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SYNTHESIS OF FURO[2,3-*c*]PYRIDINE

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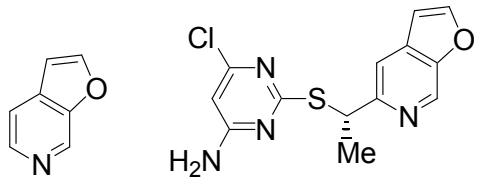
Abstract — A new synthetic strategy toward furo[2,3-*c*]pyridine (**1**) starting with *N*-benzenesulfonylpiperidin-4-one (**2**) in good yield is described. A synthesis of azasuger analog **9** is also prepared.

Furo[2,3-*c*]pyridine (**1**) is a key core structure in many bioactive molecules.[1,2] An important example is the furo[2,3-*c*]pyridine (**1**) contained in PNU-142721, a derivative reported by Morris group as a potent HIV-1 protease inhibitor (Figure 1).[3] From the synthetic strategy, main three approaches have been reported for access to this furopyridine with bicyclic fused system.[4] One is the annulation of a furan ring onto a substituted pyridine, one is the cyclization of a functionalized pyridine ring from a furan derivative, and the other is multicomponent reaction.[5,6] Fort and co-workers had studied the effect of alkyllithium on furo[2,3-*c*]pyridine.[7] In the other notable reports, the structural framework of substituted furopyridine is usually synthesized by furan ring formation involving Pd-catalyzed reactions.[8]

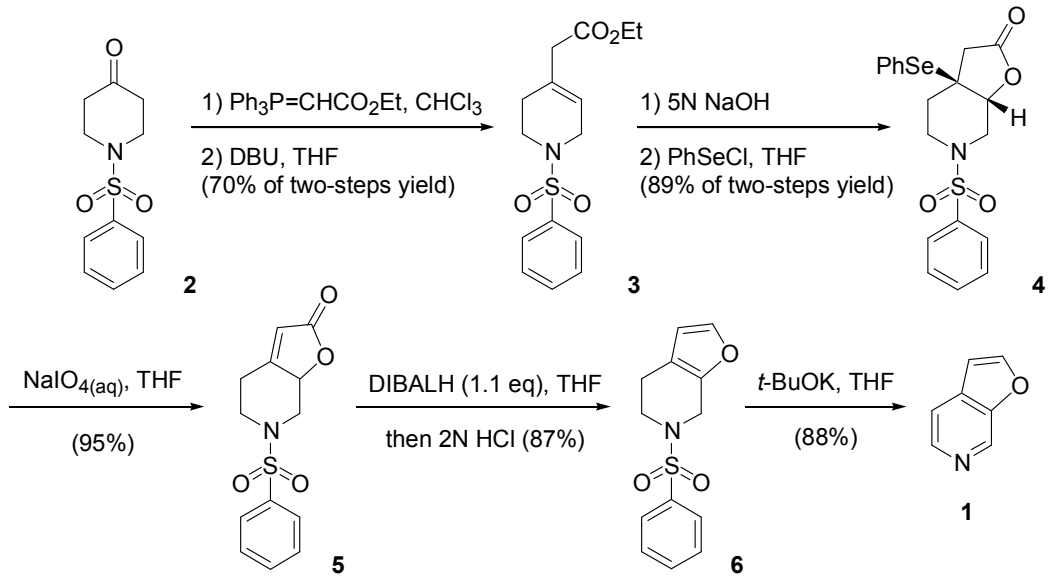


1 PNU-142721

Figure 1. Structures of furo[2,3-*c*]pyridine (**1**) and PNU-142721

In preliminary studies, we explored some concise reactions in the preparation of the tricyclic structural framework, including benzoisoquinoline, benzonaphthyridine, and tetrahydrobenzoisoquinolinol by the *N*-benzenesulfonylpiperidin-4-one (**2**).[9] It was easily synthesized from 4-hydroxypiperidine in high yields *via N*-benzenesulfonation and Jones oxidation. In order to continue our investigation, the facile synthesis of furo[2,3-*c*]pyridine (**1**) starting from known ketone (**2**) in five-steps was reported.

Ketone (**2**) was chosen as the starting material for synthesizing furo[2,3-*c*]pyridine (**1**) as shown in Scheme 1. Initially, β,γ-unsaturated ester (**3**) was provided in 70% yield of two-steps *via* (i) Wittig olefination of ketone (**2**) with $Ph_3P{=}CHCO_2Et$ in $CHCl_3$ at reflux for 10 h and (ii) DBU-mediated deconjugation of the resulting α,β-unsaturated ester in THF at reflux for 10 h.[10] Further, hydrolysis of **3** with 2N NaOH solution in THF at reflux for 15 h afforded an acid. Without purification, treatment of the corresponding acid with PhSeCl in THF at rt for 2 h isolated a sole isomer (**4**) in 89% yield of two-steps. Next, $NaIO_4$-mediated oxidative dehydroselenylation of **4** in THF at rt for 2 h provided α,β-unsaturated lactone (**5**) in 95% yield. The hydrogenated derivative of **5** had been synthesized from various sources,[11] and some of them showed the interesting biological activities.[11c] In the other hand, the iodocyclization of the acid had been studied.[12] Treatment of the acid with I_2 and $NaHCO_3$ in MeCN and followed by dehydroiodination of the resulting product with DBU was provided compound (**5**) in 35% yield of two steps. In comparison with the yield of two cyclizations, PhSeCl/$NaIO_4$ system is better.

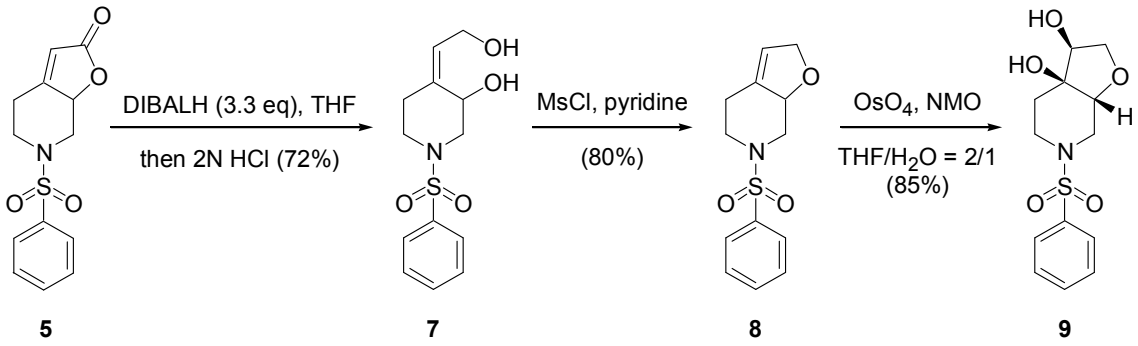


Scheme 1. Synthetic approach toward furo[2,3-*c*]pyridine (**1**)

With the successful results in hand, the reduction condition of **5** was examined. Reduction of **5** with 1.1 equivalent of DIBALH in THF at ice bath for 5 h followed by an acidic work-up afforded smoothly **6** with a formation of furan ring in 87% yield. Compound (**6**) is a reduced form of furo[2,3-*c*]pyridine. The related analogs were claimed to be useful bioactive molecule.[6a,13] The structural framework of **6** was determined using single-crystal X-ray analysis.[14] Attempts to perform the reaction with the other reducing agents (i.e., $LiBH_4$ or $LiAlH_4$) and reaction conditions failed to obtain the complex mixture. Further, furo[2,3-*c*]pyridine (**1**) was easily yielded in 88% yield by aromatization of **6** with *t*-BuOK in THF at

reflux for 1 h.[15] This typical experimental procedure offers a general and efficient preparation for the skeleton of furo[2,3-*c*]pyridine.

As shown in Scheme 2, reduction of **5** with 3.3 equivalent of DIBALH in THF at ice bath for 5 h followed by acidic work-up afforded **7** in 72% yield. Next, intramolecular cyclization of **7** with MsCl in pyridine at rt for 10 h was provided **8**. Osmylation of **8** with OsO_4/NMO combination at reflux for 10 h produced bicyclic piperidine (**9**) in 85% yield.[16] According to literature reports, hydroxylated piperidines have demonstrated their utility in the treatment of carbohydrate-mediated diseases.[17] The exhibited methodology could provide a new route for preparing azasuger analog in search of useful compounds with potential biological activities.



Scheme 2. Synthetic approach toward hexahydrofuro[2,3-*c*]pyridine-3,3a-diol (**9**)

In summary, we have successfully presented a new synthetic methodology for producing the furo[2,3-*c*]pyridine (**1**) and hydroxylated piperidine (**9**). Further studies on the biological evaluation of the desulfonated compounds of **8** and **9** are actively underway in laboratories.

EXPERIMENTAL SECTION

General. Tetrahydrofuran (THF) was distilled prior to use. All other reagents and solvents were obtained from commercial sources and used without further purification. Reactions were routinely carried out under an atmosphere of dry nitrogen with magnetic stirring. Products in organic solvents were dried with anhydrous magnesium sulfate before concentration *in vacuo*.

(1-Benzenesulfonyl-1,2,3,6-tetrahydropyridin-4-yl)-acetic acid ethyl ester (3). A solution of **2** (478 mg, 2.0 mmol) in $CHCl_3$ (10 mL) was added to a rapidly stirred solution of $Ph_3P{=}CHCO_2Et$ (770 mg, 2.2 mmol) in $CHCl_3$ (10 mL), then stirred at reflux for 10 h. The resulting mixture was concentrated under reduced pressure. Water (20 mL) was added to the residue and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Without further purification, DBU (500 mg, 3.3 mmol) was added to a solution

of the resulting crude product in THF (10 mL). The mixture was stirred at reflux for 10 h, and the reaction was quenched with water (1 mL) at rt. 1N $HCl_{(aq)}$ (10 mL) was added to the reaction mixture and the solvent was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 8/1~6/1) afforded **3** as a white solid (433 mg, 70%). mp 60-61 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{15}H_{20}NO_4S$ 310.1113, found 310.1114; ^{1}H NMR (400 MHz): δ 7.73-7.70 (m, 2H), 7.55-7.44 (m, 3H), 5.43 (s, 1H), 4.03 (q, *J* = 7.2 Hz, 2H), 3.52 (br s, 2H), 3.14 (t, *J* = 5.6 Hz, 2H), 2.90 (br s, 2H), 2.17 (br s, 2H), 1.16 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz): δ 170.57, 135.88, 132.59, 129.79, 128.82 (2x), 127.35 (2x), 120.55, 60.48, 44.49, 42.53, 41.94, 28.12, 13.92; Anal. Calcd for $C_{15}H_{19}NO_4S$: C, 58.23; H, 6.19; N, 4.53. Found: C, 58.51; H, 6.43; N, 4.72.

6-Benzenesulfonyl-3a-phenylselenyl-hexahydrofuro[2,3-*c*]pyridin-2-one (4). A solution of **3** (155 mg, 0.5 mmol) and 2N $NaOH_{(aq)}$ (5 mL) in THF (10 mL) was refluxed for 15 h. The reaction was traced by TLC until compound (**3**) was completely consumed. The reaction solution was cooled to rt and concentrated until one third of the solution remained. The remained solution was extracted with EtOAc (3 x 10 mL). The aqueous phase was cooled in ice-bath and acidified by adding 12N $HCl_{(aq)}$ to pH 2. The aqueous solution was extracted with EtOAc (3 x 20 mL) and the combined organic layers were washed with brine, dried, filtered and evaporated to afford crude acid product under reduced pressure. Without purification, PhSeCl (105 mg, 0.55 mmol) was added to a stirred solution of the resulting acid product in THF (10 mL) at rt. The reaction mixture was stirred at rt for 2 h and the solvent was concentrated under reduced pressure. Water (10 mL) was added to the residue and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 6/1~4/1) afforded **4** as a white solid (195 mg, 89%). mp 61-62 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{19}H_{20}NO_4SSe$ 438.0278, found 438.0280; ^{1}H NMR (400 MHz): δ 7.79-7.76 (m, 2H), 7.64-7.48 (m, 5H), 7.44-7.39 (m, 1H), 7.34-7.30 (m, 2H), 4.29 (t, *J* = 3.2 Hz, 1H), 3.84 (ddd, *J* = 0.8, 2.0, 13.6 Hz, 1H), 3.46 (ddt, *J* = 1.2, 4.4, 11.2 Hz, 1H), 3.18 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.87 (ddt, *J* = 4.0, 9.2, 13.6 Hz, 1H), 2.71 (d, *J* = 17.2 Hz, 1H), 2.47 (d, *J* = 17.2 Hz, 1H), 1.95-1.84 (m, 2H); ^{13}C NMR (100 MHz): δ 172.99, 137.98 (2x), 136.45, 133.03, 130.03, 129.64 (2x), 129.18 (2x), 127.33 (2x), 124.07, 78.25, 43.81, 43.77, 43.31, 41.84, 32.00.

6-Benzenesulfonyl-5,6,7,7a-tetrahydro-4*H*-furo[2,3-*c*]pyridin-2-one (5). A solution of $NaIO_4$ (107 mg, 0.5 mmol) in water (3 mL) was added to a rapidly stirred solution of **4** (175 mg, 0.4 mmol) in THF (10 mL), then stirred at rt for 2 h. The resulting mixture was concentrated under reduced pressure. Water (10 mL) was added to the residue and extracted with EtOAc (3 x 10 mL). The combined organic layers were

washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 4/1~1/1) afforded **5** as a white solid (107 mg, 95%). mp 181-182 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{14}NO_4S$ 280.0644, found 280.0645; ^{1}H NMR (400 MHz): δ 7.79-7.76 (m, 2H), 7.65-7.60 (m, 1H), 7.57-7.53 (m, 2H), 5.81 (t, *J* = 1.6 Hz, 1H), 4.87 (ddd, *J* = 0.8, 6.8, 10.0 Hz, 1H), 4.53 (ddd, *J* = 2.0, 6.8, 11.2 Hz, 1H), 4.15 (ddt, *J* = 1.6, 6.0, 12.0 Hz, 1H), 2.86 (ddd, *J* = 2.0, 3.2, 14.0 Hz, 1H), 2.75-2.67 (m, 1H), 2.39 (dt, *J* = 3.6, 12.4 Hz, 1H), 2.17 (dd, *J* = 10.0, 11.2 Hz, 1H); ^{13}C NMR (100 MHz): δ 171.87, 167.25, 136.87, 133.36, 129.43 (2x), 127.16 (2x), 114.30, 76.83, 51.80, 46.13, 28.07; Anal. Calcd for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 56.21; H, 4.98; N, 5.32.

6-Benzenesulfonyl-4,5,6,7-tetrahydrofuro[2,3-*c*]pyridine (6). A solution of DIBALH (1.0 M in THF, 0.33 mL, 0.33 mmol) was added to a stirred solution of **5** (84 mg, 0.3 mmol) in THF (10 mL) at ice bath. The mixture was further stirred for 5 h at ice bath. The reaction was quenched with 2N $HCl_{(aq)}$ (1 mL) at ice bath and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 8/1~6/1) afforded **6** as a white solid (69 mg, 87%). mp 118-119 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{14}NO_3S$ 264.0694, found 264.0695; ^{1}H NMR (400 MHz): δ 7.83-7.81 (m, 2H), 7.61-7.57 (m, 1H), 7.55-7.50 (m, 2H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.18 (d, *J* = 2.0 Hz, 1H), 4.21 (s, 2H), 3.38 (t, *J* = 5.6 Hz, 2H), 2.56 (tt, *J* = 2.0, 5.6 Hz, 2H); ^{13}C NMR (100 MHz): δ 144.80, 141.74, 136.87, 132.87, 129.10 (2x), 127.45 (2x), 115.18, 109.90, 44.00, 43.73, 22.26; Anal. Calcd for $C_{13}H_{13}NO_3S$: C, 59.30; H, 4.98; N, 4.32. Found: C, 59.53; H, 5.32; N, 4.56. Single-crystal X-Ray diagram: crystal of **6** was grown by slow diffusion of EtOAc into a solution of **6** in CH_2Cl_2 to yield colorless prism. The compound crystallizes in the monoclinic crystal system, space group P 1 21/c 1, *a*=7.6175(4) Å, *b*=19.3326(10) Å, *c*=8.3248(5) Å, *V*=1215.50(12) Å^3, *Z*=4, d_{calcd}=1.439 g/cm^3, *F*(000)=552, 2*θ* range 2.11~26.37^{o}, R indices (all data) R1 = 0.0463, wR2 = 0.0962.

Furo[2,3-*c*]pyridine (1). *t*-BuOK (56 mg, 0.5 mmol) was added to a solution of **6** (53 mg, 0.2 mmol) in THF (5 mL) at rt. The reaction mixture was stirred at reflux for 1 h. Water (1 mL) was added to the reaction mixture and the solvent was concentrated. The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 3/1~2/1) afforded **1** as a viscous oil (21 mg, 88%). ^{1}H and ^{13}C are in conformity with literature.[4a]

1-Benzenesulfonyl-4-(2-hydroxyethylidene)piperidin-3-ol (7). A solution of DIBALH (1.0 M in THF, 0.66 mL, 0.66 mmol) was added to a stirred solution of **5** (56 mg, 0.2 mmol) in THF (10 mL) at ice bath. The mixture was further stirred for 5 h at ice bath. The reaction was quenched with 2N $HCl_{(aq)}$ (1 mL) at

ice bath and the mixture was concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product under reduced pressure. Purification on silica gel (hexane/EtOAc = 8/1~6/1) afforded **7** as a white solid (41 mg, 72%). mp 84-86 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{18}NO_4S$ 284.0957, found 284.0958; ^{1}H NMR (400 MHz): δ 7.76-7.73 (m, 2H), 7.61-7.56 (m, 1H), 7.54-7.49 (m, 2H), 5.50 (t, *J* = 6.8 Hz, 1H), 4.64 (t, *J* = 3.2 Hz, 1H), 4.22 (dd, *J* = 8.4, 12.8 Hz, 1H), 4.02 (dd, *J* = 6.8, 12.8 Hz, 1H), 3.74-3.67 (m, 1H), 3.66-3.60 (m, 1H), 3.00 (br s, 2H), 2.74 (dt, *J* = 4.4, 12.8 Hz, 1H), 2.58 (dd, *J* = 2.4, 12.0 Hz, 1H), 2.45 (dt, *J* = 3.2, 11.2 Hz, 1H), 2.10 (dt, *J* = 3.2, 14.0 Hz, 1H); ^{13}C NMR (100 MHz): δ 137.76, 136.01, 132.91, 129.10 (2x), 127.49 (2x), 126.07, 63.76, 57.24, 52.74, 47.26, 31.15.

6-Benzenesulfonyl-2,4,5,6,7,7a-hexahydrofuro[2,3-*c*]pyridine (8). MsCl (35 mg, 0.3 mmol) was added to a solution of **7** (30 mg, 0.1 mmol) in pyridine (5 mL) at rt. The reaction mixture was stirred at rt for 10 h. CH_2Cl_2 (10 mL) was added to the reaction mixture and then 2N $HCl_{(aq)}$ (10 mL) was also added to the reaction mixture. The reaction mixture was extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexane/EtOAc = 3/1~1/1) afforded **8** as a white solid (23 mg, 80%). mp 92-93 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{16}NO_3S$ 266.0851, found 266.0853; ^{1}H NMR (400 MHz): δ 7.78-7.75 (m, 2H), 7.61-7.57 (m, 1H), 7.55-7.50 (m, 2H), 5.49 (br s, 1H), 4.68-4.61 (m, 1H), 4.59-4.53 (m, 2H), 4.19 (ddd, *J* = 1.6, 5.6, 10.4 Hz, 1H), 3.96 (ddt, *J* = 1.6, 5.6, 11.2 Hz, 1H), 2.53 (ddd, *J* = 1.6, 3.6, 14.0 Hz, 1H), 2.44-2.35 (m, 1H), 2.20 (dd, *J* = 3.2, 11.2 Hz, 1H), 2.07 (t, *J* = 10.4 Hz, 1H); ^{13}C NMR (100 MHz): δ 137.37, 137.05, 132.80, 129.13 (2x), 127.36 (2x), 118.49, 81.02, 75.78, 53.02, 46.83, 26.72; Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 59.03; H, 5.89; N, 5.52.

6-Benzenesulfonyl-hexahydrofuro[2,3-*c*]pyridine-3,3a-diol (9). A solution of 2% OsO_4 (5 mL, in THF) was added to a solution of **8** (16 mg, 0.06 mmol) in the co-solvent of THF (5 mL) and water (5 mL). NMO (100 mg, 50% in water, 0.43 mmol) was added the reaction mixture at reflux for 10 h. 10% $NaHSO_{3(aq)}$ (5 mL) was added to the reaction mixture and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to yield crude compound. Purification on silica gel (hexane/EtOAc = 1/1~1/2) afforded **9** as white solid (15 mg, 85%). mp 153-154 ^{o}C (recrystallized from hexane and EtOAc); HRMS (ESI, M^{+}+1) calcd for $C_{13}H_{18}NO_5S$ 300.0906, found 300.0908; ^{1}H NMR (400 MHz): δ 7.80-7.77 (m, 2H), 7.61-7.56 (m, 1H), 7.54-7.50 (m, 2H), 4.12 (dd, *J* = 5.6, 11.2 Hz, 1H), 3.96 (dt, *J* = 2.0, 13.6 Hz, 1H), 3.78-3.74 (m, 2H), 3.66-3.63 (m, 1H), 3.61 (t, *J* = 2.4 Hz, 1H), 2.72 (dd, *J* = 2.4, 13.6 Hz, 1H), 2.72-2.65 (m, 2H), 1.72-1.63 (m, 2H), 1.67 (dd, *J* = 4.0, 10.0 Hz,

1H); ^{13}C NMR (100 MHz): δ 136.97, 132.73, 129.02 (2x), 127.58 (2x), 75.42, 74.63, 73.63, 73.55, 44.82, 41.32, 30.62; Anal. Calcd for $C_{13}H_{17}NO_5S$: C, 52.16; H, 5.72; N, 4.68. Found: C, 52.53; H, 5.91; N, 4.59.

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14. CCDC 823539 (**6**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: 44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk).
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