 300 MHz), δ: 9.79 (s, 1H), 9.44 (s, 1H), 8.07 (d, 1H, J=8.7 Hz), 7.71 (d, 1H, J=8.7 Hz), 2.12 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 168.7, 149.7, 137.4, 134.4, 125.8, 121.9, 23.1. Anal. Calcd for $C_9H_7N_2OBrS$: C, 39.87; H, 2.60; N, 10.33. Found: C, 39.79; H, 2.71; N, 10.48.

7,7'-Dinitro-6,6'-bibenzothiazole (7) To a solution of 6-iodo-7-nitrobenzothiazole (**2**) (3.02 g, 10 mmol) in NMP (40 mL), CuTC (4.7 g, 25 mmol) was added under N_2. The flask was stoppered, and the reaction mixture was stirred at rt for 2 h. The mixture was poured in aq. NH_3 (10 % 500 mL), and the product was filtered off, washed with diluted NH_4OH, and water. Crystallization from xylene yielded 1.66 g (92.7 %) of pale yellow crystals, mp 312-313 °C. IR (KBr, cm^{-1}): 3043, 1603, 1514, 1323, 1308, 860, 851. ^1H NMR (DMSO-d_6, 600 MHz), δ: 9.65 (s, 2H), 8.56 (d, 2H, J=8.2 Hz), 7.68 (d, 2H, J=8.2 Hz). ^{13}C NMR (DMSO-d_6, 151 MHz), δ: 161.4, 154.6, 140.1, 133.9, 130.4, 129.3, 129.2. Anal. Calcd for $C_{14}H_6N_4O_4S_2$: C, 46.92; H, 1.69; N, 15.63. Found: C, 47.11; H, 1.44; N, 15.41.

6,6'-Diacetylamino-7,7'-bibenzothiazole (8) To a solution of 6-acetylamino-7-iodobenzothiazole (**4**) (3.22 g, 10 mmol) in NMP (35 mL), CuTC (4.7 g, 25 mmol) was added under N_2. The flask was stoppered, and the reaction mixture was stirred at rt for 3 days. The mixture was poured in aq. NH_3 (10 % 500 mL), and the obtained product was filtered off, washed with diluted NH_4OH, and water. Crystallization from DMF yielded 1.69 g (88.5 %) of colorless crystals, mp >300 °C. IR (KBr, cm^{-1}): 3448, 3245, 3074, 1683, 1593, 1523, 1279. ^1H NMR (DMSO-d_6, 300 MHz), δ: 9.33 (s, 2H), 9.16 (s, 2H), 8.15 (d, 2H, J=8.4 Hz), 7.88 (d, 2H, J=8.6 Hz), 1.77 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ: 168.8, 150.2, 135.0, 133.8, 124.6, 124.0, 122.9, 23.0. Anal. Calcd for $C_{18}H_{14}N_4O_2S_2$: C, 56.53; H, 3.69; N, 14.65. Found: C, 56.48; H, 3.78; N, 14.43.

X-Ray Crystallographic Structure Determination of 1 and 7

The data collection for both structures were carried out on Xcalibur four-circle kappa geometry single-crystal diffractometer with Xcalibur Sapphire 3 CCD detector by applying the CrysAlis Software system, Version 171.23 at 296 K.[10] Structure solutions were determined by direct method with the SHELXS program.[11] The coordinates and anisotropic thermal displacement parameters for all non-hydrogen atoms were refined by the least-squares methods based on F^2 using the SHELXL97 program.[12] The coordinates of the hydrogen atoms belonging to the phenyl and thiazolyl ring carbon atoms were generated at ideal geometrical positions [Csp^2-H 0.93 Å, U_{iso}(H) = 1.2 U_{eq}(C)] and refined applying the riding model. The molecular graphics were done using the PLATON98 program.[13]

Compound (**1**): C_7H_4NIS, M_r = 261.08, monoclinic, $P\ 2_1/a$, a = 12.3861(12) Å, b = 4.6598(4) Å, c = 13.9082(12) Å, β = 95.919(7)°, V = 798.46(12) Å^3, Z = 4, D_c = 2.172 g cm^{-3}, μ = 4.2 mm^{-1}, F(000) = 488, No. measured reflections = 8831, No. independent reflections (R_{int}) = 1725 (0.124), No. refined parameters = 92, No. observed reflections with $I \geq 2\sigma(I)$ = 1649, R = 0.0447, wR = 0.1152, R (all data) = 0.0466, wR (all data) = 0.1130, S = 1.12.

Compound (**7**): $C_{14}H_6N_4O_4S_2$, M_r = 358.37, orthorombic, $P\ bca$, a = 8.4932(7) Å, b = 14.0757(10) Å, c = 24.2363(18) Å, V = 2897.4(4) Å^3, Z = 8, D_c = 1.643 g cm^{-3}, μ = 0.4 mm^{-1}, F(000) = 1456, No. measured reflections = 34022, No. independent reflections (R_{int}) = 3142 (0.067), No. refined parameters = 217, No. observed reflections with $I \geq 2\sigma(I)$ = 3095, R = 0.0721, wR = 0.1344, R (all data) = 0.0739, wR (all data) = 0.1336, S = 1.38.

Supplementary material

CCDC 610516 & 610517 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; email: deposit@ccdc.cam.ac.uk]. Structure factors table is available from the authors.

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