COMMUNICATION

DMSO–Ac_2O promoted nitration of isoquinolines. One-step synthesis of 1-nitroisoquinolines under mild conditions

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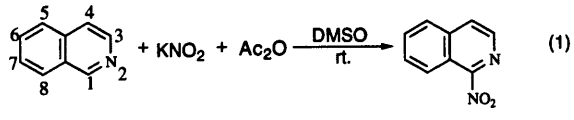
1-Nitroisoquinolines were directly prepared from the corresponding isoquinolines with potassium nitrite and acetic anhydride in DMSO in good yields.

Nucleophilic substition in the heterocyclic ring of isoquinoline **1** normally requires attack by a powerful nucleophile. In practice, amide and hydroxide ions have been employed for the nucleophilic substitution of isoquinoline at the C-1 position.[1] From calculations,[2,3] C-1 is proven to have the lowest π-electron density, which should correspond to the preferred site for the nucleophilic reaction. Other nucleophiles, including Grignard reagents[4] and organolithium compounds,[5] react with isoquinoline to yield 1-substituted-1,2-dihydroisoquinolines *via* nucleophilic addition. It is well known that addition at C-1 in isoquinoline can be achieved by successive attack with electrophilic and nucleophilic species.[6] For example, isoquinoline reacts with benzoyl chloride and potassium cyanide in dichloromethane–water to give the Reissert derivative without aromatization of the heterocyclic ring system.

Direct nitration at the C-1 position of isoquinoline has never been reported and substitution in isoquinoline under the normal nitration conditions occurs at C-5 and C-8.[7] Therefore, the preparation of 1-nitroisoquinoline **2** requires several steps. Hayashi and co-workers[8] prepared 1-nitroisoquinoline from isoquinoline in 4 steps. It involves chlorination of 1-hydroxyisoquinoline followed by replacement first by iodide ion and then by nitrite ion. The overall yield of the 4 step reaction from isoquinoline was less than 10%. Later, Taylor and co-workers[9] developed a method for the synthesis of 1-nitroisoquinoline *via* oxidation of the sulfilimine (sulfimide) prepared from 1-aminoisoquinoline to the unstable 1-nitroso-isoquinoline, followed by a second oxidation to give 1-nitroisoquinoline. As a consequence, one step nitration at the C-1 position of isoquinoline was unknown prior to the present study.

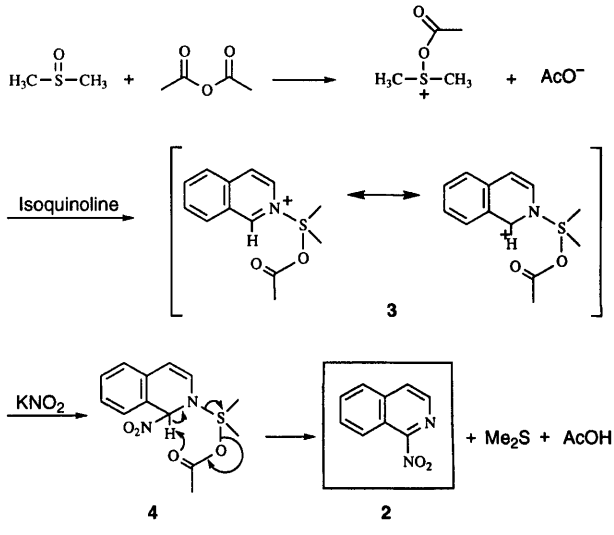
With these examples in mind we studied the direct nitration of isoquinoline with potassium nitrite and acetic anhydride in DMSO.



1 **2**

Treatment of a DMSO solution of acetic anhydride with a mixture of potassium nitrite and isoquinoline in DMSO caused the immediate appearance of a brown colour accompanied by vigorous evolution of nitrous anhydride.[10] After stirring at room temperature for 30 min, 1-nitroisoquinoline was isolated in high yield without the formation of 1-nitro-1,2-dihydro-isoquinoline. The spectral data (^1H and ^{13}C NMR) of 1-nitroisoquinoline have not been published elsewhere.[11] Therefore, the structure was established by NMR. The fact that there was no singlet at δ_H 9.14 which corresponds to the proton at C-1 of isoquinoline[12] suggests that C-1 position has been substituted without the formation of a Reissert-type compound. The two peaks at δ_H 8.32 and 8.01 are typical for the protons at C-8 and C-5, which implies that the product is not 5-nitro- or 8-nitro-isoquinoline. The two hydrogen atoms in the heterocyclic ring of isoquinoline (C-3 and C-4) have very characteristic NMR peaks, *i.e.* H-4 δ 8.45 (doublet) J 5 Hz and H-3 δ 7.98 (doublet) J 5 Hz. The yellow–white crystalline product, mp 65–66 °C, was thus identified as 1-nitroisoquinoline (lit.,[8] 65–66 °C).

In a control experiment, in the absence of acetic anhydride, nucleophilic substitution did not occur and the starting material was quantitatively recovered. As shown in Table 1, use of acetyl chloride or benzoyl chloride instead of acetic anhydride resulted in the formation of 1-nitroisoquinoline in low yield (36% and 40% respectively) but with no trace of Reissert-type compounds. However, when isoquinoline was treated with trifluoroacetic anhydride, DCC or $(COCl)_2$, no product was observed. The use of silver nitrite prevented the nitration of isoquinoline to 1-nitroisoquinoline (trace) and the starting material was recovered. In all cases tried, direct nitration by this method gave the desired 1-nitroisoquinoline without the formation of byproducts. It should be mentioned that in DMF, CH_2Cl_2, EtOH or hexane, reaction with Ac_2O and KNO_2 failed to form 1-nitroisoquinoline. From these results, it can be concluded that both DMSO and Ac_2O are crucial for the nucleophilic C-1 nitration of isoquinoline. In the presence of HMPA as a cosolvent, the reaction rate and yield were slightly increased. It seems that this method, which is analogous to the Pfitzner–Moffatt technique,[13] utilizes a complex of DMSO and Ac_2O for electrophilic attack at the N-atom to form intermediate **3** (Scheme 1). Attack of nitrite ion on intermediate



Scheme 1

Table 1 Preparation of 1-nitroisoquinoline under various conditions

Entry	Reactant (equiv.)	Solvent	Time (h)	Yield (%)[a]
1	KNO_2(6), Ac_2O(6)[b]	DMSO + HMPA	0.5	88 (7)[c]
2	KNO_2(6), Ac_2O(0)	DMSO + HMPA	24	0 (95)
3	KNO_2(6), Ac_2O(6)	DMSO	1	75 (23)
4	KNO_2(4), Ac_2O(4)	DMSO + HMPA	0.5	86 (6)
5	KNO_2(2), Ac_2O(2)	DMSO + HMPA	1	65 (25)
6	KNO_2(6), AcCl(6)	DMSO + HMPA	1	36 (17)
7	KNO_2(6), PhCOCl(6)	DMSO	1	40 (24)
8	KNO_2(6), $(CF_3CO)_2O$(6)	DMSO + HMPA	24	0 (95)
9	KNO_2(6), DCC(6)	DMSO + HMPA	24	0 (95)
10	KNO_2(6), $(COCl)_2$(6)	DMSO + HMPA	24	0 (95)
11	KNO_2(8), Ac_2O(8)	DMF[d]	24	0 (100)
12	$AgNO_2$(4), Ac_2O(4)	DMSO + HMPA	1	Trace (95)

[a] GC Yields with internal standard, yields in parentheses are unreacted starting material. [b] 1 mmol of isoquinoline, 6 mmol of KNO_2 and 6 mmol of Ac_2O are employed in 8 ml of DMSO and 2 ml of HMPA at room temp. A similar result was obtained with $NaNO_2$. [c] Isolated yields. [d] CH_2Cl_2 EtOH or hexane as a solvent were also unsuccessful.

Table 2 Synthesis of substituted 1-nitroisoquinolines[a]

Entry	Substrate	Reaction time (h)	Product	Yield (%)[b]
1	Isoquinoline	0.5	1-Nitroisoquinoline[8,9]	88
2	5-Nitroisoquinoline	2	1,5-Dinitroisoquinoline[14,15]	51
3	4-Bromoisoquinoline	2	4-Bromo-1-nitroisoquinoline[15]	55
4	3-Methylisoquinoline	2	3-Methyl-1-nitroisoquinoline[15]	50
5	5-Methoxyisoquinoline	1	5-Methoxy-1-nitroisoquinoline[15]	57

[a] 1 mmol of substituted isoquinoline, 6 mmol KNO_2 and 6 mmol of Ac_2O are employed in DMSO at room temp. [b] Isolated yield.

3 yields **4** which upon deprotonation forms 1-nitroisoquinoline. The use of activated DMSO has been widely demonstrated in oxidation reactions. To the best of our knowledge, this is the first example of the activated-DMSO promoted nucleophilic substitution of heterocyclic compounds. Under the best conditions, 1-nitroisoquinoline was isolated in 88% with 7% of unreacted isoquinoline recovered. When KNO_2 was replaced with KCN, KI or NaN_3, all attempts to make the 1-substituted isoquinolines were unsuccessful. This implies that the acidity of the C-1 proton in intermediate **4** is responsible for the success of the nucleophilic substitution with nitrite ion.

Substituted isoquinolines were also studied; all of the C-1 nitrations were successful under the same conditions, but the yields were lower than for the parent system even after a long period of time (see Table 2). Attempts to increase the product yields of substituted isoquinolines by use of excess KNO_2 and Ac_2O led to complex mixtures of products. The yields were also not improved by the use of HMPA as a cosolvent. Apparently, substituents inhibit the nucleophilic addition at the C-1 position which is higher in electron density for the substituted isoquinolines.

In summary, we have demonstrated a facile one-step synthetic method for the nitration of isoquinolines at the C-1 position, which involves the electrophilic attack of a DMSO–Ac_2O complex, followed by nucleophilic addition to this intermediate. Since the reaction is simple and mild, this method has preparative merit since 1-nitroisoquinolines are not readily accessible by other methods.[8,9]

Experimental

General procedure for the preparation of 1-nitroisoquinoline

To a solution of 0.511 g (6 mmol) of potassium nitrite in 4 ml of dimethyl sulfoxide and 2 ml of hexamethylphosphorus triamide was added 0.118 g (1 mmol) of isoquinoline. A solution of 0.572 ml (6 mmol) of acetic anhydride in 4 ml of dimethyl sulfoxide and 2 ml of hexamethylphosphorus triamide was added in small portions. After a rather vigorous reaction, the solution was stirred at room temp. for 30 min. The reaction mixture was poured into 15 ml of water and 15 ml of dichloromethane. The organic layer was separated, and the aqueous layer was extracted with two 10 ml portions of dichloromethane. The combined organic extracts were washed with 50 ml of brine, dried with anhydrous magnesium sulfate and evaporated. The crude product was purified with column chromatography. On a preparative scale, the brown gases evolved when Ac_2O is added to the DMSO solution of KNO_2 can be carried off through a long condenser tube. The crude product was purified by recrystallization from hexane to give 1-nitroisoquinoline (0.15 g, 88%), mp 65–66 °C (lit.,[8] mp 65–66 °C); $\delta_H(CDCl_3)$ 8.45 (d, *J* 5.0,† 1 H, 4-H), 8.32 (dd, *J* 8.0, 2.2, 1 H, 8-H), 8.01 (d, *J* 8.0, 1 H, 5-H), 7.98 (d, *J* 5.0, 1 H, 3-H), 7.8–7.9 (m, 2 H, 6-H, 7-H); $\delta_C(CDCl_3)$ 140.2, 139.5, 133.2, 132.2, 130.7, 127.6, 126.5, 124.3, 119.8; MS (EI, 70 eV): *m*/*z* 174 (M^+), 128 ($M^+ - NO_2$).

4-Bromo-1-nitroisoquinoline. Mp 127–130 °C; $\delta_H(CDCl_3)$ 8.54 (s, 1 H), 8.25 (dd, *J* 8.6, 0.8, 1 H), 8.20 (dd, *J* 8.6, 0.8, 1 H), 7.90–7.86 (m, 1 H), 7.79–7.75 (m, 1 H); δ_C 184.9, 141.8, 137.8, 133.5, 131.5, 127.3, 124.8, 124.7, 120.7; MS (EI, 70 eV): *m*/*z* 252, 254 (M^+, ^{79}Br, ^{81}Br), 127 ($M^+ - NO_2 - Br$) [Found: M^+, 251.9645 (^{79}Br), 253.9675 (^{81}Br). Calc. for $C_9H_5N_2O_2Br$: *M*, 251.9534 (^{79}Br), 253.9515 (^{81}Br)].

1,5-Dinitroisoquinoline. Mp 197–202 °C (lit.,[14] mp 195–200 °C); $\delta_H(CDCl_3)$ 8.72 (dd, *J* 6.0, 0.8, 1 H), 8.58–8.61 (m, 2 H), 8.48 (dd, *J* 8.7, 1.0, 1 H), 7.85 (t, *J* 8.2, 1 H); MS (EI, 70 eV): *m*/*z* 219 (M^+), 173 ($M^+ - NO_2$).

3-Methyl-1-nitroisoquinoline. Mp 120–122 °C; $\delta_H(CDCl_3)$ 8.13 (d, *J* 8.4, 1 H), 7.96 (d, *J* 8.1, 1 H), 7.68–7.73 (m, 2 H), 7.64–7.59 (m, 1 H), 2.67 (s, 3 H); δ_C 150.1, 140.1, 132.1, 129.6, 126.9, 124.5, 124.0, 117.9, 23.9; MS (EI, 70 eV): *m*/*z* 188 (M^+), 142 ($M^+ - NO_2$) (Found: M^+, 188.0569. Calc. for $C_{10}H_8N_2O_2$: *M*, 188.0586).

5-Methoxy-1-nitroisoquinoline. Mp 115–117.5 °C; $\delta_H(CDCl_3)$ 8.34 (d, *J* 5.6, 1 H), 8.29 (dd, *J* 5.6, 0.8, 1 H), 7.74 (d, *J* 8.7, 1 H), 7.60 (dd, *J* 8.5, 7.8, 1 H), 7.05 (d, *J* 7.8, 1 H), 3.99 (s, 3 H); δ_C

† *J* Values in Hz.

155.2, 153.7, 138.3, 131.0, 129.5, 119.6, 119.3, 114.2, 107.7, 55.0; MS (EI, 70 eV): m/z 204 (M^+), 158 ($M^+ - NO_2$) (Found: M^+, 204.0536. Calc. for $C_{10}H_8N_2O_3$: M, 204.0535).

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10 Potassium nitrite is slowly decomposed by acetic anhydride with the evolution of brown fumes of nitrous anhydride. Therefore, 6 equiv. of KNO_2 and Ac_2O are required to complete the reaction.
11 Only the mp and elemental analysis were given.
12 A complete ^1H NMR analysis of isoquinoline has been made: $\delta_H(CDCl_3)$ 9.14 (H-1), 8.45 (H-3), 7.50 (H-4), 7.69 (H-5), 7.56 (H-6), 7.48 (H-7), 7.85 (H-8). F. Balkau and M. L. Herffernam, *Austr. J. Chem.*, 1971, **24**, 2331.
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