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Efficient and selective synthesis of alkoxy substituted di(pyridin-2-yl)amines and *N*-arylpyridin-2-ylamines

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ABSTRACT

The formation of alkoxy substituted di(pyridin-2-yl)amines and *N*-arylpyridin-2-ylamines by nitro group reduction is described. Unexpected substitution of *ortho* with the amino at C-6 was observed during the reduction using $SnCl_2{\cdot}2H_2O$ in different alcohols. The influence of the nature of the atom at the 3- and 5-positions of nitro-substituted di(pyridin-2-yl)amines and *N*-arylpyridin-2-ylamines was investigated.

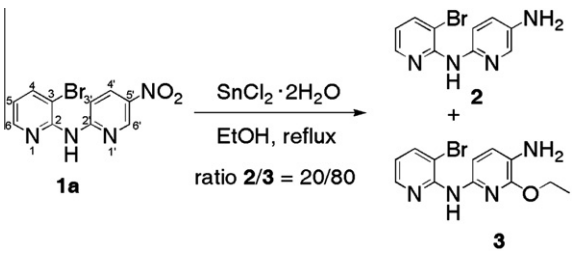
Among the wide variety of chemical structures in development as new potential drugs, small molecules based on an aminopyridine scaffold have attracted significant interest.[1] For example, a potent and novel class of mGlu5 receptor antagonists was recently indentified, based on dipyridylamines substituted at optimal positions.[1a] Also, several aminopyridine derivatives have exhibited pharmaceutical activity as antitumor[1b] or anti-infective[1c] agents.

As part of our research program, nitro dipyridinylamines were obtained through Pd-catalyzed reactions[2] or via oxidative nucleophilic substitution of hydrogen.[3] Some of these compounds were used as starting materials for the synthesis of dihydrodipyridopyrazines, a family of planar nitrogen heterocycles with potential antitumor activity.[4]

Based on our experience on the conversion of the nitro group of nitroindazole derivatives into the corresponding amino group with $SnCl_2$, in alcoholic solution, we decided to extend this reduction method, originally described by Bellamy,[5] to our nitro dipyridinylamines series, in order to prepare new bi and tri substituted compounds by a simple route.

Preliminary reduction of the nitro group of dipyridinylamine **1a** with $SnCl_2{\cdot}2H_2O$ in the presence of ethanol gave access, according to the ^1H NMR spectrum of the crude product, to a mixture of two different compounds, the desired amine **2,** and the amine **3** substituted with an ethoxy group at the *ortho* position (6′-position) (Scheme 1).

The ability of $SnCl_2$, in alcoholic solution, to form the corresponding ethoxy-substituted derivatives, was observed for the first time during the synthetic procedure developed in our laboratory to obtain the corresponding indazole derivatives starting from 7-nitroindazole, and a plausible mechanism was proposed.[6a] The reduction of aromatic nitro compounds with metals in protic solvents such as alcohols, acetic acid, water or in aqueous mineral acid, is usually presumed to proceed by way of hydroxylamine-like intermediates. Hence, we assume that the nucleophilic attack of ethanol present in the reaction mixture occurs via the lone oxygen



Scheme 1. Reduction of **1a** with stannous chloride dihydrate in ethanol.

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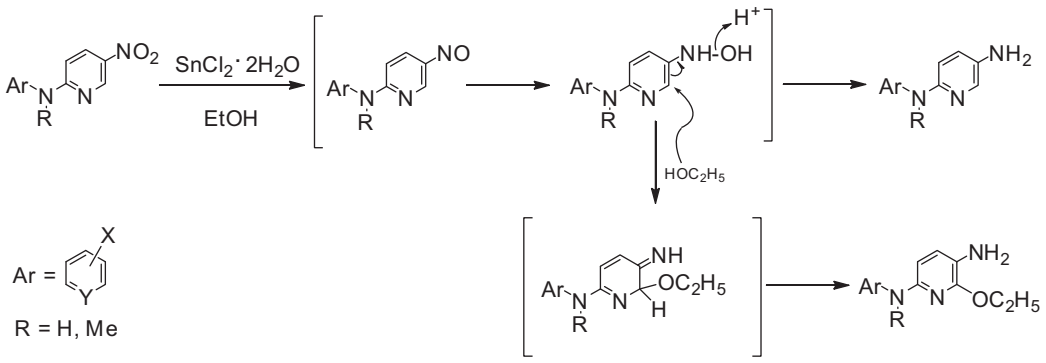
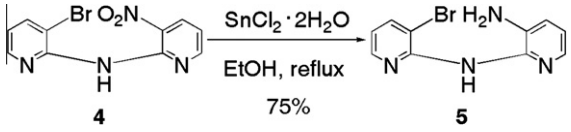


Scheme 2. Proposed mechanism for the reduction of aromatic nitrocompounds with stannous chloride dihydrate in ethanol.



Scheme 3. Reduction of **4** with stannous chloride dihydrate in ethanol.

pair (Scheme 2). This substitution proceeds during this intermediate stage of the reduction process through protonated hydroxylamine compounds.[7]

It is noteworthy that only the corresponding amine **5** was obtained when the reduction of the nitro group of dipyridinylamine **4** was carried out using the same method (Scheme 3).[2a]

These results could be related to the important role played by the position of the nitro group in this reduction reaction as was reported for nitroarenes and nitroindazoles.[6]

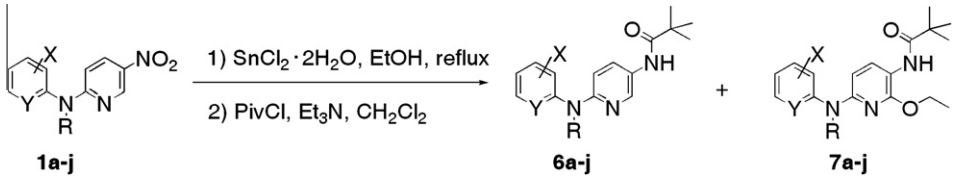
In order to show the generality and flexibility of this reaction we used different nitro-substituted dipyridinylamines **1a–h** and *N*-arylpyridin-2-ylamines **1i** and **1j** as starting materials.[8] As significant degradation of the amines was observed during separation by flash chromatography, we immediately protected this using pivaloyl chloride in dichloromethane (Scheme 4, Table 1).[9]

As shown in Table 1, the nature of groups X, Y and R led to different ratios of **6** and **7**.

First, we studied the influence of the nature of the atom at the 3-position of nitro-substituted dipyridinylamines **1a–f** (Table 1, entries 1–6). When the 3-position was occupied with a halogen or a methyl group, the major product was the amine substituted with an *ortho* ethoxy group **7a–e** (Table 1, entries 1–5). Moreover, we observed that when the reduction-protection reaction was conducted with **1a–c**, the presence of bromo **1a**, chloro **1b** or iodo **1c** substituents at the 3-position led to similar ratios of products **6** and **7**. As expected, a quite different order of reactivity was found for fluorine-substituted **1d** which afforded a ratio comparable with that obtained using the methyl-substituted compound (**1e**).

In the case of **1f** where the 3-position was vacant, we observed a decrease in the amount of **7f** compared with **7a–e** (Table 1, entry 6). On the other hand, if the halogen was at the 5-position and the 3-position was unoccupied, we registered similar behavior, the ratio of the two amines being 50/50 (Table 1, entry 8). Hence, we note the importance of the presence of a substituent at the 3-position (halogen or alkyl group) in order to obtain the product substituted with an ethoxy group as the major product.

As shown in Table 1 (entry 7) and according to ^{1}H NMR data[11] the introduction of a methyl group on the dipyridylamino N-atom



Scheme 4. Reduction of the nitro group of compounds **1a–j** and protection with pivaloyl chloride.

Table 1
Reduction of the nitro group of compounds **1a–j**

Entry	Substrate	X	Y	R	Ratio **6**/**7**[a]	Product **6** yield[b] (%)	Product **7** yield[b] (%)	Total yield[b] (%)
1	**1a**	3-Br	N	H	20/80	15[10a]	52[10b]	67
2	**1b**	3-Cl	N	H	20/80	14	50	64
3	**1c**	3-I	N	H	17/83	—[c]	78	78
4	**1d**	3-F	N	H	30/70	29	57	86
5	**1e**	3-Me	N	H	32/68	—[c]	30	30
6	**1f**	3-H	N	H	45/55	16	24	40
7	**1g**	3-Br	N	Me	75/25	60	17	77
8	**1h**	5-Br	N	H	50/50	37	32	69
9	**1i**	3-H	CH	H	80/20	50	10	60
10	**1j**	3-Br	CH	H	60/40	43	24	67

[a] Ratio determined by ^{1}H NMR spectroscopy of the crude mixture of amines.
[b] Isolated yield after separation by flash chromatography.
[c] Only trace amounts (<5%) of the purified product were isolated.

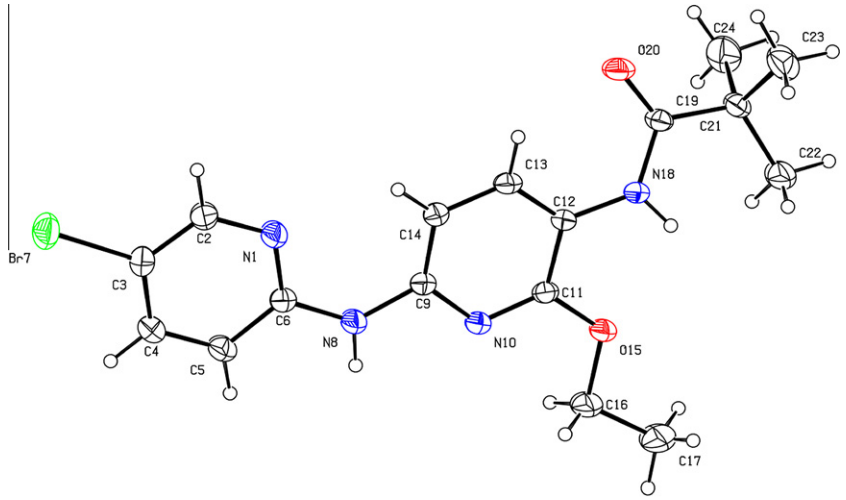
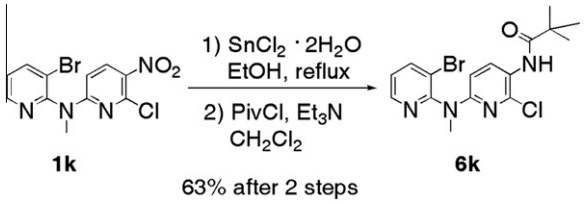
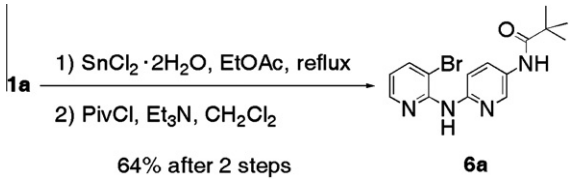


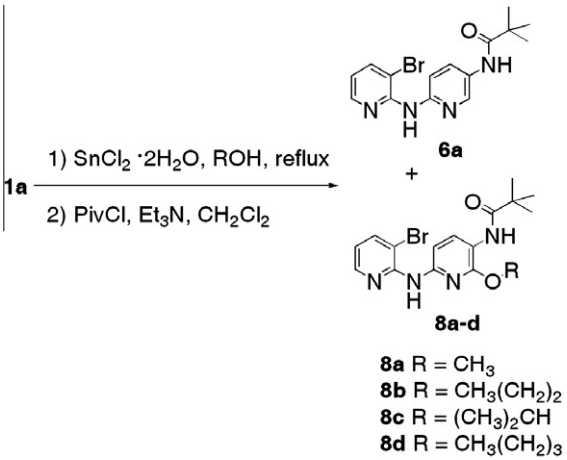
Figure 1. X-ray crystal structure of compound **7h**.



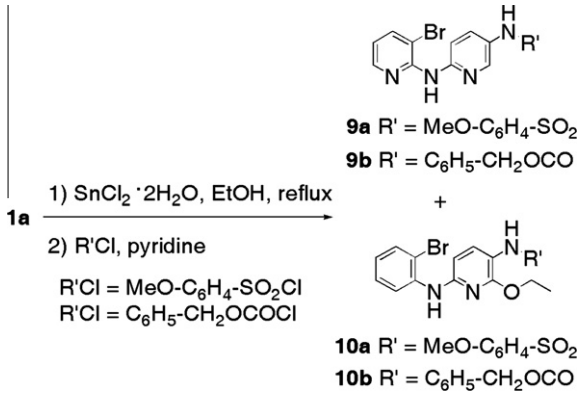
Scheme 5. Synthesis of pivalamide **6k** from *N*-(3-bromopyridin-2-yl)-*N*-(6-chloro-5-nitropyridin-2-yl)-*N*-methylamine **1k**.



Scheme 7. Reduction of **1a** in ethyl acetate and protection with pivaloyl chloride.



Scheme 6. Reduction of **1a** in different alcohols and protection with pivaloyl chloride.



Scheme 8. Reduction of **1a** and protection with 4-methoxybenzenesulfonyl chloride and benzyl chloroformate in pyridine.

Table 2
Reduction of **1a** in different alcohols

Entry	R	Product	Ratio **6a**/**8**	Product **6a** yield (%)	Product **8** yield (%)	Total yield (%)
1	CH_3	**8a**	16/84	15	75	90
2	$CH_3(CH_2)_2$	**8b**	30/70	22	56	78
3	$(CH_3)_2CH$	**8c**	70/30	45	21	66
4	$CH_3(CH_2)_3$	**8d**	50/50	33	31	64

(**1g**) led to an inversion of the proportion of the two compounds **6g** and **7g**[12] (75/25). Also, in order to compare the dipyridinylamine series with *N*-arylpyridin-2-ylamines, we used compounds **1i** and **1j** as substrates for reduction of the nitro group with $SnCl_2$ in the presence of ethanol (Table 1, entries 9 and 10). In these cases, the major compounds in the mixture were the amines **6i**,**j** as opposed to the substituted ethoxy amines **7i**,**j**.

We observed that, as with the dipyridinyl amine series, the presence of a bromide at the 3-position was important, increasing the amount of ethoxy substituted compound **7j**.

For product **7h**,[13] it was possible to isolate single crystals permitting its study by X-ray crystallography.[14] The ORTEP representation of this product clearly indicates the presence of an ethoxy group at the pyridine C-6 position (Fig. 1).

Under the same conditions, *N*-(3-bromopyridin-2-yl)-*N*-(6-chloro-5-nitropyridin-2-yl)methylamine (**1k**), gave access, only to the corresponding amine, isolated as its pivalamide **6k**, because of the presence of a substituent at the 6′-position (Scheme 5).

Table 3
Reduction of **1a** and protection with 4-methoxybenzenesulfonyl chloride or benzyl chloroformate in pyridine

Entry	R′Cl	Ratio **9**/**10**	Product **9** yield (%)	Product **10** yield (%)	Total yield (%)
1	MeO-C_6H_4-SO_2Cl	24/76	18	55	73
2	C_6H_5-CH_2OCOCl	20/80	14	64	78

Taking into account the widespread use and the high efficiency of bromo compounds for further cyclizations via palladium-catalyzed intramolecular C–C and C–N bond formation,[2,15] we chose to continue our study using *N*-(3-bromopyridin-2-yl)-*N*-(5-nitropyridin-2-yl)methylamine (**1a**) as the substrate for further investigations.

Thus, the reduction was achieved with $SnCl_2{\cdot}2H_2O$ in different alcohols, in order to introduce various alkoxy groups at the 6′-position (Scheme 6, Table 2).

In all cases, compounds **8a–d** were easily obtained, illustrating the ability to introduce various alkoxy groups.

The addition of different Lewis acids, such as $BF_3{\cdot}Et_2O$ or $Sc(OTf)_3$, to the reaction mixtures did not have any significant influence on the yields of the *ortho*-alkoxysubstituted derivatives.

The reduction of **1a** using ethyl acetate as the solvent led to the exclusive generation of the corresponding amine and no trace of substitution at the *ortho* position was observed. After protection, we obtained compound **6a** (Scheme 7).

We also used other amine protecting groups such as 4-methoxybenzenesulfonyl chloride and benzyl chloroformate in pyridine (Scheme 8). Hence, compounds **9a**, **10a** and **9b**, **10b** were obtained in good yields (Table 3).

In summary, we have studied the reduction of the nitro group of dipyridinylamines and *N*-arylpyridin-2-ylamines. All the synthetic achievements described herein are operationally simple and the corresponding bi- and trisubstituted amines were easily obtained by reduction using $SnCl_2{\cdot}2H_2O$ in an alcohol.

Moreover, it is noteworthy that the 3-bromo dipyridinylamines substituted at the 5′- and 6′-positions, represent good starting materials for other types of functionalization (e.g., cyclizations via palladium-catalyzed intramolecular C–C bond formation), in order to obtain new compounds which may be of interest for heterocyclic chemistry and medical purposes.

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8. (a) Compounds **1a–e** and **1g–h** were prepared using the method described in Ref. 3. (b) Compounds **1f**, **1i** and **1j** were prepared using the method described by El-Bardan, A. A.; El-Subruiti; G. M.; El-Hegazy, F. E.-Z. M.; Hamed, E. A. *Int. J. Chem. Kinet.* **2002**, *34*, 645–650.
9. General procedure for the preparation of compounds **6** and **7**. A mixture of dipyridinylamine or *N*-arylpyridin-2-ylamine **1a–j** and $SnCl_2{\cdot}2H_2O$ (5 equiv) in 10 mL of EtOH was heated at 60 °C. After reduction, the solution was allowed to cool. The pH was made slightly basic (pH 7–8) by the addition of 5% aqueous $KHCO_3$ before extraction with EtOAc. The organic phase was dried over $MgSO_4$. The solvent was removed to afford the amine, which was immediately dissolved in CH_2Cl_2 (10 mL) and then Et_3N (1.5 equiv) and trimethylacetyl chloride (1.1 equiv) were added. The reaction mixture was stirred at room temperature overnight, concentrated in vacuo and the resulting residue was purified by flash chromatography (eluted with EtOAc/PE).
10. (a) Compound **6a**: IR (ATR): 1506, 2960, 3440 cm^{-1}; MS: m/z = 349.0 ($[M+H]^+$, ^{79}Br), 351.0 ($[M+H]^+$, ^{81}Br); HRMS calculated for $C_{15}H_{18}N_4OBr$ $[M+H]^+$ 349.0668, found 349.0664; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.33 (s, 9H, $3CH_3$), 6.70 (dd, 1H, J = 4.8, 7.7 Hz), 7.32 (br s, 1H, NH), 7.77 (dd, 1H, J = 1.5, 7.7 Hz), 7.81 (br s, 1H, NH), 7.99 (dd, 1H, J = 2.4, 9.0 Hz), 8.20 (dd, 1H, J = 1.4, 4.7 Hz), 8.34 (d, 1H, J = 2.4 Hz), 8.42 (d, 1H, J = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 27.8 ($3CH_3$), 39.7 (Cq), 106.9 (Cq), 112.4 (CH), 116.7 (CH), 129.6 (Cq), 130.7 (CH), 139.9 (CH), 140.6 (CH), 146.3 (CH), 149.6 (Cq), 150.8 (Cq), 176.9 (Cq). (b) Compound **7a**: IR (ATR): 1426, 2962, 3441 cm^{-1}; MS: m/z = 393.0 ($[M+H]^+$, ^{79}Br), 395.0 ($[M+H]^+$, ^{81}Br), 415.0 ($[M+Na]^+$, ^{79}Br), 417.0 ($[M+Na]^+$, ^{81}Br); HRMS calculated for $C_{17}H_{22}N_4O_2Br$ $[M+H]^+$ 393.0926, found 393.0920; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.32 (s, 9H, $3CH_3$), 1.43 (t, 3H, J = 7.0 Hz, CH_3), 4.43 (q, 2H, J = 7.0 Hz, CH_2), 6.68 (dd, 1H, J = 4.8, 7.7 Hz), 7.51 (br s, 1H, NH), 7.75 (dd, 1H, J = 1.5, 7.7 Hz), 7.85 (br s, 1H, NH), 7.95 (d, 1H, J = 8.6 Hz), 8.22 (dd, 1H, J = 1.5, 4.8 Hz), 8.59 (d, 1H, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 14.8 (CH_3), 27.7 ($3CH_3$), 39.9 (Cq), 62.3 (CH_2), 103.9 (CH), 106.7 (Cq), 116.3 (CH), 117.3 (Cq), 129.3 (CH), 140.3 (CH), 145.2 (Cq), 146.6 (CH), 150.8 (Cq), 151.6 (Cq), 176.5 (Cq).
11. Compound **7g**: IR (ATR): 796, 1665, 2965 cm^{-1}; MS: m/z = 407.0 ($[M+H]^+$, ^{79}Br), 409.0 ($[M+1]^+$, ^{81}Br), 429.0 ($[M+Na]^+$, ^{79}Br), 431.0 ($[M+Na]^+$, ^{81}Br); HRMS calculated for $C_{18}H_{24}N_4O_2Br$ $[M+H]^+$ 407.1083, found 407.1098; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.29 (s, 9H, $3CH_3$), 1.30 (t, 3H, J = 7.0 Hz, CH_3), 3.46 (s, 3H), 4.24 (q, 2H, J = 7.0 Hz, CH_2), 6.08 (d, 1H, J = 5.3 Hz), 6.98 (dd, 1H, J = 4.7, 7.8 Hz), 7.75 (br s, 1H, NH), 7.88 (dd, 1H, J = 1.6, 7.8 Hz), 8.42–8.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 14.8 (CH_3), 27.7 ($3CH_3$), 37.3 (CH_3), 39.8 (Cq), 62.0 (CH_2), 101.7 (CH), 115.0 (Cq), 118.5 (Cq), 121.3 (CH), 129.3 (CH), 142.3 (CH), 147.7 (CH), 151.2 (Cq), 151.6 (Cq), 156.8 (Cq), 176.4 (Cq).
12. The structure of product **7g** was also proved by independent synthesis. Treatment of *N*-(3-bromopyridin-2-yl)-*N*-(6-chloro-5-nitropyridin-2-yl)methylamine (**1k**) with 10 equiv of NaOEt in absolute EtOH on heating gave access to the corresponding 6-ethoxy substituted derivative in a 65% yield. After reduction of the nitro group using $SnCl_2{\cdot}2H_2O$ in EtOH and protection using the same conditions we obtained the analogous compound **7g** in an 81% yield.
13. Compound **7h**: IR (ATR): 1475, 2957, 3438 cm^{-1}; MS: m/z = 393.5 ($[M+H]^+$, ^{79}Br), 395.5 ($[M+H]^+$, ^{81}Br), 415.5 ($[M+Na]^+$, ^{79}Br), 417.5 ($[M+Na]^+$, ^{81}Br); HRMS calculated for $C_{17}H_{22}N_4O_2Br$ $[M+H]^+$ 393.0911, found 393.0926; ^1H NMR ($CDCl_3$, 400 MHz) δ = 1.31 (s, 9H, $3CH_3$), 1.44 (t, 3H, J = 7.0 Hz, CH_3), 4.38 (q, 2H, J = 7.0 Hz, CH_2), 6.74 (d, 1H, J = 5.3 Hz), 7.41 (br s, 1H, NH), 7.61–7.66 (m, 2H), 7.79 (br s, 1H, NH), 8.26 (d, 1H, J = 1.5 Hz), 8.52 (d, 1H, J = 5.3 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ = 14.8 (CH_3), 27.7 ($3CH_3$), 39.9 (Cq), 62.5 (CH_2), 103.0 (CH), 110.4 (Cq), 112.1 (CH), 116.2 (Cq), 129.8 (CH), 140.0 (CH), 146.2 (Cq), 148.7 (CH), 151.8 (Cq), 152.8 (Cq), 176.6 (Cq).
14. Crystal structure data for compound **7h**: CCDC 821396. These data can be obtained free of charge at www.ccdc.cam.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.; e-mail: deposit@ccdc.cam.ac.uk.).
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