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Attempted Intramolecular Diels-Alder Reactions of 2-Azadienes: Alternative Dimerisation and Dipolar Cycloaddition Pathways

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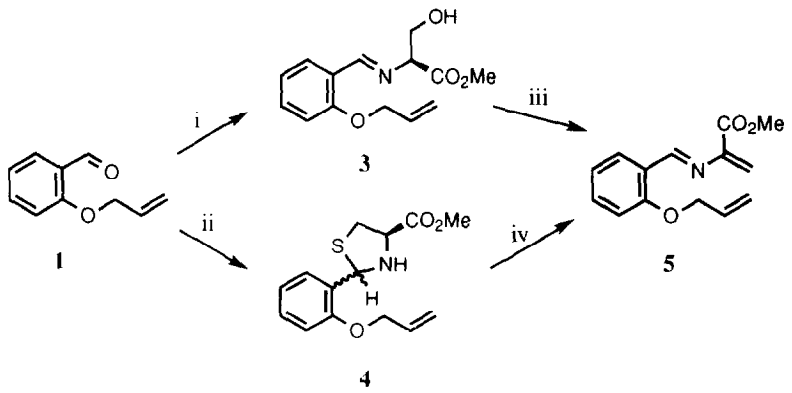
Abstract: The 2-azadiene **5** was generated from the Schiff bases of serine methyl ester and cysteine methyl ester and 2-allyloxybenzaldehyde **1**. Compound **5** failed to undergo an intramolecular Diels–Alder reaction. When it was generated in the presence of aluminium trichloride the pyridine **6a** was isolated; the structure of this pyridine indicates that the catalyst has reversed the regiochemistry of the dimersiation of **5**. The reaction of the activated allyloxybenzaldehyde **2** with cysteine methyl ester follows a different course from that of **1**. The allylic function is transferred to sulfur and the Schiff base **9** is formed. This undergoes a rapid internal 1,3-dipolar cycloaddition at room temperature to give the thienopyrrole **10**, the structure of which has been established by X-ray crystallography.

N-Arylidenedehydroamino methyl esters can be generated either by reacting thiazolidine methyl esters with silver carbonate and DBU or by the dehydration of Schiff bases of serine methyl ester with *N,N'*-carbonyldiimidazole and triethylamine. These short lived compounds undergo Diels–Alder reactions with a range of dienophiles.[1] Exceptionally, with cyclopentadiene *N*-benzylidenedehydroalanine methyl ester acts as a dienophile in the Diels-Alder reaction.[2] In order to extend these reactions to provide routes to new dehydroamino acid derivatives we investigated some intramolecular Diels-Alder reactions of 2-azadienes. The precursors were formed by condensing cysteine and serine methyl esters with 2-allyloxybenzaldehydes **1** and **2**.

The aldehyde **1**[3] was first prepared and condensed with serine methyl ester and with cysteine methyl ester. The product formed from serine methyl ester was characterised by NMR as the open chain imine **3** whereas cysteine methyl ester gave the cyclic valence tautomer, the thiazolidine **4**, which in solution is a mixture of diastereoisomers. Compounds **3** and **4** were then converted into the 2-azadiene **5** by the methods described above (Scheme 1). No intramolecular Diels-Alder reaction was observed; the only compound recovered was the aldehyde **1**, which is probably formed by hydrolysis of **5**.

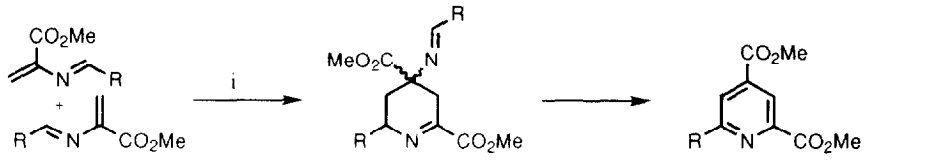
In attempt to catalyse the Diels-Alder reaction, compound **5** was first generated from the thiazolidine **4**, silver carbonate and DBU, and aluminium trichloride was then added to the reaction mixture. A new product was detected and was isolated in low yield (13%). This was identified as the pyridine **6a** on the basis of analytical and spectroscopic data. In particular, the ^{1}H NMR spectrum showed signals for H-3 and H-5 of the pyridine ring at δ 8.68 and 8.55 as doublets with a typical *meta*-coupling constant of 1.7 Hz.



i, L-Serine methyl ester HCl, Et_3N; ii L-Cysteine methyl ester HCl, $KHCO_3$; iii, *N,N*-carbonyldiimidazole, Et_3N; iv, Ag_2CO_3, DBU.

Scheme 1

This unexpected product is probably formed by dimerisation of the azadiene **5** followed by aromatisation (Scheme 2). These azadienes have been shown to dimerise easily, in the absence of a catalyst.[1,4] The interesting feature of this reaction is that aluminium trichloride apparently promotes the dimerisation by a Diels-Alder reaction in which the regioselectivity is opposite to that of the uncatalysed process. The effect of the catalyst is not limited to the dimerisation of **5**: *N*-benzylidenedehydroalanine methyl ester gave the analogous pyridine diester **6b** (23%) in the presence of aluminium trichloride.



i, $AlCl_3$.

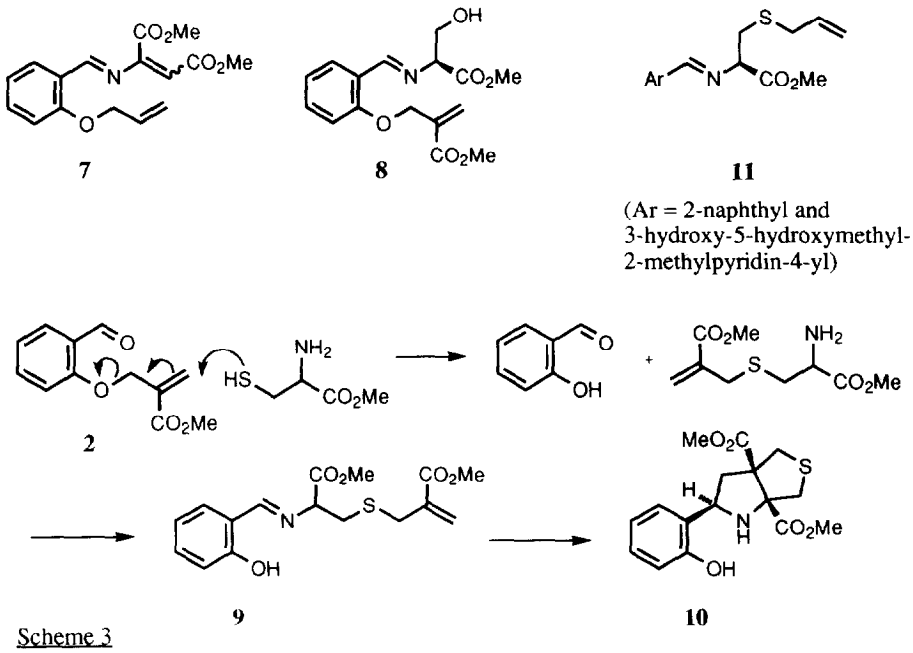
6; **a**, R = C_6H_4.2-OC_3H_4
b, R = Ph

Scheme 2

Barluenga and co-workers have previously shown that the related 2-azadiene **7** can undergo intramolecular Diels-Alder cycloaddition, but the reaction takes place at 125 °C over 30 h.[5] The azadiene **5** is much less stable than **7**; we therefore sought to promote the intramolecular Diels-Alder reaction by introducing a more reactive internal dienophile. The allyloxybenzaldehyde **2** was selected as a suitable precursor since acrylate esters have been shown to undergo intermolecular cycloaddition reactions with these 2-azadienes, and with the same regiochemistry as would be expected here. The aldehyde **2** was prepared from salicylaldehyde and was allowed to react with serine methyl ester and cysteine methyl ester. Serine methyl ester gave the expected Schiff base **8**. When this was treated with carbonyldiimidazole and triethylamine there was no evidence for the formation of a product resulting from intramolecular cycloaddition.

Cysteine methyl ester also reacted readily with the aldehyde **2** but the product, formed after 30 min., was not the expected thiazolidine. Instead, it proved to be the iomeric Schiff base **9**. Cysteine methyl ester thus first reacts with the aldehyde **2** *via* the thiol function which attacks the activated double bond and transfers the

allylic functional group from oxygen to sulfur. The *S*-allylcysteine ester then forms a Schiff base with the salicylaldehyde so produced (Scheme 3).



Scheme 3

When this reaction was carried out over a longer period of time (2.5 h) , or when the imine **9** was allowed to stand in solution at room temperature, a new product, having the same molecular formula as **9**, was formed. The structure was established by X-ray crystallography as the thienopyrrole diester **10** (Figure). This must be formed by an intramolecular 1,3-dipolar addition of an azomethine ylide which is generated from the Schiff base **9** by proton transfer. This type of prototropy is well established as a result of the work of Grigg and his co-workers. Indeed, Grigg and colleagues have previously reported two examples of intramolecular dipolar cycloaddition of azomethine ylides derived from Schiff bases **11** of *S*-allylcysteine methyl ester.[6] The cycloadduct **10** is formed under remarkably mild conditions. Grigg has suggested that an *ortho* substituent on the aryl group of the Schiff base which is capable of hydrogen bonding can promote the formation of the azomethine ylide[7] and such a substituent (the 2-hydroxy group) is fortuitously present in **9**. The stereochemistry of the cycloadduct is also consistent with that required for a hydrogen bonded azomethine ylide.

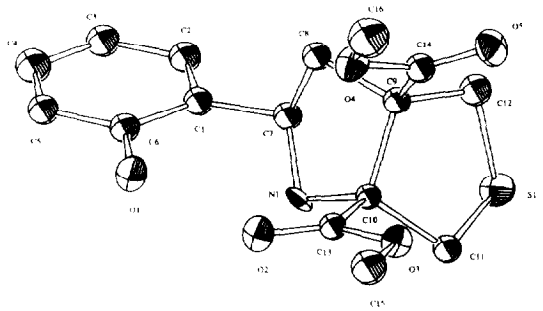


Figure. ORTEP drawing of the X-ray crystal structure of **10.**

EXPERIMENTAL

General ^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200MHz and (where indicated) on either a Bruker AMX400 instrument operating at 400 MHz or a Varian 500 instrument operating at 500 MHz. The solvent is deuteriochloroform except where indicated otherwise. Signals are singlets where no multiplicity is shown. Mass spectra were recorded under electron impact at 70 eV on a VG Micromass 7070E instrument. M.p.'s were recorded on a Reichert hot stage and are uncorrected. Flash column chromatography was performed with Merck 9385 silica as the stationary phase. Light petroleum refers to the fraction b.p. 60–80 °C.

2-Allyloxybenzaldehyde **1** was prepared by a literature procedure[3] and was isolated as an oil: δ 4.59–4.63 (2 H, m), 5.27–5.48 (2 H, m), 5.96–6.15 (1 H, m), 6.82–7.02 (2 H, m, Ar-H), 7.49 (1 H, dt, *J* 1.88 and 8.64), 7.8 (1 H, dd, *J* 1.88 and 8.22) and 10.51 (1 H); *m/z* 162 (M^+, 14%), 133 (20), 121 (53), 65 (16) and 41 (100).

2-(2'-Methoxycarbonyl)allyloxybenzaldehyde **2**. Salicylaldehyde (1.00 g, 8.2 mmol) was dissolved in dichloromethane (20 ml) and potassium hydrogencarbonate (1.16 g) was added, followed by methyl 2-(bromomethyl)acrylate[8] (1.50 g, 8.4 mmol). The reaction mixture was heated under reflux for 24 h. The solvent was then evaporated off to give a *2-[(2'-methoxycarbonyl)allyloxy]benzaldehyde* **2** (1.23 g, 68%); m.p. 56–58 °C (from ether) (Found: C, 65.4; H, 5.6. $C_{12}H_{12}O_4$ requires C, 65.5; H, 5.5%); $\nu_{max.}$ (cm^{-1}) (KBr) 1714, 1684, 1313 and 1290; δ 3.82 (3 H), 4.88–4.89 (2 H, m), 6.05–6.07 (1 H, m), 6.46–6.48 (1 H, m), 7.00–7.10 (2 H, m, Ar-H, 7.51–7.60 (1 H, m), 7.85 (1 H, dd, *J* 1.8 and 7.7) and 10.53 (1 H); *m/z* 220 (M^+, 1%), 205 (1), 161 (34), 121 (100) and 59 (52).

N-(2-Allyloxy)benzylidene-L-serine methyl ester **3**. L-Serine methyl ester hydrochloride (0.32 g, 22.6 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (0.35 ml) was added. The reaction mixture was stirred at room temperature for 10 min. in the presence of 4Å molecular sieves and a solution of 2-(allyloxy)benzaldehyde (3.68 g, ,22.6 mmol) in dry dichloromethane (10 ml) was added. The reaction mixture was stirred at room temperature for 16 h. It was then filtered and the filtrate was evaporated to dryness, giving *N*-(2-allyloxy)benzylidene-L-serine methyl ester **3** (80%); δ 3.80 (3 H), 3.90–4.15 (13H, m), 4.60–4.70 (2 H, m), 5.30–5.50 (2 H, m), 6.00–6.20 (1 H, m), 6.80–7.10 (2 H, m, Ar-H), 7.30–7.60 (2 H, m, Ar-H) and 8.80 (1 H). The imine was not characterised further.

Methyl 2-(2'-allyloxyphenyl)thiazolidine-4-carboxylate **4**. Cysteine methyl ester hydrochloride (3.45 g, 20 mmol) was dissolved in water (15 ml) and potassium hydrogencarbonate (2.0 g, 20 mmol) was added following the addition of a solution of 2-(allyloxy)benzaldehyde (3.58 g, 22 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 2.5 h, water was added and the solution was extracted with dichloromethane. The solvent was evaporated off and the residue was purified by chromatography giving *methyl 2-(2'-allyloxyphenyl)thiazolidine-4-carboxylate* **4** as an oil (4.46 g, 80%) (Found: C, 60.2; H, 6.1; N, 4.6. $C_{14}H_{17}NO_3S$ requires C, 60.6; H, 6.1; N, 5.0%); δ 2.98–3.09 (1 H, m, $SC\underline{H}_2$), 3.25–3.46 (1 H, m, $SC\underline{H}_2$), 3.79 (3 H), 3.90–3.96 and 4.22–4.26 (1 H, m, $C\underline{H}CO_2Me$), 4.57–4.61 (2 H, m, $C\underline{H}_2CH{=}CH_2$), 5.26–5.55 (2 H, $CH{=}C\underline{H}_2$), 5.83 and 6.04 (1 H, s, $C\underline{H}Ar$), 6.0–6.20 (1 H, m, $C\underline{H}{=}CH_2$), 6.83–6.99 (2 H, m, Ar-H), 7.12–7.29 (1 H, m, Ar-H) and 7.37–7.44 (1 H, m, Ar-H); *m/z* 279 (M^+, 18%), 207 (46), 148 (62), 132 (100), 86 (29) and 59 (52).

Dimethyl 6-(2'-allyloxyphenyl)pyridine-2,4-dicarboxylate. **6a**. Methyl 2-(2'-allyloxyphenyl)thiazolidine-4-carboxylate (1.76 g, 6.30 mmol) was dissolved in dry acetonitrile (30 ml). The solution was cooled to –20 °C and silver carbonate (1.73 g) was added, followed by a solution of DBU (0.17 g) in dry acetonitrile (20 ml). The reaction mixture was stirred for 2 h at 0 °C. Aluminium chloride (0.52 g) was added and the solution was

stirred overnight at room temperature. Ether was added, the mixture was filtered and the solvent was evaporated from the filtrate. The product was isolated by flash chromatography [light petroleum–ethyl acetate (3:1) then light petroleum–ethyl acetate (1:1)] giving *dimethyl 6-(2'-allyloxyphenyl)pyridine-2,4-dicarboxylate* **6a** (0.13 g, 13%), m.p. 82–82.5 °C (from ether–light petroleum) (Found: C, 66.2; H, 5.3; N, 4.1. $C_{18}H_{17}NO_5$ requires C, 66.1; H, 5.2; N, 4.3%); $\nu_{max.}$ (cm^{-1}) (KBr) 1620 and 1740; δ 3.99 (3 H), 4.03 (3 H), 4.60–4.64 (2 H, m), 5.21–5.44 (2 H, m), 5.94–6.12 (1 H, m), 6.98–7.15 (2 H, m), 7.35–7.43 (1 H, m), 7.91 (1 H, dd, *J* 1.7 and 7.7), 8.55 (1 H, d, J 1.7) and 8.68 (1 H. d, *J* 1.7); δ (^{13}C) 52.83, 52.99, 69.30, 112.83, 117.33, 121.57, 122.22, 127.95, 130.87, 131.57, 132.81, 138.22, 148.68, 156.22, 157.55, 165.26 and 165.50; *m/z* 327 (M^+, 6%), 322 (26), 213 (100), 140 (24), 59 (40) and 41 (74).

Dimethyl 6-phenylpyridine-2,4-dicarboxylate **6b** was prepared by the reaction of methyl 2-phenylthiazolidine-4-carboxylate (0.50 g, 2.24 mmol) following the procedure described for the synthesis of dimethyl 2-(2'-allyloxyphenyl)-pyridine-4,6-dicarboxylate. Workup by flash chromatography [petroleum ether-ethyl acetate (4:1) then petroleum ether-ethyl acetate (3:1)] gave *dimethyl 6-phenylpyridine-2,4-dicarboxylate* **6b** (0.07 g, 23%) m.p. 118–120 °C (from ether–light petroleum); δ 4.02 (3 H), 4.05 (3 H), 7.49–7.53 (3 H, m, Ar-H), 8.09–8.14 (2 H, m, Ar-H), 8.47 (1 H, d, *J* 1.6) and 8.57 (1 H. d, *J* 1.6) *m/z* 271.0845 (M^+, 22%) ($C_{15}H_{13}NO_4$ requires 271.0845), 213 (100), 154 (21), 127 (66) and 77 (18).

N-[(2'-Methoxycarbonyl)allyloxy]benzylidene-L-serine methyl ester **8**. L-Serine methyl ester hydrochloride (0.32 g, 2.26 mmol) was dissolved in dichloromethane (10 ml) and triethylamine (0.35 ml) was added. The reaction mixture was stirred at room temperature for 10 min. in the presence of 4Å molecular sieves and a solution of 2-[(2'-methoxycarbonyl)allyloxy]benzaldehyde (0.49 g, 2.23 mmol) in dry dichloromethane (10 ml) was added. The reaction mixture was stirred at room temperature for 16 h. The mixture was filtered and the filktrate was evaporated to dryness. Workup by flash chromatography [petroleum ether-ethyl acetate (3:1) then petroleum ether-ethyl acetate (1:1)] gave *N-[(2'-methoxycarbonyl)allyloxy]benzylidene-L-serine methyl ester* **8** (0.25 g, 34%); m.p. 128–130 °C (from ether) (Found: C, 59.7; H, 5.9; N, 4.1. $C_{16}H_{19}NO_6$ requires C, 59.8; H, 6.0; N, 4.4%); $\nu_{max.}$ (cm^{-1}) (KBr) 1240, 1263, 1722 and 1745; δ 3.73 (2 H), 3.77 (6 H), 3.93 (1 H, dd, *J* 6.45 and 10.9), 4.08–4.18 (2 H, m), 5.78 (1 H), 6.24 (1 H), 6.88–6.98 (2 H, m, Ar-H), 7.27–7.38 (2 H, m, Ar-H) and 8.42 (1 H); *m/z* 321 (M^+, 3%), 262 (55), 222 (29), 147 (91), 132 (100), and 77 (57).

N-2-Hydroxybenzylidene-S-(2'-methoxycarbonylallyl)cysteine methyl ester **9**. Cysteine methyl ester hydrochloride (3.45 g, 20.1 mmol) was dissolved in water (15 ml) and potassium hydrogencarbonate (2.0 g, 20 mmol) was added followed by a solution of 2-[(2'-methoxycarbonyl)allyloxy]benzaldehyde (5.19 g, 23.6 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 30 min. Water was added and the solution was extracted with dichloromethane. The solvent was evaporated off and the residue was purified by column chromatography giving *N-2-hydroxybenzylidene-S-(2'-methoxyarbonylallyl)cysteine methyl ester* **9** as an oil (5.76 g, 87%) (Found: C, 57.3; H, 6.0; N, 4.2. $C_{16}H_{19}NO_5S$ requires C, 57.0; H, 5.6; N, 4.15%); $\nu_{max.}$ (cm^{-1}) (neat) 1203, 1437, 1630, 1728 and 2953; δ 3.66–3.82 (2 H, m), 3.96 (2 H), 3.77 (6 H), 4.11 (1 H, dd, *J* 4.9 and 8.4), 5.69 (1 H), 6.22 (1 H), 6.77–6.99 (2 H, m, Ar-H), 7.29–7.39 (2 H, m, Ar-H) and 8.39 (1 H); *m/z* 337 (M^+, 1%), 336 (4), 304 (1), 278 (11), 218 (6), 146 (37), 135 (100), ,77 (40) and 59 (39).

Dimethyl 2-(2'-Hydroxyphenyl)tetrahydro-1H-thieno[3,4-b]pyrrole-3a,6a(6H)-dicarboxylate **10**. Cysteine methyl ester hydrochloride (3.45 g, 20.1 mmol) was dissolved in water (15 ml) and potassium hydrogencarbonate (2.0 g, 20 mmol) was added followed by a solution of 2-(2'-methoxycarbonyl)allyloxybenzaldehyde **2** (5.19 g, 23.6 mmol) in ethanol (15 ml). The reaction mixture was stirred at room temperature for 2.5 h, water was added and the solution was extracted with dichloromethane. The solvent was evaporated off. Workup by flash chromatography [light petroleum–ethyl acetate (3:1), light

petroleum–ethyl acetate (1:1) then ethyl acetate] gave a mixture of the methyl ester **9** and the dipolar addition product **10**. The dipolar addition adduct (49%) crystallized from light petroleum–ether. The solvents from crystallization were evaporated off giving N-2-hydroxybenzylidene-S-(2'-methoxyarbonylallyl)cysteine methyl ester **9** (25%) which was identified by comparision with specimen isolated earlier. *Dimethyl 2-(2'-hydroxyphenyl)tetrahydro-1H-thieno[3,4-b]pyrrole-3a,6a(6H)-dicarboxylate* **10** had m.p. 132–133 °C (Found: C, 57.0; H, 5.9; N, 4.1; S, 9.3. $C_{16}H_{19}NO_5S$ requires C, 57.0; H, 5.6; N, 4.15; S, 9.5%); $\nu_{max.}$ (cm^{-1}) (KBr) 1728, 1740 and 3325; δ 2.36 (1 H, dd, *J* 6.3 and 13.3), 2.81 (1 H, aprox. t, *J* 13.3 and 11.0), 2.93 (1 H, d, *J* 7.7), 2.99 (1 H, d, *J* 7.7), 3.66–3.75 (2 H, m), 3.71 (3 H), 3.77 (3 H), 4.95 (1 H, dd, *J* 11.0 and 6.3), 6.74–6.86 (2 H, Ar-H), 6.96-7.01 (1 H, m, Ar-H), 7.12–7.21 (1 H, m, Ar-H) and 10.13 (1 H); δ (^{13}C) 42.44, 44.33, 44.76, 52.75, 52.86, 63.02, 66.37, 80.77, 117.33, 119.09, 123.54, 128.32, 129.08, 156.81, 172.42 and 173.13; *m/z* 337 (M^+, 1%), 322 (1), 206 (15), 135 (100) and 77 (17).

Crystal data for $C_{16}H_{19}NO_5S$, **10**. M = 337.39, orthorhombic, space group $P2_12_12_1$ (#19), a = 9.755(5), b = 18.567(6), c = 8.705(6) Å, V = 1577(1) $Å^3$, Z = 4, D_c = 1.421 g cm^{-3}, F_{000} = 712, μ (Mo-Ka) = 2.20 cm^{-1}. Number of reflections collected = 1628 from colourless block, 0.200 x 0.200 x 0.300 mm. R = 0.051, R_W = 0.055 for 1172 observed reflections [$I > 3.00\sigma(I)$] and 128 variable parameters.

X-Ray intensity measurements were made at –120 ± 1 °C using the ω – 2θ scan technique to a maximum 2θ value of 50.0° on a Rigaku AFC6S diffractometer. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.

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