Synthesis of Bicyclic *N*-Methylpyrazoline and Pyrazole Derivatives from α,β-Unsaturated Ketones and *N*,*N*-Dimethylhydrazine: An Illustration of Reductive Cyclization

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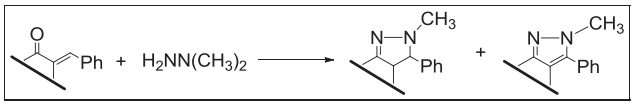

The reaction of *N*,*N*-dimethylhydrazine with α,β-unsaturated keto precursors such as 2-benzylidenecyclohexanone, 2,6-bis(benzylidene)cyclohexanone, and 3,5-bis(benzylidene)-1-methyl-4-piperidone hydrochloride provided bicyclic *N*-methylpyrazoles instead of hydrazones or any Michael addition products. The crystal structure of a representative pyrazole is reported. The proposed mechanism for the formation of the bicyclic *N*-methylpyrazole **1** is outlined.

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INTRODUCTION

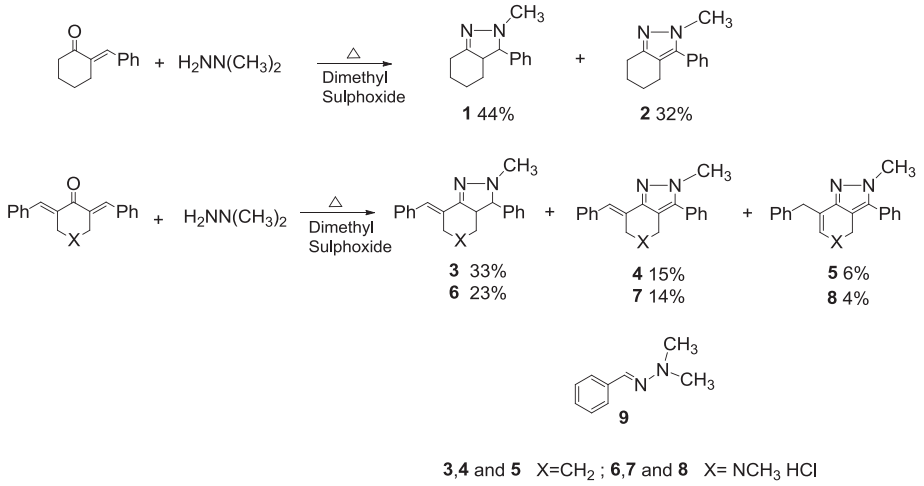
The pyrazole nucleus is a pharmaceutically important template and constitutes the key subunit in many biologically active compounds with a broad range of pharmacological activities including antidepressant [1], antimicrobial [2], and anti-inflammatory [3] activities. One of the pyrazole variants such as tetrahydroindazoles that contain a bicyclic ring is active against various cancers [4] and inflammation [5]. Other bicyclic pyrazoles, for example, pyrazolopyridines are potent antihypertensive [6] and anti-inflammatory agents [7]. One of the common methods for preparing pyrazoles involves condensation of hydrazine or hydrazine derivatives with α,β-unsaturated ketones [7–9] or 1,3-diketones [10,11]. Lee *et al*. reported a regoselective synthesis of 1,3,4,5-tetrasubstituted pyrazoles from Baylis–Hillman adducts [12]. A number of Baylis–Hillman adducts obtained from alkylvinylketones, 2-cycloalken-1-ones were converted into the corresponding pyrazole derivatives [12]. Pyrazole analogs were obtained by DDQ catalyzed oxidation of the corresponding dihydropyrazoles, which were derived from the condensation of α,β-unsaturated ketones with *N*-methylhydrazine [13]. Despite a number of methods available for the synthesis of pyrazole derivatives, some interesting bicyclic pyrazoles are difficult to access, and therefore, construction of novel methods has attracted considerable attention in recent times.

In the present study, we are reporting an interesting route towards various bicyclic *N*-methylpyrazole derivatives starting from the reaction of *N*,*N*-dimethylhydrazine with cyclic arylidene keto precursors (Scheme 1). This novel reaction is unprecedented, and therefore, it opens up a *vista* of new discoveries in organic chemistry. A thorough literature survey reveals that there are only a few reports of the reaction of dimethylhydrazine with α,β-unsaturated ketones, which led to the corresponding hydrazone derivatives. Matsumiya *et al*. prepared a dimethylhydrazone derivative of 3-methyl-2-cyclopenten-1-one [14]. A number of acyclic dimethylhydrazone derivatives of 4-phenyl-3-buten-2-ones were obtained as a mixture of E and Z isomers [15,16], and efforts were made to separate the geometrical isomers [16]. Saito *et al*. [17] reported the $TiCl_4$ catalyzed *in situ* generation of a dimethylhydrazone from 1,3-bis(benzylidene)acetone.

RESULTS AND DISCUSSION

Our initial study was focused on the readily available precursor 2-benzylidene-cyclohexanone [18], which, on reaction with *N*,*N*-dimethylhydrazine in pure ethanol or dry DMSO at 80–90°C, produced two products **1** and **2** in 44 and 32% yields, respectively, after purification with the use of column chromatography (Scheme 1) instead of forming any *N*,*N*-dimethylhydrazone adducts. It is proposed that the formation of **1** occurred by nucleophilic attack of the primary amino group of the hydrazine on the carbonyl function of the benzylidene group, initially forming a dimethylhydrazone adduct, which was stabilized by a five-membered pyrazole ring formation leading to N-demethylation via the release of methanol (Fig. 1). Compound **2** is believed to be the oxidized product of **1** [19,20]. Products **1** and **2** were identical spectroscopically with the authentic samples obtained alternatively by the

Scheme 1



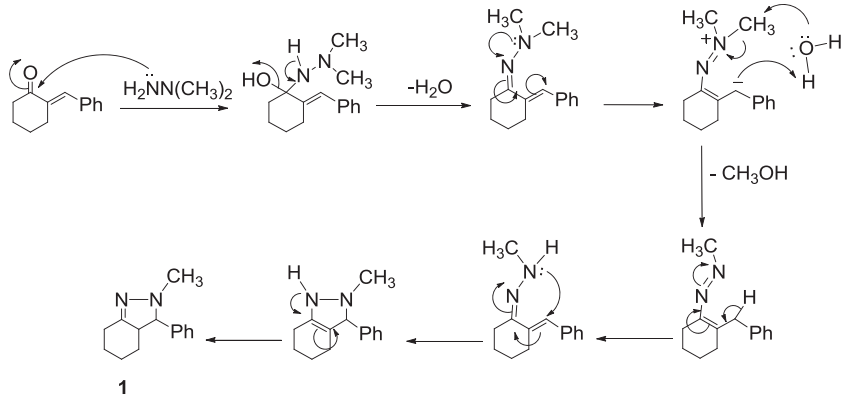


Figure 1. Proposed mechanisms for the formation of the pyrazole derivative **1**.

reaction of *N*-methylhydrazine with 2-benzylidenecyclohexanone [13] and 2-benzoylcyclohex-1-ene [13], respectively.

To evaluate the generality of this reaction, we considered other cyclic bis(arylidene)keto precursors. Condensation of dimethylhydrazine with 2,6-bis(benzylidene) cyclohexanone [18] produced the *N*-methylpyrazole derivatives **3** [21] and **4** as major products along with a minor quantity of **5**, which is obtained by isomerization of the benzylidene functional group of **4**. In the case of 3,5-bis (benzylidene)-1-methyl-4-piperidone [18], two products, namely, the *N*-methylpyrazole derivatives **6** [7] and **7**, were obtained along with minor quantities of **8**, which is a positional isomer of **7**. In this case, an additional major product was also isolated in 19% yield, which was characterized as *N*-benzylidene-*N*′,*N*′-dimethylhydrazine **9** [22] (Scheme 1). This product **9** is assumed to be formed by the Michael reaction of the primary amino group of *N*,*N*-dimethylhydrazine with the benzylidene keto group of the 3,5-bis(benzylidene)-1-methyl-4-piperidone (Fig. 2).

The compounds **1**, **3**, and **6** were isolated as only one diasterioisomeric form with the trans-orientation of the hydrogen atoms H-3 and H-3a as evidenced from ^{1}H-NMR. The proton H-3 in **1**, **3**, and **6** appeared as a doublet at 3.33, 3.68, and 3.94 ppm, respectively, with spin–spin coupling constant values ($^3J_{\text{H-3,3a}}$) of 12.86, 14.05, and 13.93 Hz, respectively, which is a characteristic of trans isomers. The corresponding cis isomers are characterized by smaller coupling constants ($^3J_{\text{H-3,3a}} = 2.0$–$5.0$ Hz)[23].

The X-ray crystal structures of **3**, which are reported for the first time in this study, further confirmed the stereochemistry and trans orientation of H-3 and H-3a protons (Fig. 3). The cyclohexyl ring in **3** exists in the sofa conformation as observed from the X-ray structure.

Various other hydrazine products such as 1-aminopiperidine and *N*-benzoylhydrazine, which lack an *N*-methyl group, were chosen to react with 3,5-bis(benzylidene)-1-methyl-4-piperidone hydrochloride to investigate the mechanism of pyrazoline ring formation. The reaction of 1-aminopiperidine and *N*-benzoylhydrazine leads to the isolation of

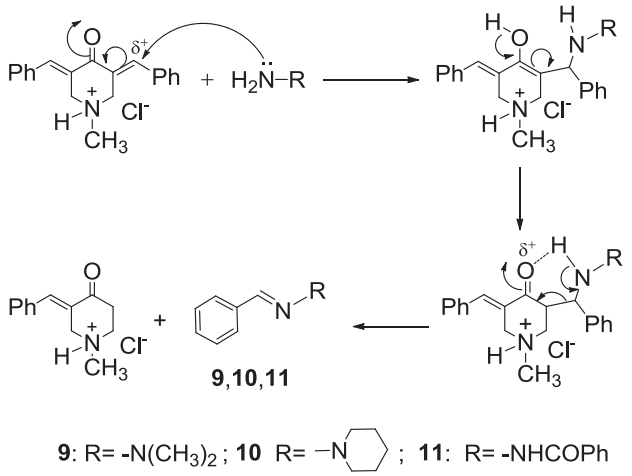


Figure 2. Proposed mechanisms for the formation of Schiff bases **9**, **10**, and **11**.

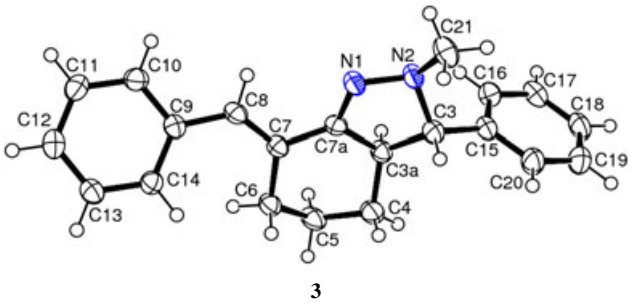


Figure 3. An ORTEP diagram of **3** with nonhydrogen displacement ellipsoids drawn at the 50% probability level. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

mainly the starting material along with minor quantities of the Schiff bases **10** and **11**, respectively, in yields of 17 and 30% (Scheme 2), which were confirmed by comparing them with authentic samples prepared by the condensation of benzaldehyde with 1-aminopiperidine [22] and *N*-benzoylhydrazine [24]. The formation of the hydrazone adduct was not observed in either of the cases. A proposed mechanism by which the Schiff bases **10** and **11** were formed is depicted in Figure 2. These results suggest that the nucleophilic attack at the carbonyl carbon is restricted as a result of the steric hindrance between the bulkier amines and phenyl groups in the substrates; only the reaction at the β-carbon is favored that leads to the formation of Schiff bases.

CONCLUSIONS

The reaction of *N*,*N*-dimethylhydrazine with arylidene-ketones derived from cyclohexanone and 4-piperidone led to the formation of bicyclic pyrazoline and *N*-methylpyrazole derivatives. These reactions illustrate an interesting phenomenon of ring cyclization via reductive N-demethylation. A further investigation of the scope of this reaction to diverse arylidene ketone libraries is proposed.

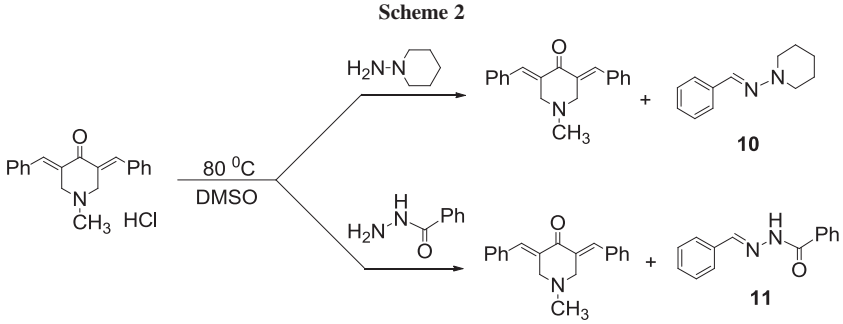
EXPERIMENTAL

All solvents are commercially available. Analytical TLC were performed on silica gel plates (60F-254 Merck, 0.25-mm thickness), and visualizing was accomplished with UV light ($\lambda = 254$ nm) and iodine. Column chromatography was performed using silica gel 60 (60–250 meshes). ^{1}H-NMR spectra were recorded on a Bruker AMX 500 FT spectrometer at 500 MHz. Mass spectra were obtained with a VG 7OSE spectrometer. Elemental analyses were obtained using an Elementar's Vario EL III microanalyzer. Melting points were undertaken using a Gallenkamp instrument and are uncorrected. The X-ray crystallographic diffractions were determined using a Nonius Kappa CCD diffractometer.

General procedure for the preparation of *N*-methylpyrazolines and pyrazoles. A mixture of the unsaturated ketone (0.01 mol) and *N*,*N*-dimethylhydrazine (0.84 g, 0.014 mol) in DMSO (24 mL) was stirred at 80–90°C for 21 h. Water (100 mL) was added to the reaction mixture, and after stirring at room temperature for 0.25 h, it was extracted with toluene (4×30 mL). The organic layer was washed with water (4×30 mL), dried over anhydrous sodium sulfate, and evaporated to dryness under reduced pressure at 50–55°C to provide a thick oil, which was chromatographed on a silica gel column with the use of hexane/ethyl acetate (95:5 v/v) as eluent to afford analytically pure compounds.

2-Methyl-3-phenyl-3,3a,4,5,6,7-hexahydro-2H-indazole (1). Yield: 44%; thick oil; ir (neat): 2928, 2860, 2779, 1492, 1446, 1162, 748, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.32 (m, 5H), 3.34 (d, 1H, $J = 12.86$ Hz), 2.70–2.49 (m, 5H), 1.88

Scheme 2



(m, 4H), 1.28 (m, 3H); ms (EI): *m/z* 214.14 (M^+). *Anal*. Calcd for $C_{14}H_{18}N_2$: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.39; H, 8.42; N, 12.96.

2-Methyl-3-phenyl-4,5,6,7-tetrahydro-2H-indazole (2). Yield: 32%; thick oil; ir (neat): 3058, 2927, 2850, 1677, 1488, 1371, 761, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.44–7.22 (m, 5H), 3.70 (s, 3H), 2.65 (t, 2H, *J* = 6.3 Hz), 2.41 (t, 2H, *J* = 6.3 Hz), 1.85–1.60 (m, 4H); ms (EI): *m/z* 212.12 (M^+). *Anal*. Calcd for $C_{14}H_{16}N_2$: C, 79.21; H, 7.60; N, 13.20. Found: C, 79.28; H, 7.40; N, 13.01.

7-Benzylidene-2-methyl-3-phenyl-3,3a,4,5,6,7-hexahydro-2H-indazole (3). Yield: 33%; mp 104°C (isopropyl alcohol); ir (KBr): 2918, 2850, 1576, 1541, 1465, 1178, 1019 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.47 (d, 2H, Ar–H, *J* = 7.2 Hz), 7.40 (t, 2H, Ar–H), 7.36 (m, 5H, Ar–H), 7.26 (m, 1H, Ar–H), 7.22 (d, =CH, *J* = 2.6 Hz), 3.68 (d, 1H, *J* = 14.0 Hz), 3.04 (d, 1H, *J* = 15.2 Hz), 2.89 (m, 1H), 2.83 (s, 3H, N–CH_3), 2.42 (m, 1H), 2.05 (m, 1H), 1.91 (m, 1H), 1.55 (m, 1H), 1.41 (m, 1H); ms (EI): *m/z* 302.14 (M^+). *Anal*. Calcd for $C_{21}H_{22}N_2$ 0.5 H_2O: C, 80.92; H, 7.38; N, 8.99. Found: C, 80.86; H, 7.38; N, 9.12.

7-Benzylidene-2-methyl-3-phenyl-4,5,6,7-tetrahydro-2H-indazole (4). Yield: 15%; mp 124°C (hexanes); ir (KBr): 2920, 2853, 1579, 1464, 1369, 1177, 1016 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.75 (d, 2H, Ar–H, *J* = 7.1 Hz), 7.43 (m, 4H, Ar–H), 7.34 (m, 4H, Ar–H), 6.86 (s, 1H, =CH), 4.17 (s, 3H, N–CH_3), 2.88 (t, 2H), 2.79 (m, 2H), 1.89 (m, 2H); ms (EI): *m/z* 300.16 (M^+, 100). *Anal*. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.83; H, 6.87; N, 9.33.

7-Benzyl-2-methyl-3-phenyl-4,5-dihydro-2H-indazole (5). Yield: 6%; thick oil; ir (KBr) 2913, 2849, 1576, 1540, 1466, 1370, 1180, 1071 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 (t, 2H, Ar–H), 7.41 (m, 8H, Ar–H), 7.25 (t, 1H, =CH), 3.91 (s, 3H, N–CH_3), 2.86 (t, 2H), 2.60 (t, 2H), 1.84 (m, 2H); ms (EI): *m/z* 301.16 ($M^+ + 1$), 300.16 (M^+), 299.15 ($M^+ - 1$); *Anal*. Calcd for $C_{21}H_{20}N_2$: C, 83.96; H, 6.71; N, 9.33. Found: C, 83.87; H, 6.53; N, 9.21.

7-Benzylidene-2,5-dimethyl-3-phenyl-3,3a,4,5,6,7-hexahydro-2H-pyrazolo[4,3-c]-pyridine (6). Yield: 23%; thick oil; ir (KBr): 2913, 2851, 2321, 1578, 1543, 1460, 1361, 1219, 1091 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.46 (d, 2H, Ar–H, *J* = 7.1 Hz), 7.38 (m, 5H, Ar–H), 7.29 (t, 4H, Ar–H and =CH), 3.94 (d, 1H, *J* = 13.9 Hz), 3.74 (d, 1H, *J* = 14.3 Hz), 3.25 (m,1H), 3.11 (dd, 1H, *J* = 2.1 Hz, *J* = 13.9 Hz), 3.03 (m, 1H), 2.84 (s, 3H, N–CH_3), 2.38 (s, 3H, N–CH_3), 2.34 (d, 1H, *J* = 10.5 Hz); ms (EI): *m/z* 317.18 (M^+). *Anal*. Calcd for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.38; H, 7.41; N, 13.06.

7-Benzylidene-2,5-dimethyl-3-phenyl-4,5,6,7-tetrahydro-2H-pyrazolo[4,3-c]pyridine (7). Yield: 14%; thick oil; ir (KBr): 2925, 2854, 1580, 1464, 1369, 1280, 1226, 1181, 1068, 1017 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.66 (d, 2H, Ar–H, *J* = 7.6 Hz), 7.43 (m, 4H, Ar–H), 7.32 (m, 4H, Ar–H), 7.01 (s, 1H,=CH), 4.18 (s, 3H, N–CH_3), 3.81 (s, 2H), 3.60 (s, 2H), 2.48 (s, 3H, N–CH_3); ms (EI): *m/z* 316.17 ($M^+ + 1$), 315.17 (M^+), 314.16 ($M^+ - 1$); *Anal*. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.80; H, 6.53; N, 13.17.

7-Benzyl-2,5-dimethyl-3-phenyl-4,5-dihydro-2H-pyrazolo [4,3-c]pyridine (8). Yield: 4%; thick oil; ir (KBr): 2913, 2852, 1576, 1464, 1368, 1230, 1183, 1017 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 (t, 2H, Ar–H), 7.39 (m, 5H, Ar–H), 7.30 (m, 3H, Ar–H), 7.19 (d, 1H, =CH, *J* = 7.3 Hz), 3.91 (s, 3H, N–CH_3), 3.69 (s, 2H), 3.54 (s, 2H), 2.45 (s, 3H, N–CH_3); ms (EI): *m/z* 316.17 ($M^+ + 1$), 315.17 (M^+), 314.16 ($M^+ - 1$); *Anal*. Calcd for $C_{21}H_{21}N_3$: C, 79.97; H, 6.71; N, 13.32. Found: C, 79.81; H, 6.62; N, 13.22.

N-Benzylidene-N′,N′-dimethylhydrazine (9). Yield: 9%; oil; ir (KBr): 2951, 2854, 2825, 2785, 1589, 1561, 1469, 1442, 1363, 1272, 1132, 1033 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.60 (d, 2H, Ar–H, *J* = 7.4 Hz), 7.35 (t, 2H, Ar–H), 7.28 (s, 1H, =CH), 7.25 (t, 1H, Ar–H), 3.00 (s, 6H, N $(CH_3)_2$); ms (EI): *m/z* 148.08 (M^+); *Anal*. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.78; H, 8.21; N, 18.73.

Benzylidene-1-aminopiperidine (10). 1-Aminopiperidine (0.3 g, 0.005 mol) was added to a stirring solution of freshly distilled benzaldehyde (0.5 g, 0.0047 mol) in ethanol (10 mL) at ~10°C. The mixture was refluxed for 3 h, and the ethanol was removed at 60°C under reduced pressure. From the crude mass, hot hexanes extraction yielded the pure product **10** as oil, 0.42 g (61%); ^{1}H-NMR ($CDCl_3$): δ 7.64 (d, 2H, Ar–H, *J* = 7.3 Hz), 7.56 (s, 1H, =CH), 7.36 (t, 2H, Ar–H), 7.25 (t, 1H, Ar–H), 3.21 (t, 4H), 1.82 (p, 4H), 1.62 (p, 2H).

Benzoic acid benzylidene-hydrazide (11). A mixture of freshly distilled benzaldehyde (2.0 g, 0.019 mol) and benzoylhydrazine (2.6 g, 0.019 mol) was heated under reflux in dichloromethane (20 mL) for 24 h. The reaction mixture was cooled to room temperature, and the solid obtained was filtered and washed with dichloromethane (2 × 10 mL). The solid was dried at 40°C under vacuum for 6 h to give **16** as a colorless solid, 3.8 g (85%); mp 203°C [lit [24] mp 203–205°C]; ^{1}H-NMR (DMSO-d_6): δ 11.85 (s, 1H, NH), 8.43 (s, 1H, =CH), 7.95 (d, 2H, Ar–H, *J* = 7.5 Hz), 7.71 (d, 2H, Ar–H, *J* = 6.9 Hz), 7.63 (t, 1H, Ar–H), 7.52 (t, 2H, Ar–H), 7.43 (m, 3H, Ar–H).

X-ray crystallography. Compound **3** was crystallized from isopropyl alcohol. Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 707837. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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