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Expeditious synthesis of C2- or N4-aryl-1,4-benzothiazin-3-one via orthogonal Pd-catalyzed C-arylation and Cu-catalyzed N-arylation

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ABSTRACT

Direct, chemo-specific arylation at C-2 or N-4 of 1,4-benzothiazin-3-one with aryl halides, based on Pd or Cu catalyst system, respectively, provided easy entry to arylated derivatives, a class of molecules not easily accessible via existing methods. Under Pd-catalysis conditions with LiHMDS as the base, N-arylation of 1,4-benzothiazin-3-one was inhibited leading to Cα-arylation of a secondary amide without the need for protection and de-protection of more acidic amido NH.

1,4-Benzothiazin-3-one (BZTZN) is a heterocyclic scaffold frequently used in drug design. For example, Sesamodil, an 2-aryl-4-methyl BZTZN compound has been clinically used as an antihypertensive and antiarrhythmic agent.[1] Compounds based on the BZTZN motif were also reported as histamine H1 antagonist,[2] anticonvulsant/antifungal agents,[3] sodium glucose co-transported 2 inhibitors,[4] Ca^{2+}-activated potassium channel opener,[5] phosphodiesterase 7 inhibitors,[6] 5-HT_3 antagonists,[7] and Na^+/H^+ exchange inhibitors.[8]

Very recently, we reported a novel one-step synthesis of BZTZNs from Cu-catalyzed coupling of readily available substituted 2-iodoanilines with 2-mercaptoacetate. This methodology allows easy introduction of structural diversity at the phenyl ring of BZTZN nuclei.[9] To further derivatize BZTZN, we were particularly interested in its C2- or N4-aryl analogs. Literature survey indicated studies on the synthesis of these types of molecules were limited. The C2-aryl-BZTZN has been synthesized via methods involving: (i) S_N2 substitution reaction of 2-aminothiophenol and alpha-haloarylacetate followed by cyclization,[10] (ii) condensation of 2-aminothiophenol and aryltrichlorocarbinol,[11] (iii) Friedel–Crafts reaction of C2-Cl derivative with benzenes bearing directing groups such as alkoxy and hydroxyl,[12] and (iv) base-mediated condensation of 2,2′-diaminodiphenyl disulfides with arylacetates.[13] A recent study on the condensation of 3-aryl-2,2-oxiranedicarbonitrile with 2-aminothiophenol included a few examples of synthesis of C2-aryl-BZTZNs.[14] The synthesis of N4-aryl-BZTZN is very rare; only isolated examples have been reported including: (i) introduction of the 4-fluorophenyl group from $Cu(OAc)_2$-mediated oxidative coupling of corresponding aryl boronic acid with a 2,2-disubstituted BZTZN,[15] (ii) *N*-(4-hydroxyphenyl) derivatization via the reaction of 4-acetoxy BZTZN with phenol,[16] (iii) phenylation via the reaction of BZTZN with phenyl bromide under refluxing condition (bp 156 °C) in the presence of excessive copper powder,[17] or lately via Cu-catalyzed coupling of *N*-(2-iodophenyl)-*N*-phenyl-2-chloroacetamide with thioacetic acid.[18] More recently, a new synthesis of *N*-aryl-BZTZN was developed from condensation of 3,4-difluorobenzonitrile with certain 2-mercapto-*N*-arylacetamides via Smiles rearrangement.[19] These existing methods suffer a number of drawbacks such as limited availability of diverse starting materials or lengthy synthesis of requisite starting materials, multi-step reaction sequences, harsh reaction conditions, narrow reaction scopes, poor regioselectivity, and in many cases, low yields. These limitations prompted us to develop convenient and general syntheses of C2- and N4-aryl BZTZNs from easily accessible starting materials.

In view of tremendous advances in Pd- and Cu-catalyzed N- and C-arylation,[20] one can envisage direct, catalytic arylation of parent BZTZN with aryl halides could provide easy access to 2- or 4-aryl BZTZNs. To our surprise, such an arylation has not been applied to BZTZN hitherto.[21] One issue associated with arylation of BZTZN is chemoselectivity between C-2 and N-4. In this regard, chemoselective arylation at C-3 and N-1 of oxindole has been investigated; while Pd-catalysis promoted C-arylation,[22a,b] Cu-catalysis favored

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N-arylation.[22a,c] Unlike oxindole bearing an amide moiety and a methylene group with comparable pK_a (~18.5), the methylene protons (pK_a ~26) in the BZTZN are less acidic than its amide NH (pK_a ~19).[23] Owing to competing N-arylation, C-arylation of BZTZN was expected to be more challenging relative to C-arylation of oxindole. Upon optimization of reaction conditions we have discovered that using lithium bis(trimethylsilyl)amide as the base chemo-specific C-arylation of BZTZN can be achieved under Pd-catalysis conditions. To the best of our knowledge, C2-arylation of BZTZN reported herein represents the first example of an inter-molecular, chemo-specific arylation at the alpha carbon of amides bearing more acidic, unprotected amido NH.[24]

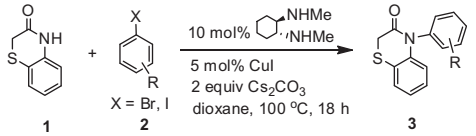
To explore Cu-catalyzed N-arylation of BZTZN, we initially adopted a catalyst system consisting of 5% CuI and 10% *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine. This combination of Cu source and ligand has proved particularly efficient in promoting amidation of aryl halides.[20b] We were pleased to find this catalyst system was also highly effective at driving N-arylation of BZTZN. As shown in Table 1, both *meta*- and *para*-substituted aryl iodides and bromides reacted smoothly under mild conditions, furnishing the desired *N*-aryl derivative as the sole product and in high yield. In all examples, no C2-aryl products were detected based on LC–MS analysis of crude reaction mixtures and/or comparison of HPLC traces of crude mixtures with those generated from Pd-catalyzed C2-arylation (vide infra). The electronic nature of substituents on the aryl ring had little effect on the reaction as aryl halides bearing electron-withdrawing (entries 3 and 4) or electron-donating (entries 5–7) groups reacted equally well. All reactions proceeded to completion after heating at 100 °C overnight; the difference in isolated yields largely resulted from material loss in workup and purification. Under standard conditions, *ortho*- substituted aryl halides were not suitable coupling partners as 1-fluoro-2-iodobenzene could not be coupled using the same catalyst system. Analogous resistance of *ortho*-substituted aryl halide was also observed in Cu-catalyzed N-arylation of oxindoles.[22a,c]

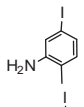
With easy access to N4-aryl-BZTZN discovered, we next turned our attention to arylation at the other reactive C2 site. Since 1998, considerable progress has been made in the area of Cα-arylation of tertiary amides but similar reaction of primary and secondary amides remains underdeveloped, presumably due to complication resulted from arylation at free NH.[25] For example, employing either Pd, Cu or Fe-catalysis conditions, arylation of 2-pyrrolidinone always occurred at the more acidic NH;[20a-b,26] no direct C-arylation was reported on this simple lactam substrate. To effect a chemospecific C-arylation of BZTZN, inhibition of N-arylation at the more acidic amido NH needs to be addressed. We selected the coupling of BZTZN **1** and PhBr as model reaction to screen reaction conditions. Initially this coupling was run in m-xylene under microwave irradiation at 150 °C using $Pd_2(dba)_3$/xantphos catalyst system. As shown in Table 2, the base appeared to have played a critical role in the C-arylation of BZTZN. Among the two bases employed in C-arylation of oxindole, K_2CO_3 was completely ineffective for C-arylation of BZTZN whereas NaO*t*-Bu yielded 50% conversion of **1** and 1:1 mixture of *C*- and *N*-phenyl products. Cs_2CO_3 was a more efficient base leading to 62% conversion with a 3:1 selectivity ratio (C– vs N–). Under otherwise identical conditions, one equivalent of the strong base lithium bis(trimethylsilyl)amide (LHMDS) did not furnish any arylation product; starting **1** was completely recovered. The fact that N-arylation was not observed after deprotonation of the amide NH by 1 equiv LHMDS suggested that chemospecific C-arylation might be possible once another equivalent of base was added to deprotonate the C-2 methylene of BZTZN. Indeed, reaction in the presence of 2.5 equiv LHMDS led to 80% conversion of starting **1** into a new compound which was determined to be 2-phenyl BZTZN after purification. HPLC comparison of the crude mixture with an authentic sample of 4-phenyl BZTZN generated from Cu-catalyzed N-arylation revealed that no N4-phenylation product was formed in this Pd-catalyzed reaction. Detailed study to understand the role of LHMDS in this reaction was not yet carried out. Presumably the amide was converted into a trimethylsilyl imidate upon deprotonation, thereby blocking reaction at the amide site. Such a dual function of LHMDS was observed by Buchwald in the Pd-catalyzed regio-specific N-arylation of amines in the presence of an amide moiety.[27]

Having identified LHMDS as a suitable base for chemospecific C2-arylation, we briefly examined how additional factors such as solvent, method of heating, and catalyst systems influenced coupling. In 1,4-dioxane the reaction also yielded C-arylation product exclusively albeit with a lower conversion. Similarly, reactions employing conventional heating retained chemospecificity but exhibited lower conversions. A small catalyst screen did not yield more successful results. With $Pd_2(dba)_3$ as Pd source, three different phosphorus ligands, namely xantphos, X-phos, or 2,2′-bis(dicyclohexylphosphino)-1,1′-biphenyl, were examined. All provided C-arylation product exclusively upon heating at 100 °C overnight with xantphos exhibiting the highest conversion (50%). Another ligand, *t*-Bu-xantphos, proved ineffective along with $[PdP(t\text{-}Bu)_3Br]_2$, a system with Pd pre-bound to bulky, electron rich phosphorus ligand.

The scope of chemospecific C-arylation of BZTZN was investigated under microwave irradiation and with $Pd_2(dba)_3$/xantphos as the catalyst system. Despite reactions with PhI, PhBr, or PhCl leading to different conversions, all afforded C-arylation products exclusively (Table 3, entries 1–3). The chemospecificity from highly reactive PhI is remarkable since similar C-arylation of oxindole employed aryl chlorides in most cases.[22a,b] A range of substituted aryl halides bearing electron-neutral, electron-donating (entries 4–8), and moderately electron-withdrawing groups (entries 9 and 10) at *ortho*, *meta*, or *para* positions reacted smoothly, furnishing the *C*-aryl products in moderate yields. Steric hindrance did not significantly affect this reaction as *ortho*-substituted substrates reacted almost equally well (entries 5 and 8). The chemospecificity of these reactions was verified by the presence of only one arylation product peak in HPLC and LC–MS trace of each crude mixture. The moderate isolated yields could be due to dehalogenation and/or catalyst deactivation, which led to 80–90% conversion

Table 1
Cu-catalyzed N-arylation of 1,4-benzothiazin-3-one **1**



Entry	**2**	Yield of **3** (%)	Entry	**2**	Yield of **3** (%)
1		92 (**3a**)	5		86 (**3d**)
2		87 (**3a**)	6		62 (**3e**)
3		65 (**3b**)	7		82 (**3f**)
4		65 (**3c**)	8		0 (**3g**)