NJC

ROYAL SOCIETY OF CHEMISTRY

PAPER

Cite this: *New J. Chem.*, 2020, 44, 1326

Efficient solvent- and temperature-tuned access to aldoxime ethers and phenolic functions by Pd-catalyzed C–O cross-coupling of aldoximes with aryl bromides and bromo-chalcones†

Reeta,[ab] T. M. Rangarajan,*[c] Kumar Kaushik,[a] Rishi Pal Singh,[c] Manjula Singh[d] and Raj Pal Singh*[a]

Received 11th October 2019,
Accepted 15th December 2019

DOI: 10.1039/c9nj05124d

rsc.li/njc

A single method with a functionality switching option was developed for the first time for the Pd-catalyzed C–O cross-coupling of aryl bromides and bromo-chalcones with aldoximes. The ligand *t*BuXPhos (**L2**) was found to be an effective supporting ligand for the Pd-catalyzed coupling of aldoximes with bromo coupling partners. The functionality switching from oxime ethers to a phenolic or hydroxy group was driven by solvent or temperature. This method offers the products in good to excellent yields in short reaction times.

Introduction

Oxime ethers are not only the fundamental constituents of pharmaceutical, bioactive (Fig. 1) and agricultural chemicals,[1] as the potent inhibitors of transthyretin amyloid fibril formation,[1a] antibiotic (cefmenoxime),[1b] antifungal[1c] (oxiconazole), antihistamine (**1a**),[1d] therapeutic agent for insomnia (eplivanserin (**1b**)),[1e,f] melanin-concentrating hormone 1 receptor antagonist (**1c**),[1g] antiplasmodial,[1h] monoamine oxidase, and acetyl cholinesterase inhibitor (**1d**),[1i] insecticidal,[1j] fungicidal,[1k] herbicidal agents,[1l] *etc.*, but also important and versatile precursors in the synthesis of various structural motifs.[2]

O-Aryl oxime ethers have received special attention due to their accessibility to numerous medicinally and synthetically important organic compounds[2] such as benzoxazole,[3a–c] dihydrobenzofuran,[3d,e] benzofurans,[3e–i] phenols,[3j] quinolines,[3k] 3-aminobenzisoxazoles,[3l] and pyrroles.[3m] Conventionally, the synthesis of *O*-aryl oxime ethers is achieved *via* (i) the condensation of *O*-aryloxyamines with carbonyl compounds[1a,3e,f,4] and (ii) *O*-arylation of oximes with activated nitro- or fluoroarene derivatives in the presence of a strong base *via* an S_NAr-type process.[1a,3e,4a,5] The former can be achieved *via* the amine exchange reaction of 2,4-dinitrophenoxyamine with phenols[3f,6] and *O*-arylation of ethyl acetohyroxamate,[1a,4d,7] or *N*-protected hydroxylamine[8] with electron-deficient aryl systems, in the presence of a strong base *via* an S_NAr-type process, and subsequent hydrolysis with acid. Recently, several other improved methods have been developed for the synthesis of aryloxyamines.[1g,3f,g,m,n,9,10]

Unfortunately, the synthesis of *O*-aryl oxime ethers by direct coupling of aryl halides and oximes is not well explored;[11a] however, several other methods are available for the coupling of ketoximes with arylboronic acids by copper catalysts[11b–f] and diaryliodonium salts,[3f,g,12] which are obtained from aryl halides, but commercially, these starting materials are relatively more expensive than aryl halides.

Moreover, similarly to oximes,[2c,14] *O*-arylaldoxime ethers are also important starting materials for the synthesis of biologically active nitriles,[2a] benzoxazoles,[3b,c] and phenols.[3i] Although aldoxime ethers have received considerable interest, no efficient methods have been reported thus far for their synthesis. Aldoxime ethers synthesized *via* the copper-mediated direct coupling of aryl coupling partners with aldoximes suffer from harsh reaction conditions and poor yields.[11a,b,d,e] T. Punniyamurthy *et al.* reported the efficient copper triflate-mediated synthesis of benzoxazoles from aldoxime ethers, which were synthesized from the condensation of aryloxyamines and benzaldehydes. The synthesis of aryloxyamines is slightly cumbersome, and hence has limited substrate scope (Scheme 1).[3b] Therefore, the synthesis of benzoxazoles through this method is likely to be less striking.

Therefore, efficient methods for the synthesis of aldoxime ethers from aryl bromides and aldoximes are in demand and need to be urgently developed.

Additionally, the introduction of phenolic function(s) in organic compounds is one of the essential synthetic tasks in organic chemistry since phenols are important synthetic intermediates of a myriad of useful compounds and constituents of

[a] *Centre for Fire, Explosive and Environment Safety, DRDO, Delhi, India. E-mail: rajcfees@gmail.com*
[b] *Department of Chemistry, University of Delhi, Delhi, India*
[c] *Department of Chemistry, Sri Venkateswara College, University of Delhi, New Delhi, India. E-mail: rangarajan93150@gmail.com*
[d] *Department of Chemistry, Shivaji College, University of Delhi, New Delhi, India*

† Electronic supplementary information (ESI) available: Detailed procedures, characterization data, and spectra. See DOI: 10.1039/c9nj05124d

