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C–H arylation of azaheterocycles: a direct ligand-free and Cu-catalyzed approach using diaryliodonium salts†

Cite this: DOI: 10.1039/c4ob01061b

Received 22nd May 2014,
Accepted 30th June 2014

DOI: 10.1039/c4ob01061b

www.rsc.org/obc

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An efficient and high yielding Cu-catalyzed direct C–H arylation of azaheterocycles including oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles has been achieved by employing easily accessible diaryliodonium salts.

Metal-mediated direct functionalization of the C–H bond is one of the powerful and promising organic tools to introduce various functional groups and construct biologically active molecules.[1] The C–H functionalization protocol is a relatively better alternative to traditional cross-coupling methods as it avoids organic halides and pre-functionalization steps. In recent years, significant attention has been devoted to C–C bond formation *via* C–H activation of heterocycles followed by their couplings with aryl halides, aryl triflates, arylboronic acids or arenes in the presence of expensive palladium, rhodium based catalysts and ligands.[2] Due to the ubiquity of heteroaromatic nuclei in a variety of natural products and synthetic therapeutic agents and organic materials, their construction and functionalization have been continuously pursued with increasing interest and special attention.[3] Particularly, C–H functionalization of bioactive heterocycles has received increasing attention due to many advantages such as the use of catalytic amounts of reagents and avoidance of activating agents, thereby generating fewer by-products. Arylazoles, especially oxadiazoles, thiadiazoles, benzoxazoles and benzothiazoles, are privileged motifs present in numerous bioactive and pharmaceutical agents (Fig. 1).[4]

In recent years, remarkable improvement in the synthesis and utilities of diaryliodonium salts has been documented.[5] Pioneering work on the selective arylation of sp^2 C–H was explored by Gaunt and co-workers using copper catalysts.[6] In 2007, Sanford and Deprez studied the arylation of sp^2 C–H involving diaryliodonium salts in the presence of the Pd-catalyst.[7] Manolikakes and Umierski have successfully developed an efficient and high yielding route to diaryl sulfones by utilizing diaryliodonium salts.[8] Recently, we have prepared 1,2,3-triazoles and diaryl sulfones effectively utilizing diaryliodonium salts.[9] In continuation of our work, we now disclose a copper-catalyzed direct C–H arylation of various azaheterocycles, *e.g.* oxadiazoles, thiadiazoles, benzoxazoles, and benzothiazoles, by employing readily accessible diaryliodonium salts.

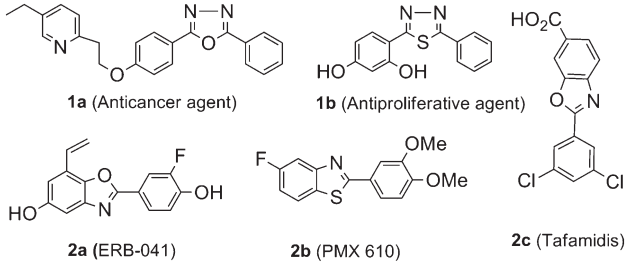

Fig. 1 Some important bioactive azaheterocycles.

Initially, the C–H arylation of easily accessible 2-phenyl-1,3,4-oxadiazole (**3a**) with diphenyliodonium salt (**5a**) was explored to generate 2,5-diphenyl-1,3,4-oxadiazole (**6a**) (Table 1). Miura *et al.* have prepared 2,5-diaryl-1,3,4-oxadiazoles based on C–H functionalization of sp^2-carbon involving copper and 1,10-phenanthroline combination at 120 °C for 4 h.[10] The C_5–H in **3a** being next to a heteroatom, initially we tried to generate an anion using bases (Na_2CO_3, Cs_2CO_3 and *t*-BuOK) in polyethylene glycol-400 (PEG-400) and DMSO. The arylation of **3a** using a catalytic amount of CuBr (20 mol%) and a stronger base (*t*-BuOK) was examined in PEG-400 at 100 °C (Table 1); CuBr triggered the arylation of **3a** after 18 h to deliver **6a** in 68% yield (Table 1, entry 2). To optimize the reaction conditions further, various bases, copper salts and solvents were screened. Interesting results were obtained, however, when an alternate form of energy, microwave (MW) irradiation, was deployed; the same reaction conducted in a focused MW system for 30 min afforded **6a** in 80% yield (Table 1, entry 3) substantiating earlier MW-enhanced acceler-

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†Electronic supplementary information (ESI) available: Detail optimization tables, typical experimental procedure and NMR spectra copies for all the compounds. See DOI: 10.1039/c4ob01061b

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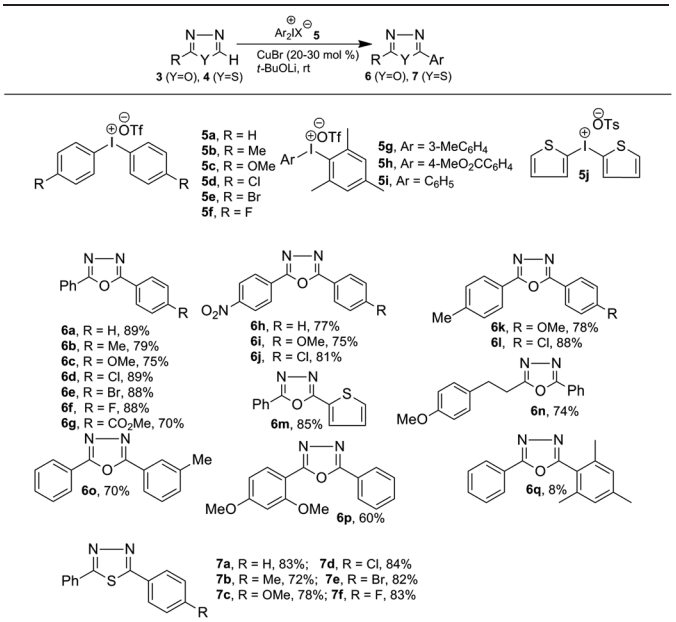
Table 1 Optimization of arylation of 1,3,4-oxadiazoles[a]

Entry[a]	Catalyst	Base	Solvent	X	Yield[e] (%)
1[b]	—	*t*-BuOK	DMSO	OTf	NR
2[b]	CuBr	*t*-BuOK	PEG-400	OTf	68
3[c]	CuBr	*t*-BuOK	PEG-400	OTf	80
4[c]	CuBr	Cs_2CO_3	PEG-400	OTf	Trace
5[c]	CuBr	K_3PO_4	PEG-400	OTf	NR
6[d]	CuI	*t*-BuOK	PEG-400	OTf	Trace
7[d]	CuBr	*t*-BuOK	DMSO	OTf	80
8[d]	CuBr	*t*-BuOLi	DMSO	OTf	89
9[d]	CuBr	Cs_2CO_3	DMSO	OTf	NR
10[d]	CuBr	*t*-BuOLi	DMSO	BF_4	65

Reaction conditions: [a] **3a** (1 equiv.), **5a** (1 equiv.), Cu catalyst (20 mol%), base (3 equiv.) was stirred in DMSO for 15 min at rt. [b] Conventional heating at 100 °C for 18–24 h. [c] Microwave irradiation at 100 °C for 15–20 min. [d] Stirring at rt for 10–15 min. NR = no reaction. [e] Yield of isolated product.

Table 2 Arylation of 1,3-azoles **3** and **4** with diaryliodonium salts **5**



ated C–C bond formation.[11] Among other bases, Cs_2CO_3 and K_3PO_4 failed to deliver **6a**. Similar fate was met by replacing CuBr with CuI; no improvement in the yield was observed. The arylation was then examined at room temperature in DMSO using a stronger base (*t*-BuOLi) when efforts were amply rewarded with a much higher yield of **6a** (89%) in 15 min by simply changing the solvent from PEG-400 to DMSO and the base from *t*-BuOK to *t*-BuOLi (Table 1, entry 8), presumably due to the better solubility of the substrate, catalyst and base in DMSO. For the arylation of **3a–e**, the use of CuBr (20 mol%) and *t*-BuOLi (3.0 equiv.) at room temperature in DMSO was the ideal optimized condition. During the arylation of oxadiazoles, we found that the use of the corresponding iodonium triflate was more effective when compared to iodonium salts with Br, OTs and BF_4 counter ions. In some cases iodonium salts with OTs or Br counterions were preferred due to their easy access.

Having optimized the reaction conditions, we explored this protocol for the arylation of various oxadiazoles **3** by utilizing different symmetrical (**5a–f**, **5j**, **5p**) and unsymmetrical (**5g–i**) diaryliodonium salts and prepared a variety of 2,5-diaryl-1,3,4-oxadiazoles **6a–q** (Table 2). Substituted oxadiazoles **3** having nitro (**3b**), tolyl (**3c**) and dimethoxyphenyl moieties were arylated smoothly to furnish **6h–l** (75–88%) and **6p** (60%) in good to excellent yields. Alkyl substituted oxadiazole (**3d**) could also be coupled to furnish **6n** in 74% yield. Interestingly, when **3a** was coupled with **5g**, **6o** was obtained in 70% yield along with **6q** in 8% yield.

Next, we carried out the arylation of structurally similar 2-phenyl-1,3,4-thiadiazole (**4**) to prepare diversely substituted 2,5-diaryl-1,3,4-thiadiazoles **7a–f** which are of paramount importance in medicinal chemistry due to their interesting biological activities (**1b**, Fig. 1).[4e,f] There is only solitary precedence for the direct C–H arylation of 1,3,4-thiadiazoles using aryl halides/aryl triflates involving $Pd(OAc)_2$, Xantphos, Cs_2CO_3 and the CuI catalytic system at 105 °C for 12 h.[12] A screening study was initiated for the reaction between **4** and **5a** by employing a catalytic amount of copper salts (CuI and CuBr) and bases (*t*-BuOK, Cs_2CO_3, K_3PO_4) in DMSO and PEG-400 at room temperature, but the phenylation did not proceed as expected. In some cases traces of **7a** was obtained (see the ESI†). Gratifyingly, the arylation of thiadiazole **4** proceeded elegantly with a catalytic amount of CuBr (30 mol%) and *t*-BuOLi (3.5 equiv.) in DMF at room temperature within 15 min and affording **7a** in 83% yield. With these optimized reaction conditions, we conducted the C–H arylation of thiadiazole **4** by employing various diaryliodonium salts **5a–f** (Table 2) and could successfully generate a variety of 2,5-diaryl-1,3,4-thiadiazoles **7a–f** in 72–84% yields.

Next the arylation of benzo-fused heterocycles[13] *e.g.*, benzoxazoles and benzothiazoles was explored to synthesize diverse 2-arylbenzoxazoles and 2-arylbenzo-thiazoles endowed with interesting biological properties (**2**, Fig. 1).[4c,d,19] Daugulis and Miura have independently studied the copper-mediated direct C–H arylation of various heterocycles using different conditions.[14] Later, Huang *et al.* reported arylation of benzoxazoles using the $Pd(OAc)_2/Cu(II)/PPh_3$ co-catalytic system.[15] In our efforts various benzoxazoles were coupled with diaryliodonium salts under the optimized reaction conditions identified for 2-aryl-1,3,4-oxadiazoles **3**. It was found that benzoxazoles **8** could react with a relatively broad range of iodonium salts **5** to afford 2-arylbenzoxazoles **10a–n** in 79–89% yields (Table 3). Substituted benzoxazoles **8b** (Me) and **8c** (Cl) furnished **10j–l** in excellent yields (80–85%); *ortho*-substituted diaryliodonium salts **5k** (OMe) and **5m** (NO_2) were well tolerated under these conditions to obtain **10h–i** in good yields.

Finally, the scope of arylation reaction was extended to benzothiazoles **9** to prepare 2-arylbenzothiazoles **11**; such C–H

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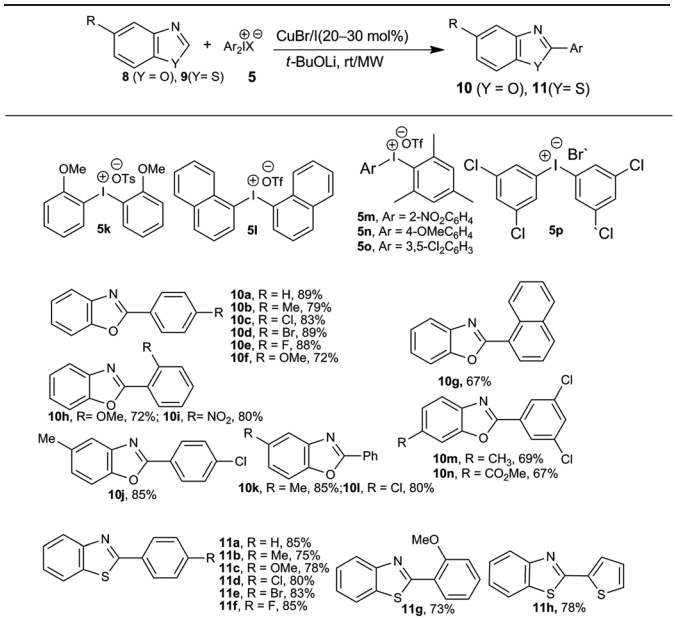
Table 3 Arylation of benzoazoles **8** and **9** with diaryliodonium salts **5**



arylations have been achieved using various catalysts such as Pd,[16] Pd/Cu/additive[17] combination and aryl halides. Our earlier optimized C–H arylation conditions, however, failed to deliver 2-phenylbenzo-thiazole (**11a**). Therefore, we explored the reaction between **9** and **5a** in the presence of CuBr by varying bases, solvents and reaction temperature from rt to 130 °C (see the ESI†). Bases such as *t*-BuOLi and AgOAc could not produce **11a** even under conventional heating. So, next we attempted the arylation of **9** with **5a** in DMF under MW irradiation; however, it was unsuccessful. Various copper salts such as CuI, $Cu(OAc)_2$, Cu/Pd and Cu/Ag catalytic combinations also failed to give **11a**. No desired product was detected by varying bases and ligand combinations (K_3PO_4/PPh_3 and K_3PO_4/1,10-phenanthroline) in the presence of CuI. After successive failures under conventional heating and at ambient temperature, the arylation reaction of **9** was performed under MW in the presence of CuI and *t*-BuOLi in DMSO or DMF. Interestingly, under these conditions formation of 2-aminothiophenol was observed instead of the desired **11a**. This indicated that the polar-aprotic solvents such as DMSO and DMF enhanced the ring opening of benzothiazole to produce aminothiophenol.[18] To diminish the ring-opening of benzothiazole, we attempted the arylation of **9** using **5a** in dioxane and obtained the desired 2-phenylbenzothiazole (**11a**) in 85% yield. Finally, we found that CuI (30 mol%) and *t*-BuOLi (3.5 equiv.) in dioxane under MW irradiation (30 min, 130 °C) were the best conditions to prepare **11a**. With an optimized set of reaction conditions, we studied the arylation of benzothiazole **9** by employing various diaryliodonium salts **5a–h** (Table 3) and prepared diversely substituted 2-arylbenzothiazoles **11a–h**.

Notably, the halo-substituted diaryliodonium salts **5d–f** afforded **6d–f**, **7d–f**, **10c–e** and **11d–f** in good to excellent yields (81–89%). The tolerance of the bromo and chloro groups is particularly useful for further synthetic manipulations by traditional cross coupling methods. In unsymmetrical iodonium salts **5g–i** and **5m–o** the bulky mesityl moiety acts as a non-transferrable group, so only **6a**, **6g**, **6o**, **10f**, **10i** and **10m** were formed selectively in excellent yields. Iodonium salts **5b–c** and **5k** with electron-donating groups (Me and OMe) delivered **6b–c**, **7c**, **10f**, **10h**, **11b–c** and **11g** in relatively good yields. The bulky naphthyl and heteroaromatic thienyl motifs were successfully transferred using iodonium salts **5j** and **5l** giving **6m**, **10g** and **11h** in excellent yields.

To illustrate the synthetic utility of this copper-catalyzed arylation of diverse azoles, we prepared various useful molecules. From the reactions of benzoazoles and iodonium salts, we successfully prepared efficient ESIPT fluorescent and chelating agents including 2-(4′-metho-xyphenyl)benzoxazole (**10f**), 2-(2′-methoxyphenyl)-benzoxazole (**10h**) and 2-(2′-methoxy-phenyl)benzothiazole (**11g**) (Table 3).[19] 2,5-Diaryl-1,3,4-oxadiazoles **6c** and **6p**, analogues of anticancer agents (**1a–b**), were easily prepared from the reactions of an appropriate oxadiazole **3** with diphenyl iodonium salts. Successful installation of the 3,5-dichlorophenyl moiety onto benzoxazole using **5p** allowed us to prepare the methyl ester (**10n**) of Tafamidis in 67% yield (Table 3).[20]

To check the feasibility of the developed protocol on the gram-scale, we conducted the reaction of 2-phenyl-1,3,4-oxadiazole (**3a**, 1 g) with diphenyliodonium triflate **5a**; **6a** was obtained in 83% yield. Arylation of various azaheterocycles involving different equivalents of base (3.0 and 3.5 equiv.) and reaction conditions (rt and MW) revealed that the acidity of the C_2–H bond plays a pivotal role. From the aforementioned results, it was observed that the reactivity of various azoles (oxadiazoles = benzoxazoles (pK_a = 24.8) > thiadiazoles > benzothiazoles (pK_a = 27.3)) parallels the acidity of C_2–H.[14b,21] Based on our results and literature reports,[22,23] mechanistically it is postulated that an initial cupration of 1,3-azoles **A** with the aid of *t*-BuOLi affords an azolyl-copper species **B**. Subsequent oxidative addition of **B** to the diaryliodonium salt facilitates the formation of an electrophilic Cu(III)-aryl species **C** with the generation of an appropriate iodoarene. Finally, the reductive elimination of **C** is assumed to afford the arylated azoles **D** with the concomitant release of the Cu(I) catalyst (Fig. 2).

In summary, we have developed a facile, high yielding, scalable and ligand-free copper-catalyzed direct C–H arylation protocol that enables the synthesis of diverse class of bioactive azaheterocycles, namely aryloxadiazoles, arylthiadiazoles, arylbenzoxazoles and arylbenzothiazoles, by employing readily accessible diaryliodonium salts. The present method offers advantages including shorter reaction times, milder reaction conditions, a wider substrate scope with high yields of the

Fig. 2 Proposed mechanism for the arylation of azoles.

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products. The arylmesityl iodonium salts can be effectively utilized to prepare appropriate arylated azaheterocycles in high yields. The generalized protocols enable easy access to an array of potentially useful molecules, halo-substituted azaheterocycles and prospective precursors to acquire complex bioactive heteroaryls.

Acknowledgements

The authors gratefully acknowledge CSIR, New Delhi and UGC, New Delhi for financial support. MP and SP thank CSIR, New Delhi for awarding Junior Research Fellowship.

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