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Short Communication

Microwave Mediated Dearylation of 2-Aryloxy-5-Nitropyridine

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Abstract

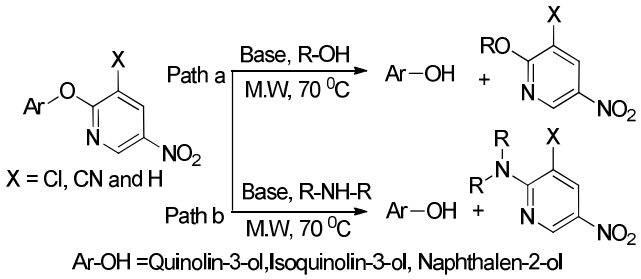
2-aryloxy-5-nitropyridine derivatives exhibited ether cleavage reaction on treatment with alcohols/amines in presence of base like K_2CO_3, Cs_2CO_3, NaOH, t-BuOK, etc. under microwave irradiation to yield corresponding phenols and 5-nitro-2-substituted pyridine.

Keywords: Microwave, dearylation, demethylation, nitropyridine, deprotection.

Introduction

Ether cleavage reaction is widely used in organic synthesis particularly in the field of natural products and in the synthesis of polyfuctional molecules[1-4]. Demethylation of aryl methyl ether is very common in organic synthesis and is carried out by a variety of reagents like BBr_3[5], BI_3[6], BF_3-etherate[7], HBr-AcOH[8], etc. The cleavage of diaryl ether is involved in organic synthesis as well as in metabolic reactions[9, 10]. Many ether cleavage reagents are reported in literature but mostly for dealkylation of aryl alkyl ether using different catalysts[11]. The most commonly used Lewis acid catalysts include $AlCl_3$[12], AlI_3[13], $BeCl_2$[14], AlH_2Cl_2[15], L- selectride[16], KF-alumina[17], lithium diphenylphosphide[18] and trimethylsilyliodide[19]. Cleavage of diphenyl ether, 1-phenoxynaphthalene, phenanthrene, 9-hydroxyphenanthrene and 9-phenoxyphenanthrene were reported by using sodium formate at higher temperature (315^0C) but the yield was very poor (~6.6%)[20]. The cleavage reaction of diaryl ether containing at least one heterocyclic ring has not got much attention. In 2005 Park et al reported the cleavage of Ar-O-Pyrazole using KOH / DMSO at 35^0C – 60^0C to get pyrazol-5-ol derivatives[21]. But this study was limited to very few examples.

Microwave-assisted organic synthesis[22] is becoming instrumental for the rapid as well as controlled[23], eco-friendly[24] and solvent free[25] synthesis. Deprotection of aromatic methyl ethers by using microwave irradiation[26] and different catalysts like pyridine hydrochloride, t-BuOK and crown ether, methanesulfonic acid, lithium iodide and solid supports were reported in the literature[27]. But none of these methods described cleavage of diaryl ether linkage using basic catalyst with quantitative yield of corresponding phenols. Also reported methods of diaryl ether cleavage were either slow or did not give quantitative yield. Herein this communication we report an efficient microwave assisted dearylation of 2-aryloxy-5-nitropyridine derivatives in presence of alcohols (R-OH) and amines (R-NH-R) using different bases like K_2CO_3, Na_2CO_3 Cs_2CO_3, NaOH, t-BuOK and NaH as catalysts (Scheme-1).



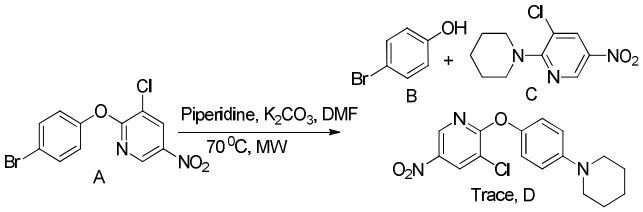
Scheme-1
Dearylation of 2-aryloxy-5-nitropyridines using alcohols (Path-a) and amines (Path-b)

Material and Methods

In a typical experiment, a weighed portion (1 mmol) of 2-aryloxy–3-chloro-5-nitro pyridine (**1**) was taken in a 5ml microwave vial and dissolved in methanol or ethanol (1.5 to 2 ml). Few drops of water were added to the solution followed by addition of 1.5 equivalent of base like K_2CO_3, Cs_2CO_3 or NaOH (1.5 equiv). The reaction mixture was then irradiated for 10-25 minutes at 70^0C under microwave and monitored by TLC using ethyl acetate and Petroleum ether (2:10) solvent system. In most of the cases reaction was completed within 10 to 25 minutes. After completion, alcohol was removed under high vacuum and to the residue water was added and extracted with ethyl acetate (3 x 15 ml). The combined organic layers were dried over Na_2SO_4 and concentrated on rotary evaporator. Purification of the crude using flash chromatography [Ethyl acetate: Petroleum ether (2:10)] yielded corresponding phenol with good yield (72-85 %). The reaction proceeded equally well using strong bases like KOtBu and NaH. In absence of alcohols or amines when we treated compound (**1**) with cesium carbonate in anhydrous DMF no ether cleavage was observed even at 80^0C for 30 minutes under microwave irradiation. Dearylation did not take place in absence of base when we treated compound (**1**) with methanol but 3-chloro-5-nitro-2-(piperidin-1-yl)pyridine was formed on treatment with piperidine.

Results and Discussion

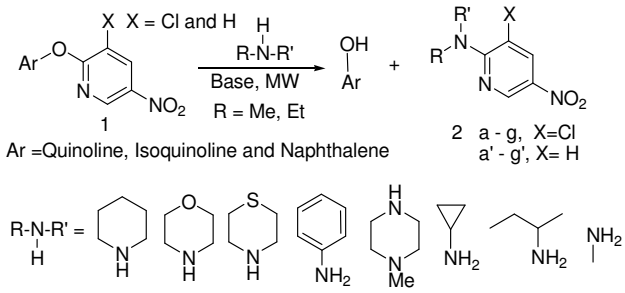
Dearylation of 2-(isoquinolin-3-yloxy)-5-nitrobenzonitrile was carried out in aqueous Na_2CO_3 to get isoquinolin-3-ol and 2-hydroxy-5-nitrobenzonitrile using microwave irradiation. But the reaction was not completed even after three hours of irradiation at 70^0C. However in the presence of alcohols (EtOH and MeOH) or amines (piperidine, morpholine, thiomorpholine, cyclopropanamine, methanamine, butan-2-amine and 1-methylpiperazine) the reaction was completed within 25 minutes under microwave irradiation at 70^0C. When the reaction was carried out in 10% aqueous H_2SO_4 only 50% conversion (on TLC) was observed after five hours of heating at 70^0C. Microwave irradiation in presence of alcohols or amines is therefore an efficient method for the cleavage of diarylethers to the corresponding phenols. Irrespective of the base, reaction time depends on the reactivity of the amines or alcohols used. In the quest of drug discovery program, for the synthesis of derivatives of 1-(4-(2-chloro-4-nitrophenoxy)phenyl) piperidine, we treated 2-(4-bromophenoxy)-3-chloro-5-nitropyridine (**A**) with piperidine in presence of potassium corbonate and palladium tetrakis (triphenylphosphine) as catalyst (Scheme-2) under microwave irradiation.



Scheme-2
Dearylation of 2-(4-bromophenoxy)-3-chloro-5-nitropyridine in presence of pireridine and K_2CO_3 in DMF

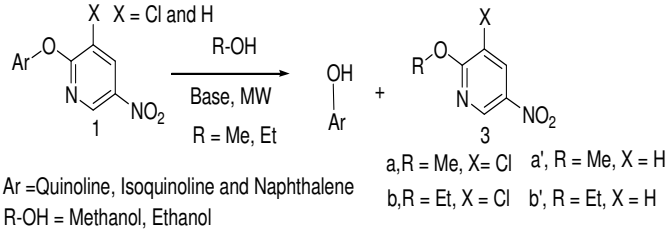
Alongwith trace amounts of the desired compound, 1- (4-(2-chloro-4-nitrophenoxy)phenyl) piperidine (**D**), we observed the formation of 4-bromophenol (**B**) and 1-(2-chloro-4-nitrophenyl)piperidine (**C**) in quantitative yield. For a comprehensive study we treated compound (**A**) with different amines in presence of potassium carbonate in DMF without using palladium tetrakis (triphenylphosphine). When the compound (**A**) was treated with aniline under similar reaction conditions formation of 3-chloro-5-nitro-N-phenylpyridin-2-amine and 4-bromophenol took longer time and 25% of starting material was recovered. However reaction with primary amine like cyclopropanamine in presence of cesium carbonate showed cleavage of ether linkage at low temperature. Methanamine reacted faster than cyclopropanamine at room temperature without using microwave irradiation and gave 2-(aziridin-1-yl)-3-chloro-5-nitropyridine in good yield. We observed same results with moderate yield using NaH or NaOH as base. Reaction with TEA in DMF/water 70^0C for 20 minutes did not give phenols.

Reaction of 2-aryloxy-3-chloro-5-nitropyridine under the same condition gave corresponding phenol and 3-chloro-5-nitropyridine derivatives (Scheme-3). Here we observed that methanamine reacted faster than other amines irrespective of base. Compound (**1**) on treatment with piperidine, morpholine, thiomorpholine, aniline, 1-methylpiperazine, methanamine butan-2-amine and cyclopropanamine in presence of K_2CO_3, Cs_2CO_3, KOtBu or NaOH (1.5 equiv) gave 2-amino-5-nitropyridine derivatives (**2**) and corresponding phenols (Ar-OH).



Scheme-3
Dearylation of 2-aryloxy-5-nitropyridines using amines

Extension of this work using methanol and ethanol instead of amine gave 3-chloro-2-methoxy-5-nitropyridine and 3-chloro-2-ethoxy-5-nitropyridine respectively (70-75%) and corresponding phenols (60-75%) under microwave irradiation in presence of base within 10-25 minutes (Scheme-4). Both 2-aryloxy-5-nitropyridine and 3-chloro-2aryloxy-5-nitropyridine reacted in presence of alcohol (R-OH) and base to give phenols and corresponding 2-alkoxy-5-nitro pyridine compounds under same reaction conditions with quantitative yield.



Scheme-4
Dearylation of 2-aryloxy-5-nitropyridines using alcohols

Analytical Data: All reagents and solvents were obtained from commercial sources and used as received. ^{1}H-NMR spectra were obtained on a 'Bruker 300 MHz' instrument equipped with a 5 mm ^{1}H/^{13}C/X (BBO) probe and the solvent indicated with tetramethylsilane as an internal standard. For all 1D and 2D experiments viz., ^{1}H, ^{13}C, COSY, HMBC, ^{13}C-HSQC and pulse program used was employed from the pulse program library of Bruker. The data obtained so, were processed and analyzed by using Bruker software, XWIN NMR version 3.5.

Analytical HPLC was run using a Zorbax Eclipse XDB-C8 3.5 µm 4.6x75 mm column eluting with a mixture of acetonitrile and water containing 0.1% trifluoroacetic acid with a 5 minute gradient of 10-100%.

3-chloro-5-nitro-2- (piperidin-1-yl) pyridine (2a): ^{1}H NMR (DMSO-d6, 300 MHz), δ = 8.93 (d, J=1.2 Hz, 1H), 8.40 (d, J=1.5 Hz, 1H), 3.60 (s, 4H), 1.62 (s, 6H). MS (ESI) = 242.67 (M+1).

4-(3-chloro-5-nitropyridin-2-yl) morpholine, (2b): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 9.04 (d, J = 2.4Hz, 1H), 8.51 (d, J = 2.4 Hz, 1H), 3.69 (s, 4H), 3.42 (s, 6H). MS (ESI) = 244.7 (M + 1)

4-(3-chloro-5-nitropyridin-2-yl) thiomorpholine (2c): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 8.94 (d, J=2.4Hz,1H), 8.41 (d, ,J=2.4 Hz, 1H), 3.60 (s, 4H), 3.12 (s, 6H). MS (ESI) = 260.75 (M+1)

3-chloro-5-nitro-N-phenylpyridin-2-amine (2d): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 8.93 (d, J= 2.4 Hz, 1H), 8.34 (d, J= 2.4 Hz, 1H), 9.44 (s, 1H), 7.75 (d, 2H), 7.33 (d, 2H), 6.98 (t, 1H). MS (ESI) = 250.2 (M+1)

1-(3-chloro-5-nitropyridin-2-yl)-4-methylpiperazine (2e): ^{1}H NMR (DMSO-d6, 300 MHz), δ = 9.01 (d, J=2.4 Hz, 1H), 8.54 (d, J=2.4 Hz, 1H), 3.75 (t, J=4.8 Hz, 4H), 3.17 (t,J=4.8 Hz, 4H), 2.21 (s, 1H). MS (ESI) = 242.65 (M^+)

3-chloro-N-cyclopropyl-5-nitropyridin-2-amine (2f): ^{1}H NMR (DMSO-d6, 300 MHz), δ = 8.95 (d, J= 2.4 Hz, 1H), 8.32 (d, J= 2.4 Hz, 1H), 7.948 (s, 1H), 2.9 (s, 1H), 0.79 (m, 2H), 0.69 (m, 2H) MS (ESI) = 214.55 (M+1)

N-sec-butyl-3-chloro-5-nitropyridin-2-amine (2g): ^{1} H NMR (DMSO-d6, 300 MHz) δ = 8.88 (d, J=2.4 Hz, 1H), 8.32 (d, J=2.4 Hz, 1H), 7.54 (d, J= 8.1 Hz, 1H), 4.28 (m, 1H), 1.67 (m, 2H), 1.21 (s,3H), 0.85 (s, 3H). MS (ESI) = 229.66 (M^+)

3-chloro-N-methyl-5-nitropyridin-2-amine (2h): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 8.92 (d, J= 2.4 Hz, 1H), 8.33 (d, J= 2.4 Hz, 1H), 7.98 (s, 1H), 2.966 (s, 3H). MS (ESI) = 188.25 (M+1)

3-chloro-2-methoxy-5-nitropyridine (3a): ^{1}H NMR (DMSO-d6, 300MHz) δ = 9.06 (d, J=2.4 Hz, 1H), 8.72 (d, J=2.4 Hz, 1H), 4.10 (s, 3H). Ms (ESI) = 189.56 (m+1)

2-methoxy-5-nitropyridine (3a'): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 9.10 (d, J=2.7 Hz, 1H), 8.50 (dd, J=2.7 Hz, 1H), 7.06 (d, J=2.7 Hz, 1H), 4.00 (s, 3H). MS (ESI) = 155.12 (M+1)

3-chloro-2-ethoxy-5-nitropyridine (3b): ^{1}H NMR (DMSO-d6, 300MHz) δ = 8.96 (d, J=2.4 Hz, 1H), 8.32 (d , J=2.4 Hz, 1H), 3.99 (s, 2H), 1.33 (s, 1H). MS (ESI) = 203.65 (M+1).

2-ethoxy-5-nitropyridine (3b'): ^{1}H NMR (DMSO-d6, 300 MHz) δ = 8.99 (d, J=2.7 Hz, 1H), 8.32 (dd, J=2.7 Hz, 1H), 6.998 (d, J=2.7 Hz, 1H), 9.98 (s, 2H), 1.23 (s, 1H). MS (ESI) = 169.15 (M+1)

Conclusion

Here we report an efficient dearylation method of 2-aryloxy-5-nitropyridine to get corresponding phenol and 2-alkoxy-5-nitropyridine and 2-amino-5-nitropyridine derivatives quantitatively using alcohols and amines respectively. Various bases were used to catalyze the reaction and it was also observed that use of different catalysts had no significant effect on the yield of the reaction. It is a microwave mediated eco-friendly method where amines and alcohols can be used for the dearylation of diaryl ethers.

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