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Oxidative nucleophilic substitution of hydrogen by primary amines in 2-nitrobenzo[b]thiophene.

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Abstract : 2-Nitrobenzo[b]thiophene on treatment with primary amines and CAN in aq.MeCN undergoes oxidative nucleophilic substitution reactions to give 2-nitro-3-aminobenzo[b]thiophenes as crystalline solids.

Keywords : Amines; oxidation; substitution.

Oxidative nucleophilic substitution of hydrogen (ONSH) in nitroarenes has currently emerged as a significant alternative pathway for the introduction of substituents in the arene ring [1]. The process, carried out as a single-pot reaction, involves two discrete steps. In the first, there is a reversible addition of the nucleophile at an electron-deficient carbon bearing hydrogen to give the σ^H adduct. The second step involves the oxidation of the σ^H adduct to yield the substituted nitroarene. The necessary conditions to be fulfilled for the success of this process have been analysed by Makosza [1]. The most critical of these is that the rate of oxidation of the σ^H adduct should be faster than that of the nucleophile itself. The best oxidant so far reported is $KMnO_4$ in liquid ammonia [2]. Although several carbanions have been used as nucleophiles in this reaction leading to the formation of C-C bonds, there are hardly any reports of the formation of C-N bonds.[1] Nitroaromatic compounds have been directly aminated at the *ortho*-positions by hydroxylamine or O-alkylhydroxylamines in the presence of a copper catalyst [4,5]. We now report a facile ONSH reaction on 2-nitrobenzo[b]thiophene in which primary amines are the nucleophiles; the preferred oxidant is ceric ammonium nitrate (CAN) in aqueous acetonitrile at ambient temperature (30^0C). The yields range from 20 to 66%.

The reaction was actually discovered during our efforts to extend the scope of the Ag^+

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[1] One such is the oxidative variant of the Chichibabin reaction [3].

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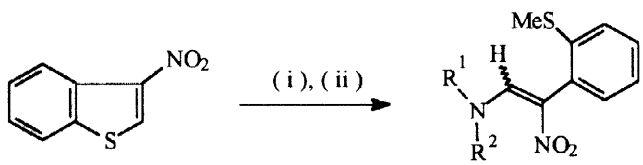
mediated ring-opening of nitrothiophenes by means of amines [6,7]. Reaction of 3-nitrobenzo[b]thiophene [8] with primary or secondary amines in the presence of $AgNO_3$, followed by methylation with MeI led to the isolation of the nitroenamines **(1)** (Scheme 1).

Scheme 1



i. EtOH, $AgNO_3$, R^1R^2NH, 30° C
ii. MeI

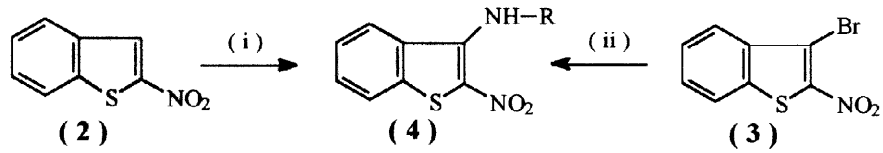
(1)

(1)	R^1	R^2	Product Yield %
a	*n*-Bu	H	50
b	C_6H_{11}	H	36
c	Ph	H	48
d	(*S*) - PhCH(Me)	H	50
e	$HOCH_2CH_2$	H	34
f	Et	Et	15
g	*i*-Pr	*i*-Pr	52
h	- $CH_2CH_2OCH_2CH_2$ -		10
i	- $CH_2CH_2CH_2CH_2$ -		35

In contrast, reaction of 2-nitrobenzo[b]thiophene [9] **(2)** with *n*-butylamine under the same conditions did not lead to any ring-opened product. The only crystalline product, obtained in 5% yield, was shown to have structure **(4a)** by analytical and spectral data.[2] This structure was confirmed by comparison with an authentic sample prepared by treatment of 3-bromo-2-nitrobenzo[b]thiophene **(3)** with *n*-butylamine [10] (Scheme 2) . It was clear that in the reaction of **(2)** with *n*-$BuNH_2$, the product **(4a)** had been formed as a consequence of ONSH, the oxidant being Ag^+. In an attempt to increase the yield of the ONSH product **(4a)** from 2-nitrobenzo[b]thiophene **(2)**, several other oxidants were tried in place of Ag^+. The yields were poor with *t*-butyl hydroperoxide/THF (14%), *N*-methylmorpholine *N*-oxide/THF (4.5%), H_2O_2/aq.THF (14%) and MnO_2/acetone (0 %).

[2] *2-Nitro-3-n-butylaminobenzo[b]thiophene* **(4a)** : Analysis: Found C, 57.47; H, 5.98; N, 10.95 Calcd.for $C_{12}H_{14}N_2O_2S$: C, 57.60; H, 5.63; N, 11.20. Ir(Nujol): ν_{max}= 1600, 1587, 1550 cm^{-1}. ^1H NMR(200MHz, $CDCl_3$, TMS): δ=1.05(t, J=6.5Hz, 3H, CH_3), 1.6(m, 2H, CH_2), 1.9(m, 2H, CH_2), 3.95(q, 2H, CH_2), 7.4(m, 1H, Ar), 7.6(m, 2H, Ar), 8.15(d, 1H, Ar), 9.45(brs, 1H, NH, exchangeable with D_2O). ^{13}C NMR(50MHz, $CDCl_3$) : δ = 13.83, 20.07, 32.17, 46.02, 120.92, 123.80, 124.97, 127.29, 129.01, 131.13, 139.54, 148.53. Ms (m/z) = 250(M+), 216, 207, 187, 179, 161, 134(100%), 121, 89, 77, 69.

Scheme 2

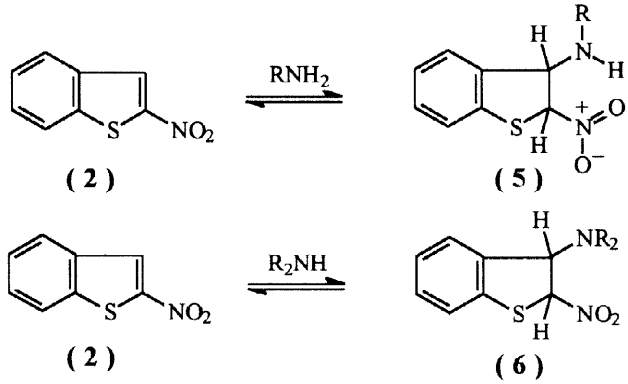


(i) R-NH_2; CAN; MeCN-H_2O. (ii) R-NH_2

Table 1
Products (4) from the ONSH reaction

Product (4)	R	Yield (%)
a	*n*-Bu	42
b	*n*-Pr	57
c	*i*-Pr	59
d	C_6H_{11}	54
e	(*S*) - Ph(Me)CH	66
f	CH_2=CH-CH_2	41
g	$HOCH_2CH_2$	42
h	MeO_2C-CH_2CH_2	20

Finally, the ONSH of **(2)** by *n*-butylamine was carried out in aq.MeCN, with ceric ammonium nitrate (CAN) as the oxidant. CAN is known to be a powerful one-electron oxidant [11,12]. Gratifyingly, the product **(4a)** was obtained in 42% yield. Other primary amines including allylamine and ethanolamine gave equally good yields of products **(4 b-g)** (Table 1). Although the esters of α-aminoacids (L-alanine, L-phenylalanine) did not react with **(2)** under these conditions, methyl β-alaninate gave a 20% yield of the product **(4h)**.[3] Surprisingly, secondary amines such as *N*,*N*-diethylamine and pyrrolidine failed to give any ONSH product under these conditions. This is perhaps due to the very low concentration of the σ^H adduct **(6)** at equilibrium. In contrast, the σ^H adduct **(5)** from primary amines would derive some stabilisation from intramolecular hydrogen bonding.



[3] All new products (1 and 4) were obtained as crystalline solids and were fully characterised by microanalysis, IR, ^1H and ^{13}C NMR and mass spectroscopy.

A typical procedure for ONSH is as follows : To a stirred solution of 2-nitrobenzo[b]thiophene **(2)** (1 mmol) in MeCN (3 ml) was added *n*-butylamine (excess; 13 mmol) at 30^0C. After 0.5 h, CAN (1.2 mmol) in water (2 ml) was added to the solution. After the complete disappearance of **(2)** in the mixture (tlc), the solid was filtered off and washed with MeCN. The filtrate and washings were combined and concentrated under vacuum. The residue was extracted with CH_2Cl_2(3x10 ml), washed with dil. HCl and brine, dried and evaporated. The residue was purified by passage through a silica gel column (EtOAc - pet.ether) and crystallized for analytical data. Orange crystals, yield: 42%, m.p. 126^0-128^0C (EtOH).

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