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Unexpected one pot C (aryl)–N bond cleavage and Questiomycin A formation from the reduction reaction of 2-amino-6-nitrophenol derivatives

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ABSTRACT

2-Amino-6-nitrophenol derivatives **5A** and **5B** have been prepared from the bromonitro phenol derivative **4** using the Buchwald conditions. While attempting one pot reduction of nitro group and deprotection of phenolic benzyl group of the compounds **5A** and **5B** separately using Pd/C in methanol under H_2 atmosphere, an unexpected C(aryl)–N bond cleavage reaction had occurred which was followed by formation of a known compound Questiomycin A (2-amino-3*H*-phenoxazin-3-one) **1** from both the compounds. In the present study, the danger of deamination of Buchwald products **5A** and **5B** under the conditions of catalytic hydrogenation and the simultaneous formation of phenoxazine **1** is disclosed.

Although significant progress has been made in the development of catalytic aryl C–N bond formation and the synthesis of Buchwald products,[1] very few methods are available[2] for the catalytic cleavage of C(aryl)–N bonds of aniline derivatives. Recently reductive deamination of *o*-acylaniline derivatives was achieved by heating the reaction with the catalyst $RuH_2(CO)(PPh_3)_3$.[3] But this method is applicable to limited substrates containing *ortho* directing group. Further, cleavage of C(aryl)–N bonds requires either expensive reagents[2] or harsh conditions.[3] Therefore, there is a demand to develop methods for deamination reactions to prepare important organic synthons. Herein we report one pot C (aryl)–N bond cleavage (catalytic deamination) of two Buchwald products **5A** and **5B** with Pd/C under the atmosphere of Hydrogen in methanol followed by Questiomycin A formation.

Questiomycin A is the core structure of pharmaceutical active compounds like actinomycin, Plectosphaeroic Acid A and cinnabarinic acid. It belongs to the structural class of phenoxazine and can be isolated from *Streptomyces* species and some fungi and marine bacteria *Actinomadura* sp.M048.[4,5] It has been thoroughly investigated for many bio activities like anticancer[6] and antimicrobial.[7] It is an antibiotic and is obtained from *Penicillium expansum*, a resident fungal strain of the orbital complex Mir.[8] It is weakly active against bacteria, fungi, plants, and tumor cell lines, and inhibits aromatase and sulfatases.[4] Questiomycin, like other phenoxazines, stimulates cell growth and shows an ability to form stable free radicals.[9] Recently, Questiomycin A has been shown to inhibit pulmonary metastasis caused by mouse melanoma cells.[10]

Questiomycin A and its derivatives are usually prepared by enzymatic oxidation of *o*-aminophenols using laccases and horseradish peroxidases[11] and the chemical syntheses involve oxidation of *o*-aminophenols catalyzed by TBHP/diphenyl diselenide,[11] cobaloxime(II) derivatives,[12] Co(salen)[13] or Mn–porphyrin complexes.[14]

Despite general chemical oxidative methods and enzymatic methods for the synthesis of 2-amino-3*H*-phenoxazin-3-one from 2-aminophenol, to our knowledge only a reductive method[15] is available for the synthesis of Questiomycin A which is published very recently. In this method authors used dissolving metal conditions for the reduction of 2-nitrophenol derivatives. These conditions are complicated and harsh in practice. The catalytic hydrogenation conditions we have been reporting here are novel, and performed at room temperature with easily available reagents.

Apart from the use of phenoxazine moieties as pharmaceutically active compounds, the derivatives of these compounds have also been used widely in dye sensitized solar cells (DSSC).[16–21] These simple moieties usually are known as competent laser dyes, and have not been explored much as building blocks in current small-molecule based light emitting diode materials.[22] Several phenoxazine derivatives have been prepared and used in the function of emitting materials,[23] semiconducting transistors and

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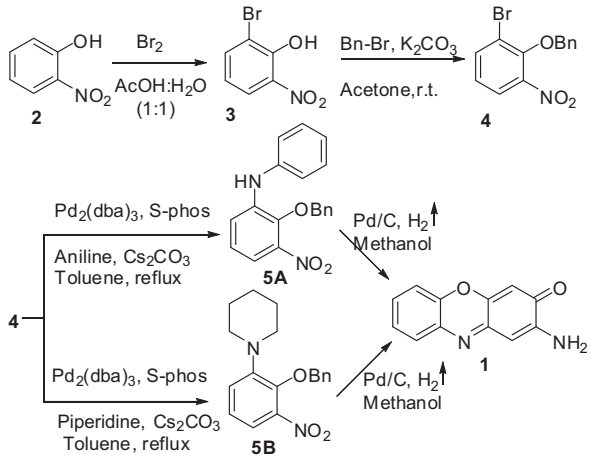
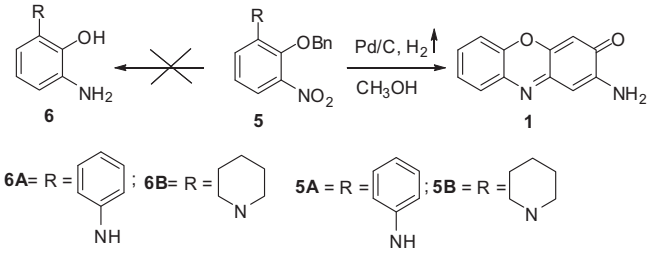


Scheme 1.

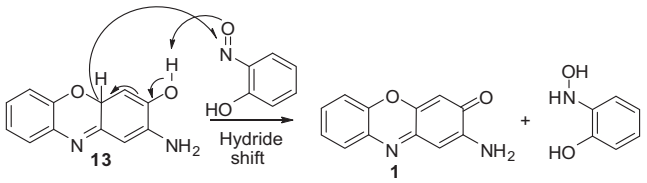


Scheme 2.

electroluminescent tools.[24,25] These simple moieties have also been used as building blocks in organic semiconductors.[25]

Regardless of the availability of derivatives and their synthetic methods, there is a constant need to develop and explore synthetic structures of phenoxazine moieties in order to get compounds which are more efficient for DSSC. In this quest we are interested in synthesizing derivatives with different amine functionalities over the tricyclic core of the phenoxazine moieties.

We started the synthetic route from 2-nitrophenol **2**. Bromination of the same with molecular bromine in 1:1 acetic acid and water at room temperature yielded a sole bromophenol **3**. The structure of the compound was confirmed by ^{1}H NMR, which showed characteristic peaks at δ 7.98 (d), δ 7.67 (dd) and at δ 7.08 (d). The phenolic group of the obtained compound **3** was protected with benzyl bromide in refluxing acetone in the presence of potassium carbonate to yield compound **4**. The compound **4** was confirmed by its ^{1}H NMR spectrum which showed characteristic peaks at δ 5.2 (s) for two benzylic protons and at δ 7.3 to δ 7.45 (m) for 5 protons. The obtained compound **4** was then reacted



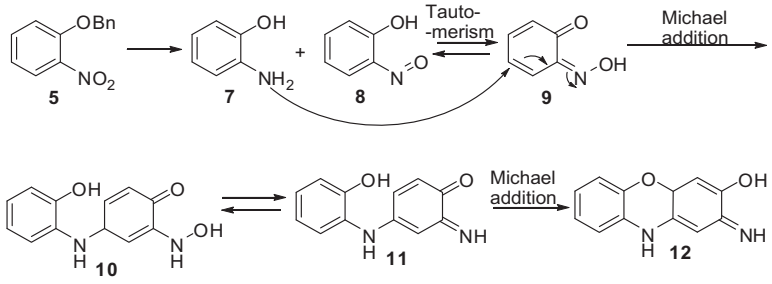
Scheme 4.

separately with aniline and piperidine under Buchwald conditions using $Pd_2(dba)_3$, S-phos and Cs_2CO_3 in toluene at 110 °C to furnish the Buchwald products **5A** and **5B**, respectively (Scheme 1). The structure of the compound **5A** was confirmed by its ^{1}H NMR spectrum which showed characteristic peaks at δ 5.64 (broad singlet) for –NH proton and two multiplets at δ 6.90–7.05 and δ 7.20–7.49 for aniline and benzyl aromatic protons. The structure of the compound **5B** was confirmed by its ^{1}H NMR spectrum which showed characteristic peaks at δ 3.09 (t) for 4 protons of two methylene groups of piperidine ring adjacent to nitrogen and at δ 1.64–1.76 (m) for 4 protons and at δ 1.50–1.63 (m) for 2 protons of piperidine ring.

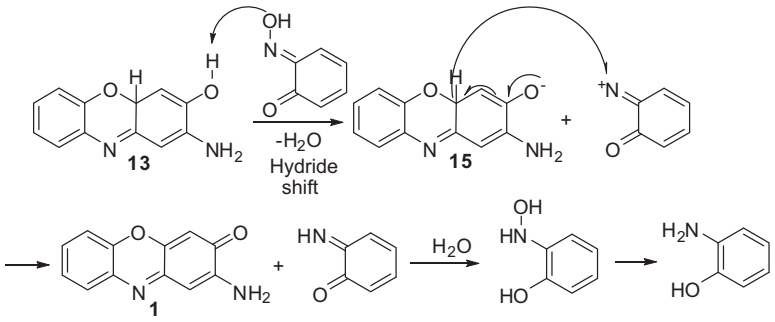
At this juncture, with the compounds **5A** and **5B** in hand, we wanted to get the desired reduction products **6A** and **6B** respectively. When one pot catalytic hydrogenation reaction to de-protect benzyl group and simultaneous reduction of Nitro group using 10% Pd on Carbon (wet) in Methanol was attempted under the atmosphere of Hydrogen created with a balloon of Hydrogen gas, a more polar spot on TLC was observed and surprisingly the R_f value of the compounds obtained in both the reactions matched exactly on TLC. The reaction mixture was then filtered and the solvents were evaporated on rotary evaporator under reduced pressure to obtain the crude products which were then purified by column chromatography separately using silica gel (60–120 mesh size) to get a red colored dye in overall 45% of yield (Scheme 2).

Analysis of both the compounds using ^{1}H NMR showed identical pattern of peaks and confirmed the absence of peaks for aniline and piperidine moieties. The spectrum showed peaks at δ 6.48 (s) for 1 proton, 6.42 (s) for 1 proton. At 6.76 a broad singlet was observed for two protons which is a characteristic peak of $-NH_2$ protons. The rest of the peaks were observed in aromatic region at δ 7.77 (d) for one proton, δ 7.47–7.36 (m) for 3 protons. The mass spectrum of both the compounds showed (M+1) peak at 213 confirming the mass of the Questiomycin A. The compound was further confirmed by matching the analytical data of Questiomycin A **1** with the reported compound.[7]

Although the mechanism for deamination reaction is uncertain, the probable mechanisms are depicted in Schemes 3–5. The electron density is high around C(aryl)–N bond, therefore it could easily get adsorbed over the Pd metal surface, which could be reduced with the adsorbed Hydrogen and cleave the C(aryl)–N bond to yield the compound **5**. Further, the benzylic deprotection



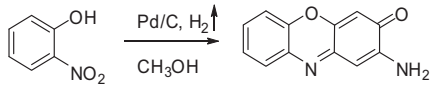
Scheme 3.



Scheme 5.

and the nitro group reduction of compound **5** could yield amino compound **7** and nitroso compound **8**. The first Michael reaction of aminophenol **7** and the compound **9** which is a tautomer of **8** could furnish compound **10**. The compound **11** which is a tautomer of compound **10** could undergo an intramolecular Michael addition reaction to yield iminophenol **12** (Scheme 3).

Being an oxidizing agent, the intermediate *o*-nitrosophenol **8** or its quinoneimine form **9** could act like benzoquinone and react with *o*-aminophenol derivative **13** which is a tautomer of *o*-iminophenol derivative **12** in the fashion shown in either Scheme 4 or 5 to furnish the final compound Questiomycin A **1**. The mechanism is further supported by the catalytic hydrogenation of *o*-nitrophenol using Pd/C in methanol under the atmosphere of hydrogen, which afforded Questiomycin-A in overall 48% yield.



Conclusion

In conclusion, an unexpected result was observed in the method to cleave C(aryl)–N bond of 2-amino-6-nitrophenol derivatives using easily available catalytic hydrogenation conditions. Very few methods are available for the cleavage of C(aryl)–N bond.[2,3] The deamination intermediates reacted further in the reaction conditions to yield Questiomycin-A which is a novel synthetic reductive method for the synthesis of the pharmaceutically interesting class of 2-aminophenoxazin-3-one. We believe the method disclosed is suitable for the synthesis of several related 2-aminophenoxazin-3-one derivatives.

Synthesis of 2-(benzyloxy)-3-nitro-*N*-phenylaniline (5A)

The benzylated compound **4** (1 g, 3.2 mmol), $Pd_2(dba)_3$ (20 mg, 0.021 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (20 mg, 0.048 mmol), cesium carbonate (1.96 g, 6.0 mmol) were taken in a clean and dry sealed tube. Then toluene (20 ml) was added with syringe. The reaction mixture was stirred under nitrogen at 90 °C. After 15 min aniline (0.4 ml, 8.6 mmol) was added drop by drop with the help of syringe. The mixture was allowed to stir for 24 h at 90 °C. Then the reaction mixture was filtered, diluted with ethyl acetate (50 ml) and the organic layer was washed successively with water (3 × 50 ml) and with brine solution. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to get reddish brown precipitate which was purified by column chromatography using EtOAc/Hexane (1:9 mixture) as an eluent to afford red color dye (750 mg, 2.3 mmol). Mp 92–98 °C. Anal. Calcd for $C_{19}H_{16}N_2O_3$ (320.34): C, 71.24; H, 5.03; N, 8.74; O, 14.98. Found: C, 71.22; H, 5.00; N, 8.71; O, 14.95. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.56(d, 1H, J = 2.7 Hz), 7.36 (m, 7H), 7.19 (dd, 1H, J = 8.7, 2.7 Hz), 6.99 (m, 4H), 5.64 (s, 2H), 5.18 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 146.38, 142.63, 140.89, 137.30, 136.06, 129.72, 128.79, 128.30, 127.26, 124.01, 121.87, 117.88, 117.37, 114.83, 72.18 ppm.

Synthesis of 1-(2-(benzyloxy)-3-nitrophenyl) piperidine (5B)

Following the procedure mentioned above for the synthesis of **5A**, piperidine (0.4 ml, 4.0 mmol) was added drop wise with the syringe and the reaction mixture was stirred for 24 h at 90 °C. Then the reaction mixture was filtered, diluted with ethyl acetate (50 ml), and the organic layer was washed successively with water (3 × 50 ml) and with brine solution. The organic layer was dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure to get reddish brown precipitate which was purified by column chromatography using EtOAc/Hexane (1:9 mixture) as an eluent to afford red color dye (700 mg, 2.24 mmol). Mp 55–61 °C. Anal. Calcd for $C_{18}H_{20}N_2O_3$ (312.36): C, 69.21; H, 6.45; N, 8.97; O, 15.37. Found: C, 69.18; H, 6.43; N, 8.94; O, 15.35. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.38 (m, 3H), 7.04 (m, 1H), 5.15 (s, 1H), 3.09 (t, J = 5.4 Hz, 2H), 1.7 (m, 2H), 1.57 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.08, 140.80, 136.33, 130.64, 128.92, 127.29, 127.11, 125.55, 122.78, 117.29, 72.25, 51.05, 25.79, 24.06 ppm.

Synthesis of 2-amino-3*H*-phenoxazin-3-one (1)

To the solution of Buchwald product **5** (200 mg) in methanol (5 ml) was added wet 10% Pd/C (10 mg) and the reaction mixture was stirred for 5 h under the pressure of hydrogen balloon. The reaction mixture was then filtered, washed the solids with EtOAc (2 × 10 ml), and the combined solvents were evaporated on a rotary evaporator under reduced pressure to get the crude product which was purified by column chromatography using EtOAc/Hexane (1:4) to get a red colored dye (60 mg, 0.28 mmol in case of **5A**) and (56 mg, 0.26 mmol in case of **5B**). Mp 147–152 °C (sublimation). Anal. Calcd for $C_{12}H_8N_2O_2$ (212.20): C, 67.92; H, 3.80; O, 15.08; N, 13.20. Found: C, 67.90; H, 3.78; O, 15.05; N, 13.17. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.76 (d, 1H, J = 7.8 Hz), 7.41 (m, 3H), 6.73 (m, 2H), 6.48 (s, 1H), 6.42 (s, 1H).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.09.080.

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