Synthesis and crystal structures of some new 2-(diphenylamino)-4,5-disubstituted thiazole derivatives

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The reactions of diphenylamine and benzoyl isothiocyanates with phenacyl bromide or methyl 2-bromoacetate in the presence of triethylamine yield 2,4,5-trisubstituted thiazole derivatives. The molecular structures of [2-(diphenylamino)-4-phenylthiazol-5-yl](*o*-tolyl) methanone and methyl 4-(4-chlorophenyl)-2-(diphenylamino)thiazole-5-carboxylate have been fully determined by means of single crystal X-ray diffraction methods.

Keywords: diphenylamine, benzoyl isothiocyanate, phenacyl bromide, methyl 2-bromoacetate, 2,4,5-trisubstituted thiazoles

Thiazoles are some of the most commonly encountered heterocycles amongst compounds of biological interest and in bioactive natural products of microbial and marine origin. They exhibit important biological activities such as antitumour, antifungal, antibiotic, antiviral and antibacterial properties.[1–6] In nature, the thiazolium ring is the chemically active centre in the coenzyme derived from vitamin B_1.[7] Synthetic thiazoles also occupy a prominent position in drug discovery processes and this ring system is found in a number of marketed drugs.[8,9] Several methods for the synthesis of thiazole derivatives have been developed,[10–16] of which the most widely used is the Hantzsch synthesis.[17] In recent years, the synthesis of many new 2,4,5-trisubstituted thiazole derivatives with varied biological activities has been developed.[18–22]

In this paper we have fully characterised some new 2,4,5-trisubstituted thiazole derivatives **5a**–**c** and **6a**–**c** which were prepared by condensation of diphenylamine and benzoyl isothiocyanates with phenacyl bromide or with methyl 2-bromoacetate (Scheme 1).

Results and discussion

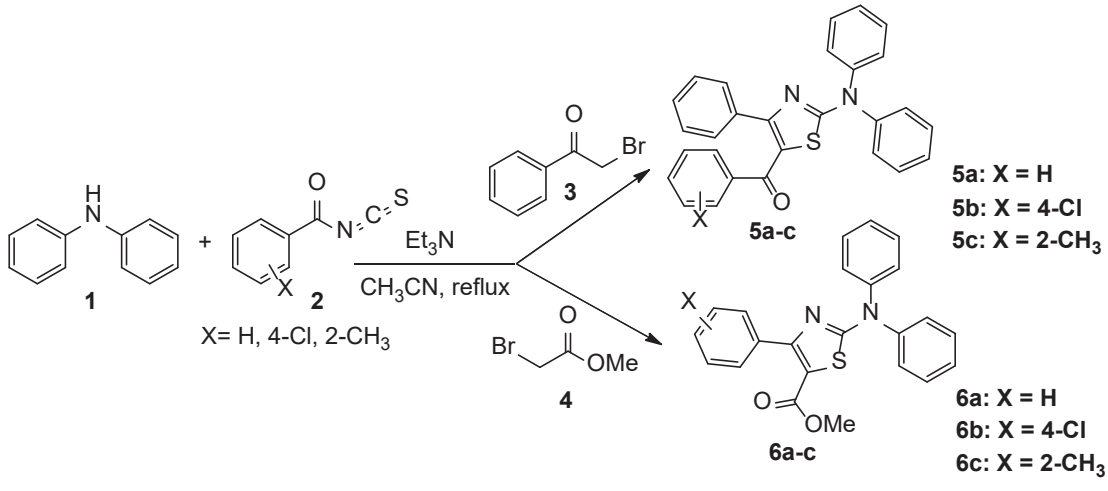
The reactions of diphenylamine and benzoyl isothiocyanates with phenacyl bromide in refluxing acetonitrile in the presence of triethylamine furnished 2,4,5-trisubstituted thiazole derivatives **5a**–**c**. The molecular and crystal structure of compound **5c** has been fully elucidated by means of X-ray diffraction analysis.

The ^{1}H NMR spectrum of compound **5c** showed a singlet at δ 2.39 for the CH_3 protons and the protons of the phenyl rings gave rise to characteristic signals in the aromatic region of the spectrum (δ 6.80–7.53). The ^{13}C NMR spectrum of compound **5c** showed CH_3 and C=O signals at 19.8 and 190.4 ppm respectively. In the IR spectrum of compound **5c**, the C=O stretching band was observed at 1600 cm^{-1}. The mass spectrum of **5c** displayed the molecular ion peak (M^+) at *m/z* 446.

A proposed mechanism for the preparation of **5** is outlined in Scheme 2. Addition of diphenylamine to the aroyl isothiocyanates affords intermediate **7**. Nucleophilic substitution on the bromomethyl group of **3** by sulfur produces **8**, from which an intramolecular cyclisation reaction results in intermediate **9**. The latter is in equilibrium with intermediate **10** which undergoes cyclisation and dehydration to afford product **5**.[23]

The synthetic route for preparation of compounds **6a**–**c** is outlined in Scheme 1. These compounds were prepared by a one-pot condensation of the benzoyl isothiocyanates with methyl 2-bromoacetate and diphenylamine in the presence of triethylamine.

Compounds **6a**–**c** were characterised by means of IR, ^{1}H NMR, ^{13}C NMR and mass spectrometric methods together with elemental analysis. The molecular and crystal structure of compound **6b** has been fully elucidated by means of X-ray diffraction analysis.



Scheme 1 Preparation of 2,4,5-trisubstituted thiazole derivatives **5a–c** and **6a–c**.

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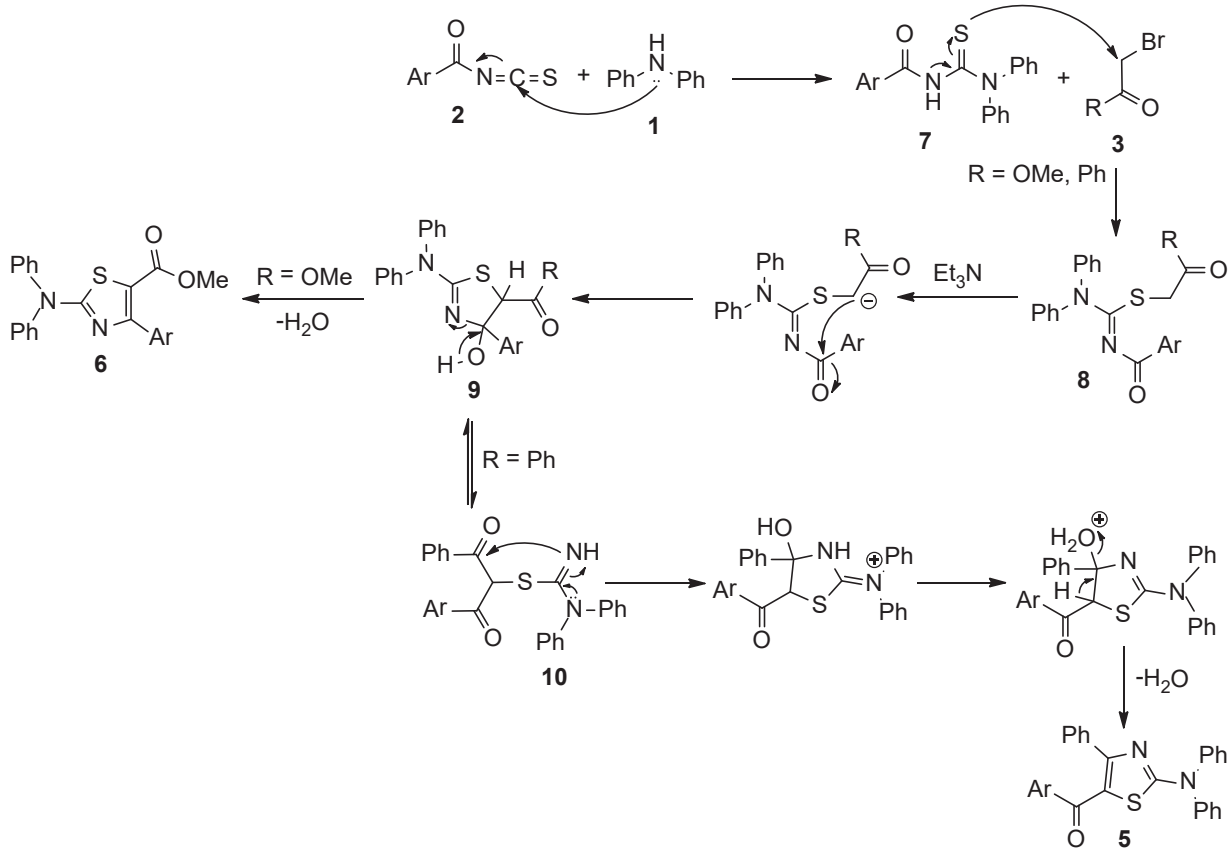

Scheme 2 Proposed mechanism for the formation of **5** and **6**.

The ^{1}H NMR spectrum of **6b** showed a singlet at δ 3.73 for the OCH_3 proton and the phenyl ring protons gave rise to characteristic signals in the region 7.28–7.79 ppm. The ^{13}C NMR spectrum of **6b** showed OCH_3 and C=O carbons at 51.9 and 169.8 ppm respectively. In the IR spectrum of **6b**, the C=O and C–O bands were observed at 1696 and 1247 cm^{-1} respectively. The mass spectrum of **6b** displayed the molecular ion peak (M^+) at *m/z* 420.

A proposed mechanism for the preparation of **6** is outlined in Scheme 2. The reaction starts with the formation of **7** by addition of diphenylamine (**1**) to the aroyl isothiocyanate **2**. Subsequent nucleophilic alkylation of **7** with methyl bromoacetate yields intermediate **8**. Cyclisation and dehydration of **8** affords thiazoles **6**.

Experimental

All reagents were purchased from Merck and Fluka and were used without further purification. The structures of the compounds were determined on the basis of their elemental analyses, IR, ^{1}H NMR and ^{13}C NMR spectroscopy, mass spectra and single-crystal X-ray analysis. Melting points were measured on an Electrothermal 9100 apparatus. IR spectra were measured on a Shimadzu IR-460 spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz respectively on a Bruker Ultrashield 400 Avance III with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded on an Agilent Technology (HP) 5973 mass spectrometer operating at an ionisation potential of 70 eV. Elemental analysis for C, H and N were performed using a PerkinElmer CHNS-O Elemental Analyser. Benzoyl isothiocyanates were prepared according to the reported procedure.[24]

Synthesis of 2-(diphenylamino)-4,5-disubstituted-thiazole derivatives; general procedure

A solution of triethylamine (0.10 g, 1 mmol) in acetonitrile (1 mL) was added dropwise to a stirred solution of diphenylamine (0.17 g, 1 mmol), the substituted benzoyl isothiocyanate (1 mmol) and phenacyl bromide (0.20 g, 1 mmol) or methyl 2-bromoacetate (0.15 g, 1 mmol) in acetonitrile (5 mL) and the mixture was refluxed for 2 h. After completion of the reaction, which was monitored by TLC, the product was filtered off and recrystallised from ethanol.

[2-(Diphenylamino)-4-phenylthiazol-5-yl](phenyl)methanone (**5a**): Orange crystals; yield 80% (0.35 g); m.p. 212–214 °C (lit.[25] 214–215 °C); IR (KBr) (ν_{max} cm^{-1}): 3050 ($CH_{aromatic}$), 1599 (C=O), 1334 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06–7.17 (m, 5H, ArH), 7.26–7.37 (m, 5H, ArH), 7.43–7.48 (m, 4H, ArH), 7.51–7.55 (m, 6H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.3 (C), 126.2 (4CH), 126.9 (2CH), 127.6 (2CH), 127.7 (2CH), 128.6 (CH), 129.3 (2CH), 129.8 (4CH), 130.0 (2CH), 131.7 (CH), 134.7 (C), 137.9 (CH), 144.2 (2C), 158.1 ($C4_{thiazole}$), 170.6 ($C2_{thiazole}$), 189.1 (C=O); MS *m/z* (%): 432 (M^+, 100), 431 ([M – 1]$^+$, 78), 385 (18), 355 (13), 225 (16), 133 (24), 105 (35), 77 (62). Anal. calcd for $C_{28}H_{20}N_2OS$ (432.54): C, 77.75; H, 4.66; N, 6.48; found: C, 77.80; H, 4.61; N, 6.44%.

(4-Chlorophenyl)[2-(diphenylamino)-4-phenylthiazol-5-yl]methanone (**5b**): Orange crystals; yield 90% (0.42 g); m.p. 185–187 °C; IR (KBr) (ν_{max} cm^{-1}): 3060 ($CH_{aromatic}$), 1610 (C=O), 1331 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (dt, 2H, ^3J = 7.6 Hz, ^4J = 2 Hz, ArH), 7.18 (t, 2H, ^3J = 8.0 Hz, ArH), 7.28–7.37 (m, 5H, ArH), 7.43–7.56 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 124.2 (C), 126.2 (4CH), 127.0 (2CH), 127.8 (2CH), 127.9 (2CH), 129.3 (2CH), 129.8 (4CH), 131.2 (2CH), 131.9 (CH), 133.2 (C), 134.6 (C), 137.9 (C), 144.1 (2C), 156.7 ($C4_{thiazole}$), 170.6 ($C2_{thiazole}$), 188.8 (C=O); MS *m/z* (%): 466 (M^+, 100), 465 ([M – 1]$^+$, 74), 389 (9), 194 (18), 225 (18), 167 (28), 105 (34), 77 (57). Anal. calcd for $C_{28}H_{19}ClN_2OS$ (466.98): C, 72.02; H, 4.10; N, 6.00; found: C, 71.99; H, 4.10; N, 5.84%.

[2-(Diphenylamino)-4-phenylthiazol-5-yl](o-tolyl)methanone (**5c**): Orange crystals; yield 78% (0.35 g); m.p. 180–182 °C; IR (KBr) (ν_{max} cm^{-1}): 3050 ($CH_{aromatic}$), 1600 (C=O), 1331 (C–N); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (s, 3H, CH_3), 6.82 (t, 1H, ^3J = 7.6 Hz, ArH), 6.99–7.14 (m, 6H, ArH), 7.27–7.33 (m, 4H, ArH), 7.44 (t, 4H, ^3J = 7.6 Hz, ArH), 7.51 (m, 4H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.8

(CH_3), 124.9 (CH), 126.2 (4CH), 126.9 (2CH), 127.3 (2CH), 128.5 (CH), 128.7 (2CH), 129.5 (2CH), 129.8 (4CH), 129.9 (C), 130.5 (CH), 134.4 (C), 136.3 (C), 138.6 (C), 144.1 (2C), 159.2 ($C4_{thiazole}$), 171.1 ($C2_{thiazole}$), 190.4 (C=O); MS *m/z* (%): 446 (M^+, 73), 391 (34), 328 (100), 252 (35), 118 (64), 105 (16), 91 (72), 77 (38). Anal. calcd for $C_{29}H_{22}N_2OS$ (446.56): C, 78.00; H, 4.97; N, 6.27; found: C, 77.93; H, 4.92; N, 6.18%.

Methyl 2-(diphenylamino)-4-phenylthiazole-5-carboxylate (**6a**): Yellow crystals; yield 77% (0.30 g); m.p. 213–215 °C (lit.[26] 212.1–212.6 °C); IR (KBr) (ν_{max} cm^{-1}): 1700 (C=O), 1332 (C–N), 1250 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H, OCH_3), 7.28–7.32 (m, 2H, ArH), 7.41–7.49 (m, 11H, ArH), 7.80–7.82 (m, 2H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.8 (OCH_3), 112.1 (C), 126.2 (4CH), 126.8 (2CH), 127.6 (2CH), 129.1 (CH), 129.8 (4CH), 129.9 (2CH), 134.4 (C), 144.2 (2C), 159.4 ($C4_{thiazole}$), 162.2 ($C2_{thiazole}$), 169.7 (C=O); MS *m/z* (%): 386 (M^+, 100), 385 ([M – 1]$^+$, 92), 327 (14), 225 (15), 180 (13), 133 (15), 105 (2), 77 (37). Anal. calcd for $C_{23}H_{18}N_2O_2S$ (386.47): C, 71.48; H, 4.69; N, 7.25; found: C, 71.57; H, 4.70; N, 7.30%.

Methyl 4-(4-chlorophenyl)-2-(diphenylamino)thiazole-5-carboxylate (**6b**): Yellow crystals; yield 83% (0.35 g); m.p. 192–194 °C; IR (KBr) (ν_{max} cm^{-1}): 1696 (C=O), 1333 (C–N), 1247 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.73 (s, 3H, OCH_3), 7.28–7.34 (m, 2H, ArH), 7.37–7.39 (m, 2H, ArH), 7.42–7.48 (m, 8H, ArH), 7.78 (dt, 2H, ^3J = 6.8 Hz, ^4J = 2.0 Hz, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 51.9 (OCH_3), 112.2 (C), 126.2 (4CH), 126.9 (2CH), 127.8 (2CH), 129.8 (4CH), 131.4 (2CH), 132.7 (C), 135.0 (C), 144.1 (2C), 158.0 ($C4_{thiazole}$), 162.1 ($C2_{thiazole}$), 169.8 (C=O). MS *m/z* (%): 420 (M^+, 100), 419 ([M – 1]$^+$, 90), 361 (15), 225 (22), 194 (22), 167 (33), 123 (22), 77 (45). Anal. calcd for $C_{23}H_{17}ClN_2O_2S$ (420.91): C, 65.63; H, 4.07; N, 6.66; found: C, 65.72; H, 4.10; N, 6.70%.

Methyl 2-(diphenylamino)-4-(o-tolyl)thiazole-5-carboxylate (**6c**): Yellow crystals; yield 70% (0.28 g); m.p. 188–190 °C; IR (KBr) (ν_{max} cm^{-1}): 1710 (C=O), 1325 (C–N), 1256 (C–O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.73 (s, 3H, OCH_3), 7.19–7.25 (m, 2H, ArH), 7.30–7.37 (m, 4H, ArH), 7.40–7.46 (m, 8H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.9 (CH_3), 51.7 (OCH_3), 104.8 (C), 125.9 (2CH), 126.9 (4CH), 127.7 (2CH), 128.3 (CH), 129.8 (CH), 130.51 (2CH), 131.1 (2CH), 135.1 (C), 136.7 (C), 142.3 (C), 144.2 (2C), 163.7 ($C2_{thiazole}$), 166.6 (C=O); MS *m/z* (%): 400 (M^+, 77), 399 ([M – 1]$^+$, 40), 341 (100), 259 (30), 212 (27), 169 (30), 147 (60), 77 (57). Anal. calcd for $C_{24}H_{20}N_2O_2S$ (400.49): C, 71.98; H, 5.03; N, 6.99; found: C, 71.89; H, 5.03; N, 7.04%.

Crystal structure analysis

The X-ray diffraction measurements of **5c** and **6b** were made at room temperature on a Bruker APEX II[27] single crystal diffractometer equipped with an area detector using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). Orange and yellow prismatic crystals of **5c** and **6b** were mounted on glass fibres and used for data collection. Cell constants and orientation matrices for data collection were obtained by least-squares refinement of diffraction data from 999 reflections. The structures were solved by direct methods and refined by full-matrix least-squares procedures (based on F_o^2),[28–30] first with isotropic thermal parameters and then with anisotropic thermal parameters in the last cycles of refinement for all the non-hydrogen atoms for both structures. The hydrogen atoms were introduced into the geometrically calculated positions and refined riding on the corresponding parent atoms. CCDC990840 for compound **5c** and CCDC989214 for compound **6b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via*
https://summary.ccdc.cam.ac.uk/structure-summary-form

A summary of the crystal data, experimental details and refinement results for **5c** and **6b** is given in Table 1.

An ORTEP view of compound **5c** is shown in Fig. 1 together with the atomic labelling scheme. A list of the most important bond distances and angles is reported in Table 2. The molecule consists of five rings, A (C1, C2, C3, N1, S) for the thiazole, B (C5, C6, C7, C8, C9, C10, C11) for the tolyl and C (C12, C13, C14, C15, C16, C17), D (C18, C19, C20, C21, C22, C23) and E (C24, C25, C26, C27, C28, C29) for the phenyl groups, which are nearly planar and are twisted with respect to the mean plane of the thiazole unit with dihedral angles of 58.94(1)°, 42.00(1)°, 35.16(1)° and 77.71(1)° respectively for A^B, A^C, A^D and A^E. The part of the molecule consisting of the thiazole ring and atoms C4, N2, C18 and C24 is nearly planar and the atom O deviates from it by 0.2910(1) Å. The N–C24 and N2–C18 bond distances are similar [1.444(2) Å and 1.434(2) Å respectively]

Table 1 Crystal data, collection and refinement details for compounds **5c** and **6b**

	5c	**6b**
Formula	$C_{29}H_{22}N_2OS$	$C_{23}H_{17}ClN_2O_2S$
Formula weight	446.56	420.90
Crystal system	Monoclinic	Triclinic
Space group	C2/c	P-1
Unit cell dimensions	a = 24.621(2) Å	a = 9.578(2) Å
	b = 10.1400(9) Å	b = 10.192(3) Å
	c = 20.4896(19) Å	c = 11.606(3) Å
		α = 71.807(4)°
	ß = 114.336(2)°	ß = 69.400(4)°
		γ = 87.865(4)°
Volume	4660.8(7) Å^3	1004.1(4) Å^3
Z	8	2
Density (calculated) g cm^{-3}	1.273	1.392
F(000)	1872	436
Absorption coefficient	0.163 mm^{-1}	0.317 mm^{-1}
Data collected	37204	14371
Unique data (R_{int})	7135	6091
Observed reflections	4135	3838
Parameters/restraints	299/0	263/0
Final R_1[a], wR_2[b] (Obs. data)	0.0486, 0.1170	0.0496, 0.1202
Final R_1[a], wR_2[b] (all data)	0.0975, 0.1384	0.0869, 0.1395
Goodness of fit on F^2 (S)	1.016	1.025
CCDC	990840	989214

[a] $R_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$.
[b] $wR_2 = [\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]]$.

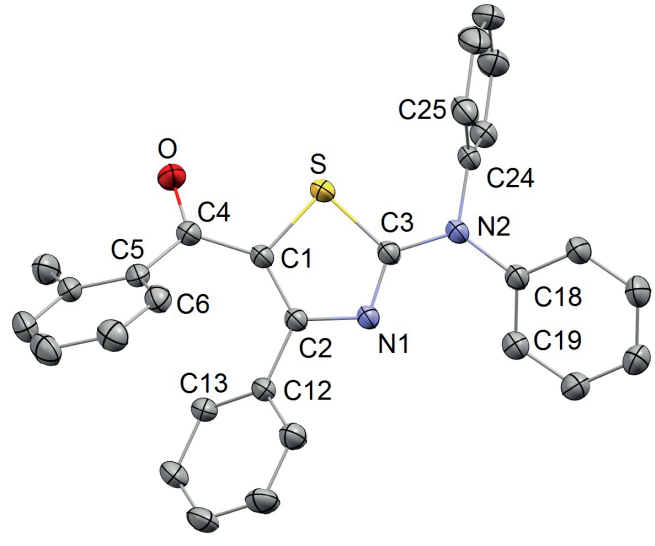

Fig. 1 ORTEP view and atom-numbering scheme of compound **5c**. The ellipsoids are drawn at the 30% probability level.

Table 2 Selected bond distances and bond angles for compound **5c**

Bond lengths/Å	
C1–C2	1.380(2)
C1–C4	1.462(2)
C1–S	1.7381(14)
C2–N1	1.3757(19)
C2–C12	1.4805(19)
C3–N1	1.3142(18)
C3–N2	1.3667(18)
C3–S	1.7394(15)
C4–O	1.2294(19)
C4–C5	1.490(2)
C18–N2	1.434(2)
C24–N2	1.4436(19)
Bond angles/°	
C2–C1–C4	134.66(13)
C2–C1–S	109.85(11)
C4–C1–S	115.46(11)
N1–C2–C1	115.63(12)
N1–C2–C12	117.06(13)
C1–C2–C12	127.29(13)
N1–C3–N2	125.52(13)
N1–C3–S	115.76(11)
N2–C3–S	118.72(11)
O–C4–C1	119.14(15)
O–C4–C5	121.01(15)
C1–C4–C5	119.66(14)
C3–N1–C2	110.20(12)
C3–N2–C18	124.77(12)
C3–N2–C24	116.76(12)
C18–N2–C24	118.47(11)
C1–S–C3	88.49(7)

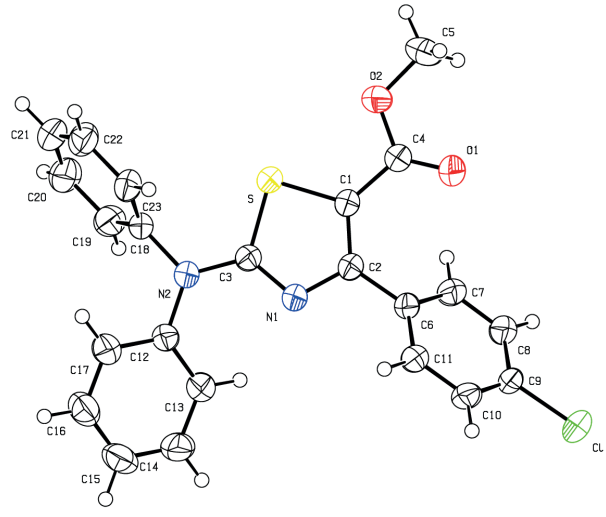

Fig. 2 ORTEP view and atom-numbering scheme of compound **6b**. The ellipsoids are drawn at the 50% probability level.

and are longer than N2–C3 [1.367(2) Å]. Considering the crystal packing of the molecule no notable intermolecular contacts are present.

An ORTEP view of the molecular structure of compound **6b** is shown in Fig. 2 together with the atomic labelling scheme. A list of the most important bond distances and angles is reported in Table 3. The molecular structure of compound **6b** strongly resembles that reported in the literature.[31] In the

Table 3 Selected bond lengths and bond angles for compound **6b**

Bond lengths/Å	
C1–C2	1.378(2)
C1–C4	1.467(2)
C1–S	1.7364(17)
C2–N1	1.372(2)
C2–C6	1.475(2)
C3–N1	1.312(2)
C3–N2	1.373(2)
C3–S	1.7443(17)
C4–O1	1.201(2)
C4–O2	1.341(2)
C5–O2	1.444(2)
C12–N2	1.430(2)
C18–N2	1.441(2
Bond angles/°	
C2–C1–C4	128.25(15)
C2–C1–S	109.82(12)
C4–C1–S	121.75(13)
N1–C2–C1	115.58(15)
N1–C2–C6	116.51(15)
C1–C2–C6	127.73(15)
N1–C3–N2	124.43(15)
N1–C3–S	115.12(12)
N2–C3–S	120.40(13)
O1–C4–O2	123.04(16)
O1–C4–C1	125.50(17)
O2–C4–C1	111.44(15)
C3–N1–C2	110.74(14)
C3–N2–C12	123.33(14)
C3–N2–C18	118.27(13)
C12–N2–C18	118.40(13)
C4–O2–C5	115.51(15)
C1–S–C3	88.66(8)

molecular structure of compound **6b**, the COOMe group is nearly planar and it shows a dihedral angle of 6.59(1)° with the plane of the thiazole ring. As seen from the value of the torsion angle S–C1–C4–O1 [172.70(5)°], the molecule has the C=O and S in an *anti*-periplanar conformation. Similarly, the exocyclic N2 atom and C12 and C18 attached to it, which form a planar moiety, are almost coplanar with the thiazole ring, due to the conjugation of the N-atom lone pair with the thiazole system. The dihedral angle between this mean plane and that of the thiazole system is 4.67(1)°. The mean plane of the 4-chlorophenyl moiety has a dihedral angle of 48.21(1)° with the thiazole-ring plane. In the crystal packing of the molecule there are no strong intermolecular contacts.

Conclusion

The present study reports the synthesis of 2,4,5-trisubstituted thiazole derivatives by condensation of diphenylamine and benzoyl isothiocyanates with phenacyl bromide or with methyl 2-bromoacetate. Single crystal X-ray diffraction analysis confirms the identity of the compounds.

We are grateful to the University of Sistan and Baluchestan Research Council for the partial support of this research.

Received 15 November 2015; accepted 28 February 2016
Paper 1503715 doi: 10.3184/174751916X14610676453088
Published online: 13 May 2016

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