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Copper-Catalyzed Arylation Reaction in the Synthesis of New Derivatives of Angular Triazaphenoxazinone

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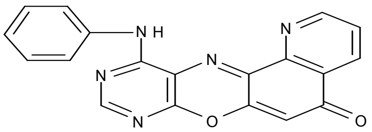
Abstract

The synthesis of 11-(*N*-substituted)-angular triazaphenoxazinone via copper catalyzed *N*-arylation reaction is reported. The key intermediate, 7-chloro-5, 8-quinolinequinone was obtained in a five-step reaction, starting from 8-hydroxyquinoline. This was coupled with 4, 5-diamino-6-hydroxypyrimidine, in the presence of sodium acetate under anhydrous condition to afford 11-amino-1, 8, 10-triazabenzo[a]phenoxazin-5-one. The new derivatives were obtained by the reaction of 11-amino-1, 8, 10-triazabenzo[a]phenoxazin-5-one with substituted potassium/lithium phenyltriolborates, under the catalytic influence of copper (II) acetate in the presence of trimethylamine *N*-oxide, and 4Å molecular sieve. Products were obtained in good yield (70-80%). Structures were established by spectra and analytical data. These tetracyclic heterocycles absorb light in the visible region (400-700nm), which makes them applicable as laser dyes.

Keywords: synthesis, triazaphenoxazinone, copper catalyzed N-arylation reaction

1. Introduction

Phenoxazines are tricyclic heterocycles consisting of two benzene rings fused to an oxazine structure **(**En. Wiktionary. Org/wiki/07/02/2012**)**. They are found in the actinomycinsm **(**Brockman & Muxfeldt 1956**)**, in various insect pigments called ommochromes (Butenandt *et al.* 1960), and in some microorganism metabolites (Anzai *et al.* 1960). Chemically, they can be synthesized by oxidative condensation of *o*-aminophenol and its derivatives (Gerber & Lochvalier 1964). Phenoxazines are very useful compounds, which form the nuclei of several other important compounds. Phenoxazine derivatives have been used as drugs, colourant in textile industries among others. Their pharmacological activities span a wide spectrum as sedatives, tranquilizers, antiepileptic, CNS depressant, anti-tumor, antibacterial to mention but a few. They also show some usefulness as biological stain (Eregowda *et al.* 2000).). Angular phenoxazine, derivatives with highly improved biological activities have been synthesized **(**Shirley *et al.* 1964**)**. In view of this, several molecular modifications have been carried out on phenoxazine ring, among which are benzo[a]phenoxazine (Goldstein & SemelitchZ 1919**)**, benzo[c]phenoxazine(Kehrmann & Golstein 1919) and three-branched phenoxazine(Okafor & Okoro 1990). Owing to the quest for aza analogues of angular phenoxazines, several molecular modifications has also been made, which include, three-branched benzoxazinophenothiazine ring system (Okafor 1987), Y-shape mono and diazabenzothiazinophenoxazine ring system (Okafor *et al.* 1992) and angular triazaphenoxazinone (Okoro et al. 2009). We now wish to report the successful synthesis of some derivatives of angular triazaphenoxazinone via copper catalyzed *N*-arylation reaction.



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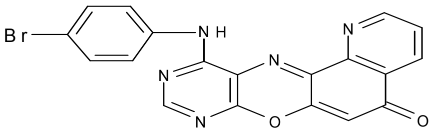

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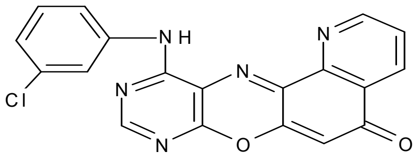

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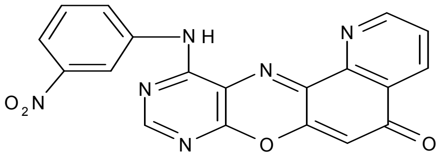

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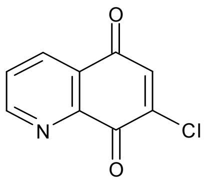

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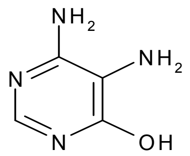

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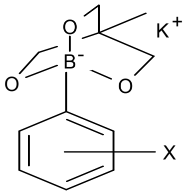

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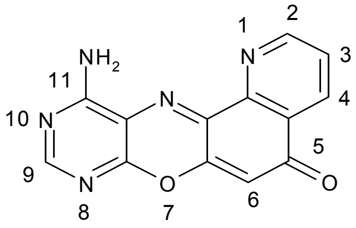

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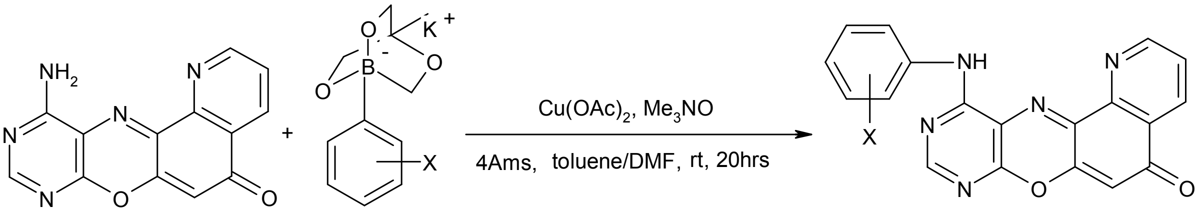
2. Result and Discussion

We first started by synthesizing 7-chloro-5, 8-quinolinequinone **5** in a five step reaction beginning from 8-hydroxyquinoline as reported by Petrow and Sturgeon (1954) and substituted potassium/lithium phenyltriolborates **7** using Yu X et al protocol (Yu *et al.* 2008). The reaction of 7-chloro-5, 8-quinolinequinone **5** and 4, 5-diamino-6-hydroxypyrimidine **6** yielded 11-amino-1, 8, 10-triazabenzo[a]phenoxazin-5-one **8.**

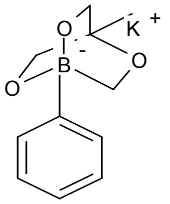
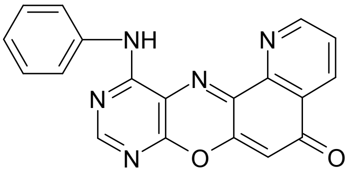
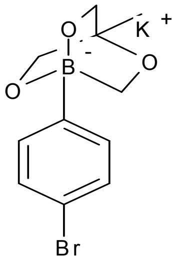
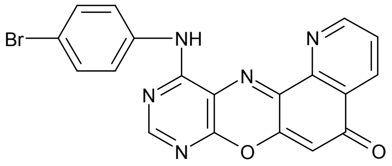
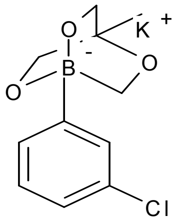
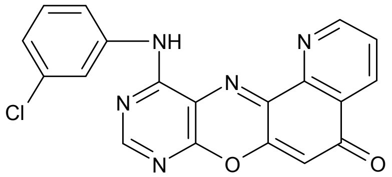
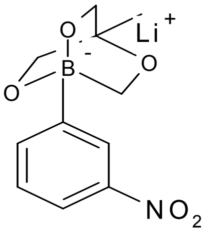
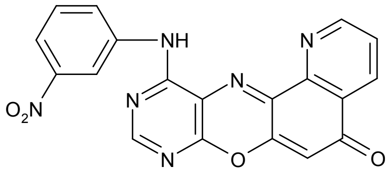
The reaction of 11-amino-1, 8, 10-triazabenzo[a]phenoxazin-5-one **8** and substituted potassium/lithium phenyltriolborates **7**, under the catalytic influence of copper (II) acetate in the presence of trimethylamine *N*-oxide, and 4Å molecular sieve, furnished the aminotriazabenzo[a]phenoxazinones in good yields. Elemental analyses and spectroscopy are consistent with the assigned structures.



8 **7** **1 - 4**

Ms= molecular sieve.

Table 1: Cu-catalyzed *N*-arylation of 11-amino-1, 8, 10-triazabenzo[a]phenoxazin-5-one. 8[a]

Entry	Substituted aryltriolborate	Product		Yield[b] %
1			1	80
2			2	77
3			3	74
4			4	70

[a] Reactions of **8** (1mmol) with aryltriolborates were performed using Cu(OAc)$_2$ (0.1mmol), Me$_3$NO (1.1mmol) and 4Å molecular sieve (300mg) at room temperature for 20h.

3. Experimental

3.1 General

Melting points were determined using Scott scientific melting point apparatus and are uncorrected. Ultraviolet and visible spectra were recorded on Jenway 6405 UV/Vis spectrophotometer. Absorption maxima are given in nanometer (nm) and (logε) in parenthesis. Infrared spectra were obtained on FTIR-8400S and absorption were in wave number (cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were determined on Variant 200MHz NMR machine and chemical shifts are in parts per million using tetramethylsilane as internal standard. The following abbreviations are used: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet). 7-Chloro-5, 8-quinolinequinone **5** and substituted potassium/lithium phenyltriolborates were synthesized as described. All chemicals were purchased from Zayo-Sigma (local vendor) and used as supplied.

3.2 General Procedure for Cu-Catalyzed N-Arylation of Compound 8 with Derivatives of Aryltriolborate.

To a round bottom flask of 100ml, copper acetate (0.1mmol), trimethylamine N-oxide (1.1mmol), 4Å molecular sieve (300mg) and the substituted aryltriolborate (1.5mmol), in toluene (30ml) and DMF (5ml) were stirred for 5 minutes at room temperature; compound **8** (1mmol) was then added. The mixture was stirred for 20hrs at room temperature. After the 20 hrs, the solvents were allowed to evaporate and then the product is washed with ice, filtered, dried and the residue re-crystallized using ethanol.

3.2.1 11-(Phenylamino)-1, 8, 10-Triazabenzo[A]Phenoxazin-5-One 1

Brown powder, yield: 80%. UV-VIS (ethanol) λ_{max} (log ε): 206(2.156); 268(1.27); 360(1.117); 426(0.985); 500(0.651)nm. IR (nujol) υ_{max}: 674 and 753cm^{-1}(C-H, out of plane); 1272 cm^{-1}(C-O-C, >N-H ar.) and 3439cm^{-}

^{1}(ar. C-H) cm^{-1}. H^{1}NMR (DMSO$_{-d6}$) δ: 8.40(d, 2H, C_2 and C_4 protons); 7.90(d, 2H, C_3 and C_9 protons); 8.0-7.80(m, 5H, monosubstituted benzene); 6.50(s, 1H, C_6 proton); 3.40(s, b, 1H, >NH). ^{13}CNMR (DMSO$_{-d6}$) ppm: 173.7 (>C=O and C-NH$_2$); 142.87(>C=C< and >C=N) and 131.40-127.53(ar. carbon). Anal. Calcd. For $C_{19}H_{11}N_5O_2$; C, 66.86; H, 3.23; N, 20.53. Found: C, 66.70; H, 3.31; N, 20.50.

3.2.2 11-(4-Bromophenylamino)-1, 8, 10-Triazabenzo[A]Phenoxazin-5-One 2

Brown powder, yield: 77%. UV-VIS (ethanol) λ_{max} (log ε): 219(2.536); 271(2.176); 360(1.512); 424(1.398); 500(0.921)nm. IR (nujol) υ_{max}: 686, 752cm^{-1}(C-H, out of plane); 1273cm^{-1}(>N-H ar, C-O-C); 1608cm^{-1}(C=O); 3438cm^{-1}(ar. C-H). H^{1}NMR (DMSO$_{-d6}$) δ: 8.20(d, 2H, C_2 and C_4 protons); 7.90(d, 2H, C_3 and C_9 protons) 7.30(s, 1H, C_6 proton); 3.40(s, 1H, >NH). ^{13}CNMR (DMSO$_{-d6}$) ppm: 176.38ppm((>C=O and C-NH$_2$); 142.87(>C=C< and >C=N) and 131.39-127.54(ar. carbon). Anal. Calcd. For $C_{19}H_{10}N_5BrO_2$; C, 54.29; H, 2.38; N, 16.67; Br, 19.05. Found: C, 54.30; H, 2.29; N, 16.70; Br, 19.00.

3.2.3 11-(3-Chlorophenylamino)-1, 8, 10-Triazabenzo[A]Phenoxazin-5-One 3

Brown powder, yield: 74%. UV-VIS (ethanol) λ_{max} (log ε): 207(2.163); 211(1.933); 217(1.570); 274(1.093); 360(0.853); 499(0.575)nm. IR (nujol) υ_{max}: 675cm^{-1}(C-H, out of plane); 1274cm^{-1}(>N-H ar. C-O-C); 1648cm^{-1}(C=O); 3433cm^{-1}(ar. C-H). H^{1}NMR (DMSO$_{-d6}$) δ: 8.80(d, 2H, C_2 and C_4 protons); 7.90(d, 2H, C_3 and C_9 protons); 7.60(m, 4H, Ar-H); 3.50(s, b, 1H, >NH). ^{13}CNMR (DMSO$_{-d6}$) ppm: 140(>C=C< and >C=N) and 132-128(ar. carbon). Anal. Calcd. For $C_{19}H_{10}N_5ClO_2$; C, 60.72; H, 2.66; N, 18.64; Cl, 9.45. found: C, 60.80; H, 2.59; N, 18.75; Cl, 9.50.

3.2.4 11-(3-Nitrophenylamino)-1, 8, 10-Triazabenzo[A]Phenoxazin-5-One 4

Brown powder, yield: 70%. UV-VIS (ethanol) λ_{max} (log ε): 207(2.027); 216(1.777); 245(1.640); 360(1.155); 420(0.865); 498(0.865); 659(0.700)nm. IR (nujol) υ_{max}: 678, 748cm^{-1}(C-H, out of plane); 1273cm^{-1}(>N-H ar. C-O-C); 1644cm^{-1}(C=O); 3462cm^{-1}(ar. C-H). H^{1}NMR (DMSO$_{-d6}$) δ: 8.40(d, b, 2H, C_2 and C_4 protons); 7.80(s, b, 2H, C_3 and C_9 protons); 3.50(s, b, 1H, >NH). ^{13}CNMR (DMSO$_{-d6}$) ppm: 140(>C=C< and >C=N) and 132-128(ar. carbon). Anal. Calcd. For $C_{19}H_{10}N_6O_4$; C, 59.07; H, 2.59; N, 21.76.

4. Conclusion

Copper catalyzed *N*-arylation reaction is recommended for coupling reactions.

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