Synthesis of o-aryloxime

A dissertation

Submitted in partial fulfilment

As a project work

For the Degree of

Master of Science in Chemistry

By

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&

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Finally we express my special thanks to our friends & my family members.

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All of yours sincerely,

Sagarika Pattanayak

Manaswini Nayak

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CERTIFICATE

This is to certified that Sagarika Pattanayak and Manaswini Nayak worked together in my laboratory to conduct the experiments on "**Synthesis of O-aryloxime**" at department of chemistry,NIT Rourkela.

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Abstract

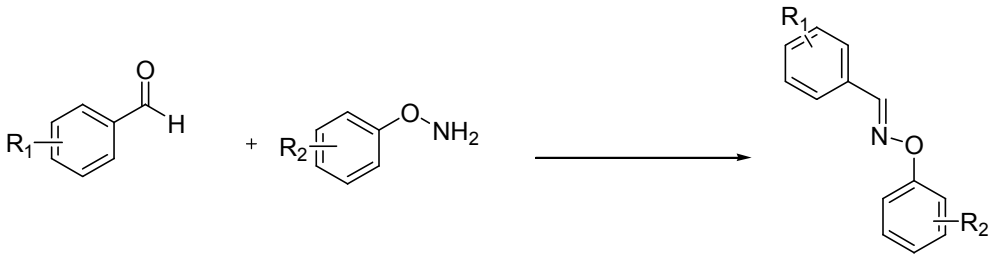
An efficient CuI catalyst for the O-arylation of Benzaldoxime with aryl iodide has been developed.Here Benzaldooxime serves as an efficient for C-O cross-coupling thereby allowing for the preparation of *O*-aryloxime from simple aryl halide.This is a single step synthesis Short reaction times and broad substrate scope, including heteroaryl coupling partners, allow access to *O*-aryloximes that would be difficult to prepare in a single step by traditional methods. This one-step formation of the dN-O-Ar linkage givesaccess to a range of oxime ethers in good to moderate yields.

Introduction

O-aryloxime ethers are valuable synthetic targets molecules due to their wide occurrence in a variety of bioactive oxime linkage, as a synthon for the synthesis of benzofurans,[1] benzisoxazoles, and benzoxazoles.[2] The bisoaryl oxime ethers act as a potent inhibitors of transthyratin amyloid fibril formations.[3] The O-aryloxime ethers are key structural motifs in many drug scaffolds and bioactive compounds. The oxime ether moiety are present in a number of bioactive compounds and show broad spectrum biological activity like antiviral[4], anti-inflammatory[5], antibiotics,[6] antifungal[7] and antidepressant[5]. The oxime ethers are present in a number of commercialized drugs like enviroxime, pifoxime, cefixime, pralidoxime, oxiconazole, and fluvoxamine[8]. O-aryl oxime ethers have potential application in medicinal and bioorganic chemistry. For example some act as inhibitors of protein chaperone Hsp 90,[9] some others show good neuroleptic activities.[10] The wide applications of oxime ethers in medicine, biology and chemistry made people interested for their synthesis.

The most common approach for the synthesis of oxime ethers is the condensation of aldehydes or ketones with O-aryloxyamines (Scheme 1).

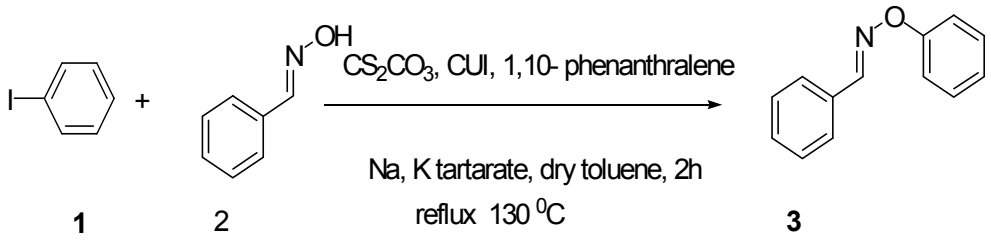
Scheme 1



Though the aldehydes and ketones are commercially available but O-aryloxyamines are required to synthesize prior to use which is relatively difficult.

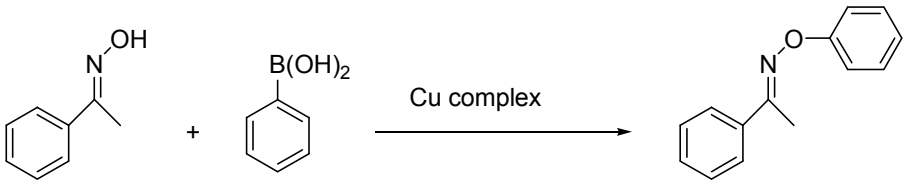
Recently, transition metal catalyzed coupling reactions reveals as a useful strategy for the synthesis of C-C and C-hetero bonds. Despite the significant progress in this area, O-arylation of oximes is rarely reported. For e.g. Maitra and Co-workers reported a ligand assisted Cu catalysed route for the synthesis of o-aryl oxime ethers (Scheme-2)

Schem-2



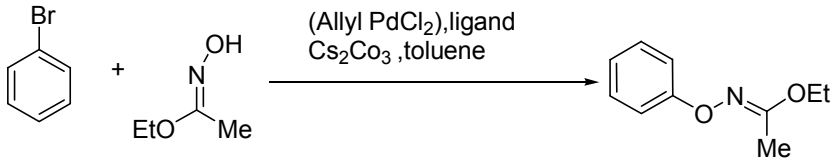
Recently Cai and co-workers reported the polymer supported copper complex for the synthesis of O-aryloxime ethers by the cross-coupling of oximes with aryl boronic acids (Scheme 3).[12]

Scheme-3



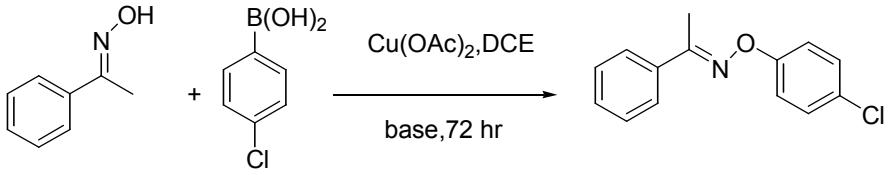
Buchwald reported the Pd-catalyzed O-arylation of Ethyl Acetohydroximate for the synthesis of O-arylhydroxylamines (Scheme 4)[13]

Scheme -4



Meyer and co-workers synthesized the O-aryloxime ethers by the Copper acetate catalyzed cross-coupling of oximes with phenyl boronic acids (Scheme 5).[14]

Scheme-5



The presence of limited reports on o-arylation of oximes reasons us to consider this project for our training purpose. We follow the procedure reported by Maitra et al. for the C-O cross-coupling reaction to yield O-aryl oxime.

We prepared the oximes by following the reported procedures (Scheme-6). Benzaldehyde reacted with hydroxyl amine hydrochloride in methanol at room temperature to afford the oxime.

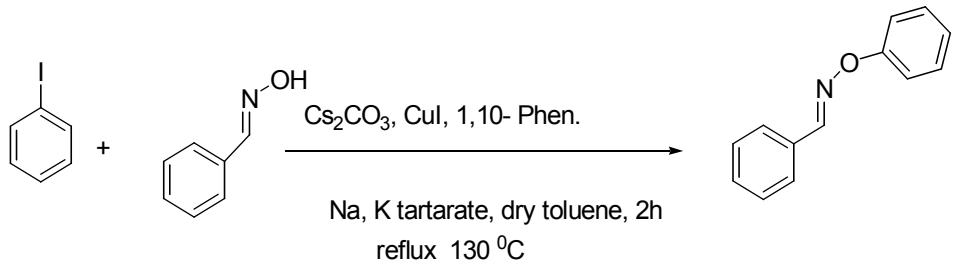
Scheme-5

Procedure:

0.48 mL (4.52 mmol) of benzaldehyde was stirred in methanol (10 mL) in a 100 mL one-neck round bottom flask. 375 mg (4.31 mmol) of hydroxylamine hydrochloride was added to the above mixture and the stirring was continued for over night at room temperature. Water was added to the resulting mixture and the organic layer was extracted with dichloromethane and concentrated under vacuo. The crude mixture was purified by column chromatography to get the pure compound, benzaldoxime as a yellow oil.

Benzaldoxime undergo cross-coupling reaction with iodobenzene in presence of CuI lead to the O-aryl oxime in 40% yield as crystalline solid (Scheme 6).

Scheme-6



Preparation of synthesis of o-aryl oxime

In a 50 ml two neck round bottom flask 1 gm (8.26mmol) oxime was added in dry toluene. Followed by the addition of 5.38 gm (16.5 mmol) of Cs_2CO_3 under inert atmosphere. The resulting mixture was stirred at 110 ^{0}C for 15 min. To the resulting yellow suspension 0.92 mL (8.26 mmol) of iodo benzene was added followed by 0.29 gm (1.62 mmol) of 1,10-phenanthroline and 0.69 gm (2.47 mmol) of sodium potassium tartarate. After 5 min 0.314 gm (1.65 mmol) of CuI was added to the above mixture. The resulting mixture was refluxed for overnight. After completion of the reaction the solution was filtered and water was added to the filtrate. The organic layer was extracted with dichloromethane and the solvent was evaporated by rotary evaporator. The crude mixture was purified by column chromatography using ethyl acetate and petroleum ether as the eluent to get the pure compound. M. P.: 110^{0}C

The product has been characterised by ^{1} H-NMR ($CDCl_3$, ppm) δ 8.34 (1H), δ 7.71 (m, 2H), δ 7.44–7.20 (m, 7H), δ 7.10 (m, 1H)

The product was also characterised by ^{13}C-NMR

^{13}C-

NMR($CDCI_3$,ppm) δ 149.1 (s), δ134.7 (d), δ 131.01(d), δ 130.66(s),δ 129.98(d), δ 129.21(d) δ129.08(d), δ 128.70(d), δ 121.80(d)

But this NMR data is not matched with the reported data given by Maitra and co workers

(Ref. De, P.; Pandurangan, K. N.; Maitra, U., Wailes S. *Org. Lett.*, **2007***, 9*, 2767)

In conclusion we repeated the procedure reported by Maitra et. al. for the synthesis of O-arylation of oximes.

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