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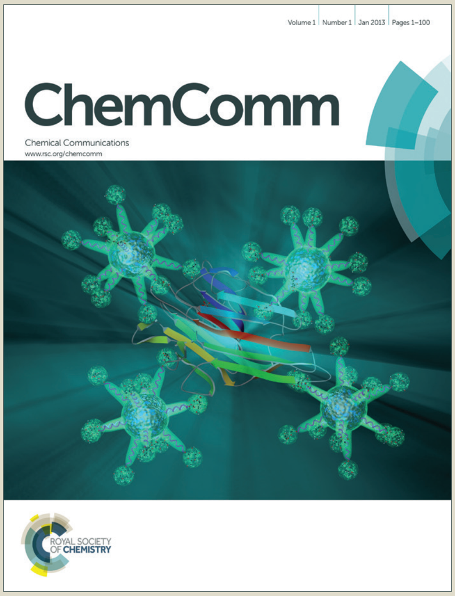

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Copper-Catalyzed Aerobic Carboxygenation and N-arylation of [1,2,3]Triazolo[1,5-a]pyridines towards pyridinium triazolinone ylides

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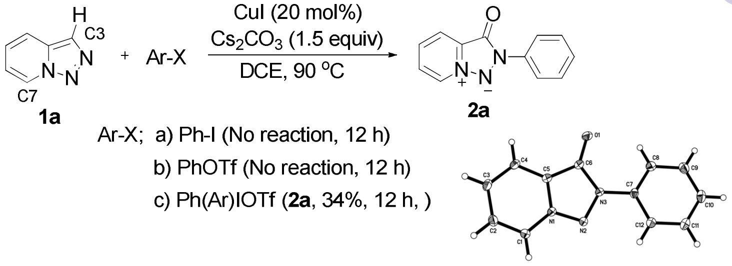
Copper-catalyzed aerobic oxyarylation of [1,2,3]Triazolo[1,5-a]pyridines is developed. Notably molecular oxygen was utilized as one of the reagents and the transformation resulted in the formation of novel pyridinium triazolinone ylides. A basic mechanism for the one-pot process is proposed and further functionalization of the ylidic products were also presented.

[1,2,3]-Triazoles are important nitrogen-rich heterocycles having widespread application in medicine, biology and material science.[1] [1,2,3]Triazolo[1,5-a]pyridines constitute key yet unique members of the triazole family. They also offer potential access to biologically important pyridine derivatives, energetic and small molecule fluorescent materials.[2] Though homogeneous transition metal-catalysis has made significant strides in making functionalized monocyclic-triazoles, the reports on functionalization of triazolopyridines have been scant and features only a single report based on transition metal-catalysis till date.[2c] This dearth in activity and the potential of these derivatives inspired us to venture into the functionalization of [1,2,3]Triazolo[1,5-a]pyridines and this report discloses the initial findings.

At the outset, we set out to explore the possible C/N-arylations of triazolopyridines as a continuum of our own interest in metal-catalyzed directed and non-directed arylations of nitrogen containing organic molecules.[3] Copper salts were the preferred catalysts and the initial attempts with iodobenezene and phenyl triflate as coupling partners for the model triazolopyridine substrate (**1a**) were disappointing (Table 1, entries a & b). Employing a more electrophilic phenyl(mesityl)iodonium triflate[4] having a non-labile mesityl moiety did induce reactivity and the starting materials gave way to a new product in 12 h at 90 °C. Comprehensive X-ray structural elucidation unambiguously confirmed the product to be an unexpected zwitter-ionic pyridinium triazolinone ylide (**2a**, 34%) produced as a result of C7-oxygenation and N-arylation.[5, 6] We attributed the oxygenation to the molecular oxygen present in the reaction flask and incorporation of it was confirmed through carrying out the reaction under ^{18}O (*vide infra*). Product **2a** possessed a novel heterocyclic structure to the best of our knowledge and the observed catalytic C-H oxygenation using molecular oxygen as the reagent is a transformation of great interest owing to the apparent economic and environmental advantages.[7] Driven by these prospects, we went on to fine-tune the reaction efficiency (See SI for optimization studies). Copper(I) salts were generally more effective than Cu(II) and a relatively more cationic Tetrakis(acetonitrile)copper(I) hexafluorophosphate was found to be the catalyst of choice (no reaction was observed in the absence copper).

Table 1. Scope of arene electrophiles towards oxyarylation of **1a**



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Electronic Supplementary Information (ESI) is available: Experimental procedure and characterization data of new compounds. CCDC for **2a** is 1035312 and CCDC for **3a** is 1035311. See DOI: 10.1039/c000000x/

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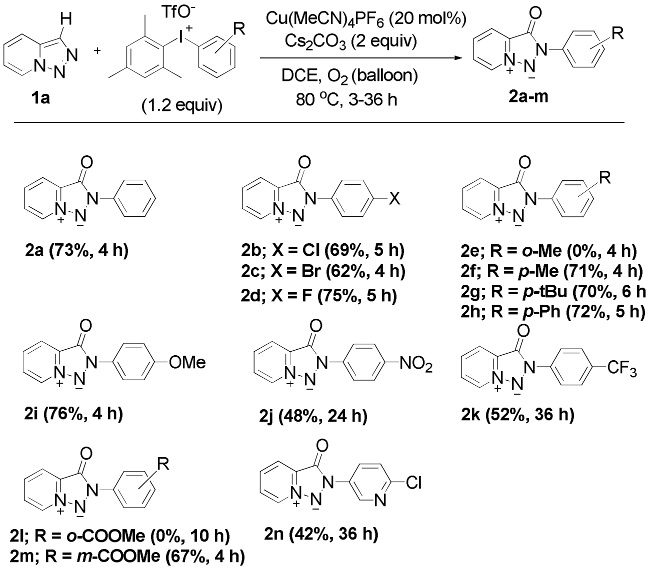
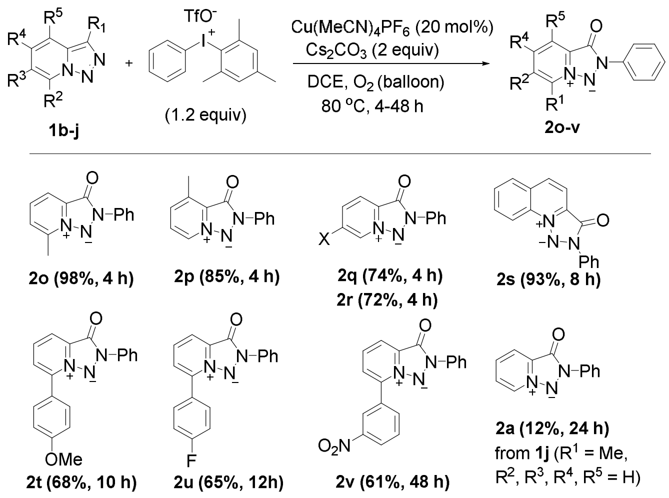
Common ligands for copper led to sluggish reactions possibly due to competitive binding with the metal centre. Expectedly an oxygen atmosphere accelerated the reaction and curiously the transformation was of a very solvent and a base-sensitive one. Polar coordinating solvents like DMF, t-BuOH and dioxane induced either decomposition or no-reaction and caesium carbonate stayed as the optimal base. (see SI for details). Having identified the optimal conditions, the scope of different aryl(mesityl)iodonium triflates to oxyarylate the model substrate (**1a**) was tested (Table-2, entries **2a-n**). Gratifyingly, the reaction accommodated a range of electronically different groups on the labile aryl ring with electron-withdrawing groups having a noticeable deceleration effect (Table 2, compare **2a**, **2i**, **2j** & **2k**). Useful synthetic handles like halogens, nitro and ester were among the groups that could be installed (Table 2, entries **2b-d**, **2j**, and **2m**). A heterocylic aromatic ring was also N-arylated notwithstanding the mediocre isolated yield (Table 2, entry **2n**) The reaction seemed to be averse to steric effects on the *ortho*-position of the transferred aryl group as was evidenced from the *o*-methyl and *o*-ester substitutions (Table-2, entry **2e** & **2l**).

Table 2. Reaction scope with different aryl(mesityl)iodonium triflates

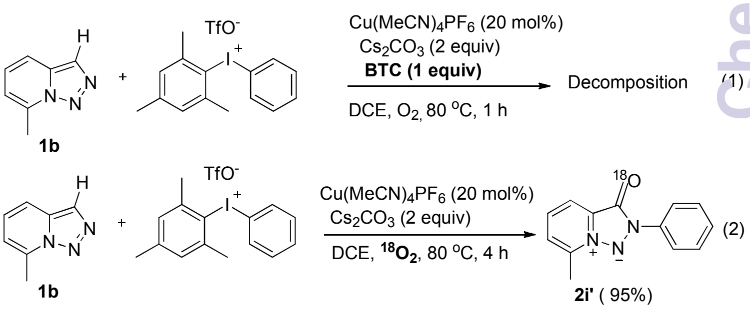


Having established the effectiveness of electronically different aryl partners, we next turned to investigate if the same could be extended to different [1,2,3]Triazolo[1,5-a]pyridine substrates (Table 3, entries **2o-v**). These compounds were easily synthesized by the oxidative cylization of the corresponding hydrazones and were found to be mostly stable to the reaction conditions.[8] Phenyl(mesityl)iodonium triflate was employed as the model electrophile and standard reaction conditions were applied. It was found that the presence of a methyl group significantly improved the reaction rate (Table 3, **2o** & **2p**). It was noteworthy that halogen substituents were tolerated under the reaction reactions with no competing dehalogenation or C-arylation (Table 3, **2q** & **2r**). Aryl substituents on C7 were permissible[9] with both *p*-anisyl and *p*-fluorophenyl groups offering useful yields whereas a more electronically deactivating *m*-nitrophenyl moiety took longer reaction time (Table 3, **2t**, **2u** and **2v**). [1,2,3]triazolo[1,5-a]quinolone also underwent the reaction smoothly to deliver the corresponding ylide product (Table 2, **2s**). Interestingly, oxygenation of a C3-methyl substituted carbon was also observed as demethylation of **1j** took to the formation of **2a** (Table 3, last entry).

Table 3. Substrate scope for the oxyarylation reaction



The precise redox mechanism of the oxyarylation reaction seems to be rather complex and as of now we are able to propose only a speculative picture. The highly oxidative reaction conditions (molecular oxygen, hypervalent iodine) point towards a Cu(II)/Cu(III) catalytic cycle and the oxygenation is taken to follow a radical pathway through putative copper(II)-peroxo species.[7,10] The involvement of radicals was experimentally supported by the observation that a radical scavenger like 2,6-Di-*tert*-butyl-*p*-cresol (BHT) totally inhibited the model reaction (Scheme 1, eq.1). Utilization of an ^{18}O atmosphere incorporated the isotopically labelled oxygen at the carbonyl group of the product **2i′** (Scheme 1, eq.2).



Scheme 1. Mechanistic studies

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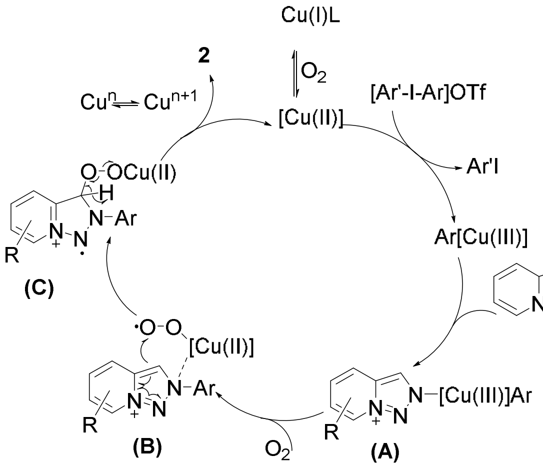
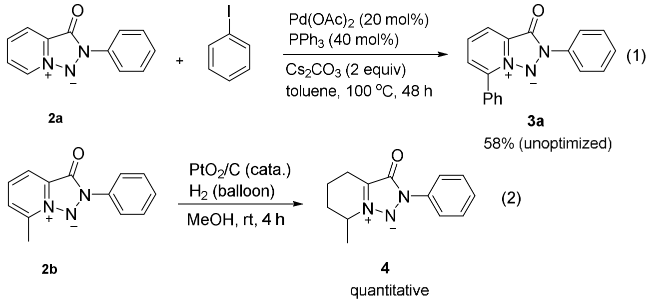
Decomposition of the model reaction was observed under strict inert conditions even in the presence of 1 equivalent of the copper salt. These observations testify the role of molecular oxygen as the oxygenation reagent as well as the oxidant (*vide infra*).

Based on these observations a tentative mechanism was proposed (Scheme 2). Cu(II) species that was generated by the swift aerobic oxidation of Cu(I) undergoes an oxidative-aryl transfer (probably disproportionation-induced) to form an aryl-Cu(III) species.[10, 11, 12] The highly electrophilic Cu(III) complex was then coordinated to the triazole nitrogen. Reductive elimination of the intermediate **A** followed by reoxidation of the copper(I) center led to the formation of peroxo-copper(II) species **B**. The C-O bond formation is conceived through a homolytic electron redistribution driven by the ensuing aromatization of the pyridinium ring forming the transient N-radical **C**.[13] Elimination of Cu^{II}-OH followed by single electron reduction of the nitrogen center in **C** would generate the product thereby closing the catalytic cycle.[14]



Scheme 2. Plausible mechanism

We have also briefly investigated the synthetic potential of the oxyarylation-derived triazolinone ylides **2**. (Scheme 3, eq. 1 & 2). The azopyridinium moiety in these compounds offers an activated aromatic ring and taking advantage of it we were able to induce a palladium-catalyzed *ortho*-selective direct arylation on **2a** to produce the C7-arylated derivative **3a** (Scheme 3, eq. 1).[15, 16] The pyridinium ring could also be subjected to mild catalytic hydrogenation as was shown with **2b** to yield the corresponding tetrahydropyridininum ylide **4**. (Scheme 3, eq. 2). The reductive cleavage of the N-N bond of these compounds would open access to a variety of substituted pyridines/piperidines though our initial trials towards this target were met with little success.[17] Triazolinones are known to be useful pharmacophores[18] in drug discovery and our oxyarylated ylidic structures could be interesting complementary additions to this library. Present research is largely inclined towards these directions.



Scheme 3. Synthetic modifications of pyridinium triazolinone ylides

Conclusion

In summary, an aerobic, copper-catalyzed tandem oxyarylation of [1,2,3]Triazolo[1,5-a]pyridines using aryliodonium triflates is reported. The one-pot reaction led to the formation of pyridinium triazolinone ylides which are novel heterocyclic structures. The synthetic modification of these molecules is briefly addressed and ongoing efforts are directed towards further manipulation of their potential to be synthetic precursors and fluorescent probes.

Acknowledgements

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