

# One-step synthesis of substituted 4,7-bis[alkyl(aryl)imino]-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-dienes

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**Abstract**—Alkyl-(aryl) isocyanides react with benzoyl isothiocyanate in the presence of dialkyl acetylenedicarboxylates or dibenzoylacetylene in one-pot to afford highly substituted 4,7-bis[alkyl(aryl)imino]-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-dienes, with double insertion of the isocyanide, in 38–45% yields (based on the isocyanide).

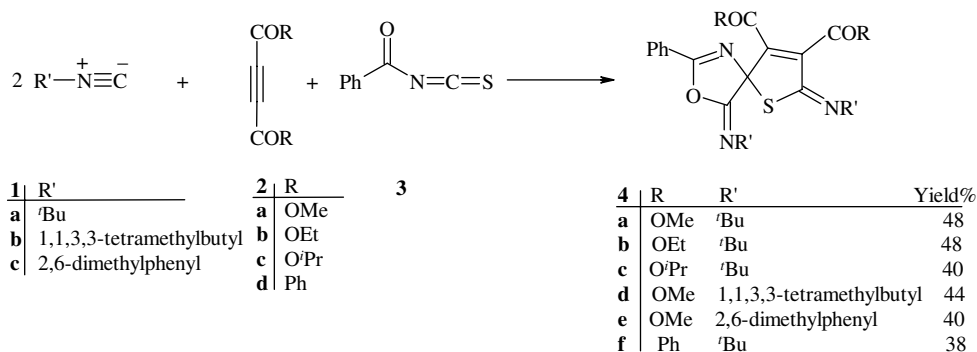
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Isocyanides are compounds with an extraordinary functional group; its unusual valence structure and reactivity have been discussed for over one and a half centuries.<sup>1</sup> Isocyanides are the only class of stable organic compounds with a formally divalent carbon. Owing to its reactivity, the isocyanide group differs fundamentally from other functional groups. One of the classic themes in the chemistry of isocyanides is heterocyclic synthesis.<sup>2,3</sup>

Multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution, and generally high yields of products, have attracted much attention in the context of combinatorial chemistry. Of pivotal importance in this area are the isocyanide based

MCRs such as the versatile Ugi and Passerini reactions.<sup>1–5</sup> MCRs have been used to create diversity oriented and biased combinatorial libraries, and for the synthesis of highly complex natural products.

In this letter, we describe a four-component condensation in which alkyl(aryl) isocyanides react with benzoyl isothiocyanate in the presence of dialkyl acetylenedicarboxylates or dibenzoylacetylene in one-pot to afford dialkyl 4,7-bis[alkyl(aryl)imino]-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-diene-8,9-dicarboxylates (**4a–e**) or [8-benzoyl-4,7-bis[(*tert*-butylimino)-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-dien-9-yl](phenyl)methanone (**4f**), with double insertion of the isocyanide, in 38–45% yields (based on the isocyanide, [Scheme 1](#)). To our



**Scheme 1.**

**Keywords:** Four-component reaction; Isocyanides; Azaspiroheterocycle.

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knowledge, the spirocyclic system **4** is unprecedented. Compounds **4a–f** are stable in the solid state and in aprotic organic solvents.

The reaction proceeded spontaneously in  $\text{CH}_2\text{Cl}_2$ , and was complete within a few hours. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of the crude products clearly indicated the formation of **4** (experimental procedure footnote<sup>6</sup>). The structures of compounds **4a–f** were deduced from their elemental analyses and their IR,  $^1\text{H}$ , and  $^{13}\text{C}$  NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate  $m/z$  values.

A single-crystal X-ray diffraction study confirmed the identity of compound **4b**.<sup>7</sup> An ORTEP diagram of **4b** is shown in Figure 1.

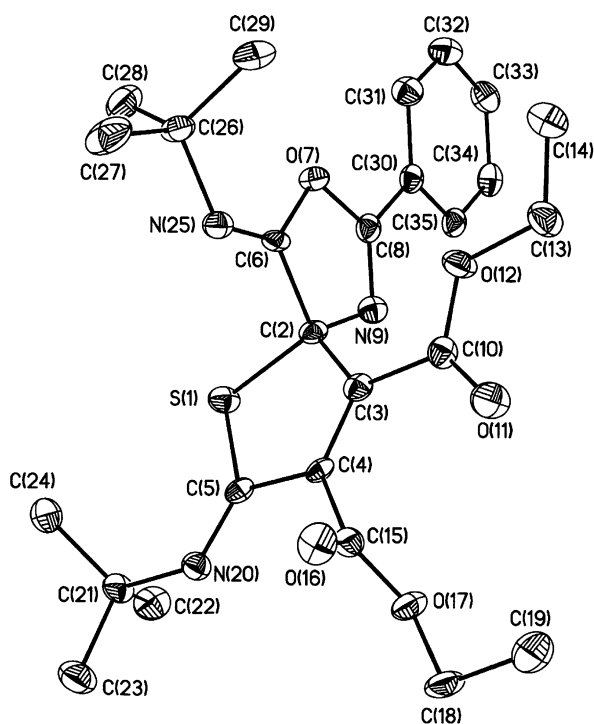


Figure 1. ORTEP diagram of X-ray crystal structure of **4b**.

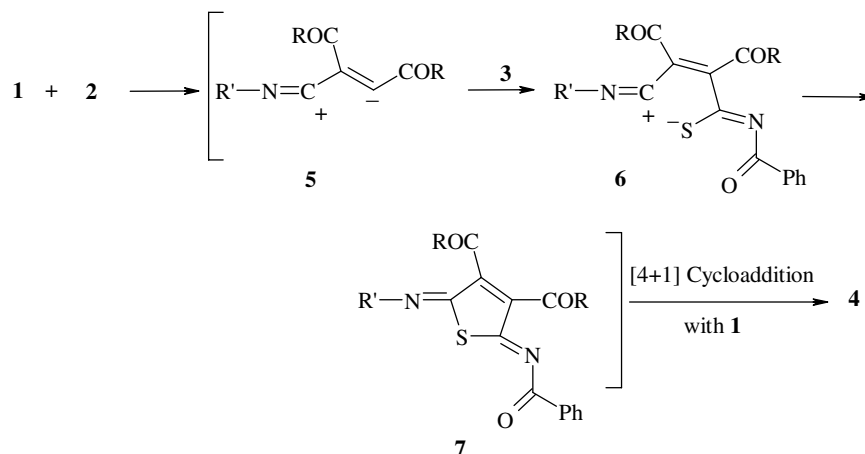
The  $^1\text{H}$  NMR spectrum of **4a** exhibited four single sharp lines readily recognized as arising from *tert*-butyl ( $\delta$  1.33 and 1.37 ppm) and methoxy ( $\delta$  3.90 and 3.96 ppm) protons along with multiplets ( $\delta$  7.50–8.02 ppm) for the aromatic protons. The  $^1\text{H}$  decoupled  $^{13}\text{C}$  NMR spectrum of **4a** showed 18 distinct resonances in agreement with the proposed structure. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **4b–f** are similar to those of **4a** except for the alkoxy and aromatic moieties, which exhibited characteristic signals with appropriate chemical shifts.

Mechanistically, it is conceivable that the reaction involves the initial formation of a 1:1 zwitterionic intermediate **5** between the isocyanide and the acetylenic compound,<sup>2–4</sup> which undergoes further reaction with **3** to produce **6**. Cyclization of intermediate **6** leads to **7**, which produces **4** by [4+1] cycloaddition<sup>8,9</sup> with **1** (Scheme 2).

This reaction provides a simple entry to the one-pot synthesis of dialkyl 4,7-bis[alkyl(aryl)imino]-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-diene-8,9-dicarbonylates and [8-benzyoyl-4,7-bis[(*tert*-butylimino)-2-phenyl-3-oxa-6-thia-1-azaspiro[4.4]nona-1,8-dien-9-yl](phenyl)methanone of potential synthetic interest. The present procedure has the advantage that, not only is the reaction performed under neutral conditions, but also the substances can be mixed without any activation or modification.

## References and notes

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Scheme 2.

I.; Nasiri, F.; Djahaniani, H. *Mol. Divers.* **2004**, *8*, 431–435.

6. Typical procedure for the synthesis of **4**: To a stirred solution of benzoyl isothiocyanate (0.16 g, 1 mmol) and dimethyl acetylenedicarboxylate (0.12 ml, 1 mmol) in 10 ml  $\text{CH}_2\text{Cl}_2$  was added *tert*-butyl isocyanide (0.16 g, 2 mmol) dropwise at  $-10^\circ\text{C}$  over 10 min. The reaction mixture was then allowed to warm up to room temperature and stand for 24 h. The solvent was removed under reduced pressure and the residue was recrystallized from diethyl ether to produce **4a**: yellow crystals; yield: 0.22 g (48%), mp  $182\text{--}184^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1744 (shoulder), 1734 and 1623 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.33$  ( $\text{CMe}_3$ ), 1.37 ( $\text{CMe}_3$ ), 3.90 (3H, s,  $\text{OCH}_3$ ), 3.96 (3H, s,  $\text{OCH}_3$ ), 7.50 (2H, t,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH), 7.60 (1H, t,  $^3J_{\text{HH}} = 7.7$  Hz, CH), 8.02 (2H, d,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.3$  ( $\text{CMe}_3$ ), 29.6 ( $\text{CMe}_3$ ), 52.6 ( $\text{OCH}_3$ ), 52.7 ( $\text{OCH}_3$ ), 55.8 (C–N), 57.9 (C–N), 87.2 (C), 126.1 (C), 128.4 (2CH), 128.8 (2CH), 133.0 (CH), 138.2 (C), 148.7 (C), 151.4 (C), 153.6 (C), 161.2 (C), 163.8 ( $\text{C}=\text{O}$ ), 164.3 ( $\text{C}=\text{O}$ ) ppm. Anal. Calcd for  $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$  (471.6): C, 61.13; H, 6.20; N, 8.91. Found: C, 61.19; H, 6.15; N, 8.98.

Compound **4b**: Pale yellow crystals; yield: 0.24 g (48%), mp  $176\text{--}177^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1738 (shoulder), 1730 and 1623 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.09$  (3H, t,  $^3J_{\text{HH}} = 7.2$  Hz,  $\text{CH}_3$ ), 1.34 (9H, s,  $\text{CMe}_3$ ), 1.37 (3H, t,  $^3J_{\text{HH}} = 7.2$  Hz,  $\text{CH}_3$ ), 1.39 (9H, s,  $\text{CMe}_3$ ), 4.06 (1H, ABX<sub>3</sub>,  $^2J_{\text{HH}} = 14.2$  Hz and  $^3J_{\text{HH}} = 7.2$  Hz, CH), 4.19 (2H, ABX<sub>3</sub>,  $^2J_{\text{HH}} = 14.2$  Hz and  $^3J_{\text{HH}} = 7.2$  Hz, 2CH), 4.38 (2H, ABX<sub>3</sub>,  $^2J_{\text{HH}} = 14.2$  Hz and  $^3J_{\text{HH}} = 7.2$  Hz, 2CH), 7.50 (2H, t,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH), 7.60 (1H, t,  $^3J_{\text{HH}} = 7.8$  Hz, CH), 8.05 (2H, d,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 13.7$  ( $\text{CH}_3$ ), 14.2 ( $\text{CH}_3$ ), 28.3 ( $\text{CMe}_3$ ), 29.7 ( $\text{CMe}_3$ ), 55.8 (C–N), 57.9 (C–N), 61.7 ( $\text{OCH}_2$ ), 61.7 ( $\text{OCH}_2$ ), 87.2 (C), 126.2 (C), 128.4 (2CH), 128.8 (2CH), 133.0 (CH), 138.1 (C), 148.7 (C), 151.5 (C), 153.6 (C), 160.8 (C), 163.4 ( $\text{C}=\text{O}$ ), 164.2 ( $\text{C}=\text{O}$ ) ppm. Anal. Calcd for  $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$  (499.6): C, 62.50; H, 6.66; N, 8.41. Found: C, 62.46; H, 6.70; N, 8.44.

Compound **4c**: Pale yellow crystals; yield: 0.21 g (40%), mp  $173\text{--}175^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1734 (shoulder), 1731 and 1692 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.01$  (3H, d,  $^3J_{\text{HH}} = 6.2$  Hz,  $\text{CH}_3$ ), 1.15 (3H, d,  $^3J_{\text{HH}} = 6.2$  Hz,  $\text{CH}_3$ ), 1.31 (9H, s,  $\text{CMe}_3$ ), 1.33 (3H, d,  $^3J_{\text{HH}} = 6.2$  Hz,  $\text{CH}_3$ ), 1.34 (3H, d,  $^3J_{\text{HH}} = 6.2$  Hz,  $\text{CH}_3$ ), 1.38 (9H, s,  $\text{CMe}_3$ ), 4.97 (1H, sept,  $^3J_{\text{HH}} = 6.2$  Hz, CH), 5.26 (1H, sept,  $^3J_{\text{HH}} = 6.2$  Hz, CH), 7.48 (2H, t,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH), 7.58 (1H, t,  $^3J_{\text{HH}} = 7.7$  Hz, CH), 8.02 (2H, d,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 21.5$  ( $\text{CH}_3$ ), 21.6 ( $\text{CH}_3$ ), 21.7 ( $\text{CH}_3$ ), 21.8 ( $\text{CH}_3$ ), 28.3 ( $\text{CMe}_3$ ), 29.8 ( $\text{CMe}_3$ ), 55.8 (C–N), 57.7 (C–N), 69.40 (O–CH), 69.8 (O–CH), 87.3 (C), 126.3 (C), 128.3 (2CH), 128.8 (2CH), 132.9 (CH), 137.9 (C), 148.7 (C), 151.3 (C), 153.5 (C), 160.3 (C), 163.0 ( $\text{C}=\text{O}$ ), 164.1 ( $\text{C}=\text{O}$ ) ppm. Anal. Calcd for  $\text{C}_{28}\text{H}_{37}\text{N}_3\text{O}_5\text{S}$  (527.7): C, 63.73; H, 7.07; N, 7.96. Found: C, 63.68; H, 7.10; N, 8.01.

Compound **4d**: Pale yellow crystals; yield: 0.25 g (44%), mp  $111\text{--}113^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1737 (shoulder), 1732 and 1622 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.00$  (9H, s,  $\text{CMe}_3$ ), 1.01 (9H, s,  $\text{CMe}_3$ ), 1.33 ( $\text{CH}_3$ ), 1.38 ( $\text{CH}_3$ ), 1.41

( $\text{CH}_3$ ), 1.44 ( $\text{CH}_3$ ), 1.62 (2H, AB system,  $\Delta\nu_{\text{AB}} = 55$  Hz,  $J_{\text{AB}} = 14.3$  Hz,  $\text{CH}_2$ ), 1.69 (2H, AB system,  $\Delta\nu_{\text{AB}} = 72$  Hz,  $J_{\text{AB}} = 14.3$  Hz,  $\text{CH}_2$ ), 3.68 (3H, s,  $\text{OCH}_3$ ), 3.88 (3H, s,  $\text{OCH}_3$ ), 7.51 (2H, t,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH), 7.61 (1H, t,  $^3J_{\text{HH}} = 7.7$  Hz, CH), 8.06 (2H, d,  $^3J_{\text{HH}} = 7.7$  Hz, 2CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 27.6$  ( $\text{CH}_3$ ), 28.2 ( $\text{CH}_3$ ), 29.4 ( $\text{CH}_3$ ), 29.5 ( $\text{CH}_3$ ), 31.6 ( $\text{CMe}_3$ ), 31.7 ( $\text{CMe}_3$ ), 31.9 ( $\text{CMe}_3$ ), 32.0 ( $\text{CMe}_3$ ), 52.4 (OMe), 52.5 (OMe), 54.9 (C–N), 56.1 (C–N), 59.1 ( $\text{CH}_2$ ), 61.4 ( $\text{CH}_2$ ), 87.3 (C), 126.2 (C), 128.5 (2CH), 128.8 (2CH), 133.0 (CH), 137.1 (C), 148.8 (C), 149.8 (C), 152.6 (C), 161.3 (C), 163.8 ( $\text{C}=\text{O}$ ), 164.7 ( $\text{C}=\text{O}$ ) ppm. Anal. Calcd for  $\text{C}_{32}\text{H}_{45}\text{N}_3\text{O}_5\text{S}$  (583.8): C, 65.84; H, 7.77; N, 7.20. Found: C, 65.89; H, 7.81; N, 7.24.

Compound **4e**: Orange crystals; yield: 0.23 g (40%), mp  $141\text{--}143^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1734 (shoulder), 1730 and 1628 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 2.07$  (H, s,  $\text{CH}_3$ ), 2.17 (H, s,  $\text{CH}_3$ ), 2.25 (6H, s, 2 $\text{CH}_3$ ), 3.19 (OMe), 3.89 (OMe), 6.90 (1H, t,  $^3J_{\text{HH}} = 7.6$  Hz, CH), 6.98 (2H, t,  $^3J_{\text{HH}} = 7.6$  Hz, 2CH), 7.03 (1H, t,  $^3J_{\text{HH}} = 7.6$  Hz, CH), 7.10 (2H, d,  $^3J_{\text{HH}} = 7.6$  Hz, 2CH), 7.46 (2H, t,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH), 7.60 (1H, t,  $^3J_{\text{HH}} = 7.8$  Hz, CH), 7.97 (2H, d,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 17.9$  ( $\text{CH}_3$ ), 18.0 ( $\text{CH}_3$ ), 18.5 (2 $\text{CH}_3$ ), 52.5 (OMe), 53.6 (OMe), 85.4 (C), 124.3 (CH), 124.3 (CH), 125.4 (2C), 125.6 (C), 126.4 (C), 126.6 (2C), 127.4 (CH), 127.5 (CH), 127.9 (2CH), 128.7 (2CH), 128.8 (2CH), 133.4 (CH), 143.3 (C), 145.9 (C), 150.1 (C), 155.3 (C), 160.8 (C), 162.6 (C), 164.7 ( $\text{C}=\text{O}$ ), 166.5 ( $\text{C}=\text{O}$ ) ppm. Anal. Calcd for  $\text{C}_{32}\text{H}_{29}\text{N}_3\text{O}_5\text{S}$  (567.6): C, 67.71; H, 5.15; N, 7.40. Found: C, 67.76; H, 5.20; N, 7.43.

Compound **4f**: Yellow powder; yield: 0.21 g (38%), mp  $184\text{--}186^\circ\text{C}$ . IR  $\nu/\text{cm}^{-1}$  (KBr): 1720 (shoulder), 1716 and 1660 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR (500.1 MHz,  $\text{CDCl}_3$ ):  $\delta = 1.28$  (9H, s,  $\text{CMe}_3$ ), 1.46 (9H, s,  $\text{CMe}_3$ ), 7.18 (2H, t,  $^3J_{\text{HH}} = 7.6$  Hz, 2CH<sub>meta</sub>), 7.28 (2H, d,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH<sub>ortho</sub>), 7.38–7.56 (7H, m, 3CH<sub>para</sub> and 4CH<sub>meta</sub>), 7.74 (2H, d,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH<sub>ortho</sub>), 8.10 (2H, d,  $^3J_{\text{HH}} = 7.8$  Hz, 2CH<sub>ortho</sub>) ppm.  $^{13}\text{C}$  NMR (125.7 MHz,  $\text{CDCl}_3$ ):  $\delta = 28.1$  ( $\text{CMe}_3$ ), 29.8 ( $\text{CMe}_3$ ), 55.6 (C–N), 57.7 (C–N), 89.3 (C), 126.9 (C), 127.9 (2CH), 128.2 (2CH), 128.6 (2CH), 128.7 (2CH), 129.3 (2CH), 129.6 (2CH), 133.0 (CH), 133.4 (CH), 133.6 (CH), 136.9 (C<sub>ipso</sub>), 137.2 (C<sub>ipso</sub>), 147.1 (C<sub>ipso</sub>), 148.6 (C), 152.4 (C), 155.2 (C), 165.2 (C), 190.5 ( $\text{C}=\text{O}$ ), 191.7 ( $\text{C}=\text{O}$ ). Anal. Calcd for  $\text{C}_{34}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$  (563.7): C, 72.44; H, 5.90; N, 7.45. Found: C, 72.39; H, 5.93; N, 7.49.

7. CCDC-270105 contains the supplementary crystallographic data for **4b** ( $\text{C}_{26}\text{H}_{33}\text{N}_3\text{O}_5\text{S}$ ),  $F_w = 499.61$ , triclinic, space group  $P-1$ ,  $Z = 2$ ,  $a = 8.81(3)$  Å,  $b = 11.11(3)$  Å,  $c = 14.80(5)$  Å,  $\alpha = 84.54(10)^\circ$ ,  $\beta = 77.65(10)^\circ$ ,  $\gamma = 69.51(11)^\circ$ ,  $V = 1324(7)$  Å<sup>3</sup>,  $D_{\text{calcd}} = 1.253$  g cm<sup>−3</sup>,  $R = 0.0440$ ,  $R_w = 0.0750$ ,  $-11 \leq h \leq 11$ ;  $-14 \leq k \leq 13$ ;  $-26 \leq l \leq 15$ ; Mo ( $\lambda = 0.71073$  Å),  $T = 120(2)$  K. These data can be obtained free of charge from Cambridge Crystallography Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk.
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