Copper Catalyzed Intramolecular *N*-arylation for Synthesis of 6*H*-benzo[*b*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazines

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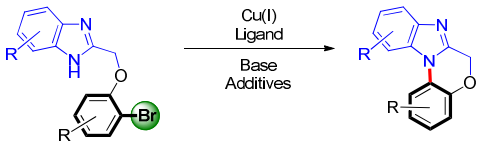
Introduction

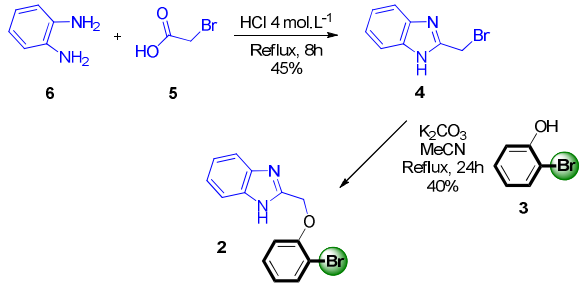
The construction of the C−N bond is of fundamental and immense importance in organic synthesis because of its high prevalence in natural products, pharmaceuticals, and materials. Of all C−N bond-forming reactions, the C−N bond formation through Ullmann and Buchwald-Hartwig reaction represents an attractive and robust approach to the synthesis of nitrogen-containing compounds, has significantly contributed to the streamlining of the synthesis of small molecule pharmaceutical agents.[1] In particular, benzimidazo[1,2-*d*][1,4]oxazines derivatives have attracted considerable interest due to their remarkable biological and medicinal activities.[2] However, the methods for the preparation of these heterocycles remain rare, employing multi-step synthesis, expensive reagents, harsh conditions, and thus avoiding their large scale application in industry.[3] In this sense, Here we report a preliminary studies of chemical transformation through Ullmann cyclization that allows the facile construction of benzimidazo[1,2-*d*][1,4]oxazines moiety (scheme 1).



Scheme 1. Synthesis of benzimidazo[1,2-*d*][1,4]oxazines moiety through Ullmann reaction.

Results and Discussion

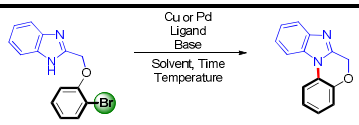
Following scheme 2, the synthesis of benzimidadole core (**4**) is a straightforward process starting from 1,2-diaminobenzeno (**6**) and bromoacetic acid (**5**) in acid medium.[4] Treatment of **4** with 2-bromophenol (**3**) in basic medium provides the intermediate compound **2**.[5]



Scheme 2. Synthesis of benzimidazole **2**.

Several attempts for intramolecular N-arylation through Buchwald-Hartwig reaction were unsuccessful for synthesis of benzimidazo[1,2-*d*][1,4]oxazines core **1** (table 1, entries 1-5).[1a,6] However, just first endeavor through intramolecular Ullmann reaction[7] yield 78% of product 2 (entry 6).

Table 1. Suitable conditions for intramolecular C-N arylation.



	Catalyst (mol %)[a]	Ligand (mol%)	Base (equiv.)	Solv.	T (°C)	Yield (%)[b]
1	$Pd(OAc)_2$ (5)	PPh_3 (20)	KOAc (1.2)	DMF	150	0
2	$Pd(OAc)_2$ (5)	PPh_3 (20)	K_2CO_3 (1.1)[c]	DMF	100	0
3	$Pd(PPh_3)_4$ (10)	-	K_2CO_3 (1.5)	DMF	100	0
4	$Pd(OAc)_2$ (5)	XPhos (10)	NaOt-Bu (2.0)	DMA	100	0
5	$Pd(OAc)_2$ (3)	BINAP (3)	Cs_2CO_3 (3.0)	Toluene	110	0
6	CuI (5)	1,10-Phenanthroline (10)	Cs_2CO_3 (3.0)	Xylene	120	78

[a] 0.25 mmol of **2**, under argon atmosphere and deoxygenated solvents (5.0 mL) for 24h; [b] isolated yields; [c] 30 mol% of AgOPiv.

With this methodology in hands, the effect of ligand, base, solvent and temperature of the intramolecular Ullmann reaction are under evaluation. Furthermore, we will investigate the reaction scope, also aiming the synthesis of sulfur and selenium derivatives for biological and medicinal purposes.

Conclusions

In summary, we have shown a straightforward synthesis of 6*H*-benzo[*b*]benzo[4,5]imidazo[1,2-*d*][1,4]oxazines through Intramolecular Ullmann *N*-arylation reaction. The next steps are evaluate the reaction conditions and scope, also replacing oxygen atom by another chalcogens (S, Se) for biological and medicinal purposes.

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