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Syntheses of Indolizinones From an Intramolecular One-Pot Process of *gem*-Dibromoolefins

Cite this: DOI: 10.1039/x0xx00000x

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Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/x0xx00000x

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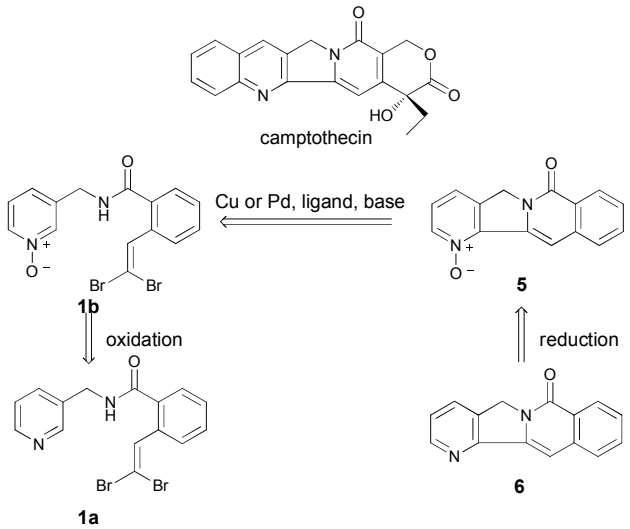
Transition-metal-catalyzed C−H activation has recently emerged as a powerful tool for syntheses of natural products and bioactive compounds. We developed an efficient sequential one-pot intramolecular C−N bond formation and direct C−H arylation method to construct a series of unusual indolizinone scaffolds using *gem*-dibromoolefins in moderate to good yields under mild conditions.

Transition-metal-catalyzed C−H activation has emerged as a powerful tool for the formation of carbon–carbon and carbon–heteroatom bonds.[1] C−H activation strategy has been successfully applied for the syntheses of natural products and bioactive compound.[2] With selective C−H activation in the aromatic and heteroaromatic compounds, some complex polycyclic heterocycles have been constructed efficiently.[3] One-pot C−H activation coupling with other reaction would be more efficient and useful for the construction of many structural interesting motifs.[4]

Gem-dibromoolefins, as bidentate electrophiles, have been found to be versatile intermediates in constructing various heterocyclic motifs.[5] With catalyzed inter- or intramolecular nucleophilic reactions, such as Heck,[6] Ullmann,[7] Sonogashira,[8] Suzuki[9] and Buchwald[10] reactions, two new C−C and/or C−N bonds can be formed in one step by using *gem*-dibromoolefins as the building block. Many facile methods for the formation of polycyclic heteroaromatics have been developed from *gem*-dibromoolefins.[5a,5d-f,6-10] In conjunction with our study of *gem*-dibromoolefins for the syntheses of heterocycles,[11] we have developed a facile and efficient method to construct indolizinone compounds via an intramolecular one-pot amination and C−H activation process with *gem*-dibromoolefins through an unexpected cyclization mode. Most of the compounds obtained are novel polycyclic heterocycles, and may be of great interest in drug discovery.

We initiated our investigation aiming for construction of the camptothecin framework by employing pyridinyl compound (**1a**) as the precursor for the synthesis of indolizinone **6**. As the C−H functionalization of pyridines moiety is often hampered by its poor electron density of the aromatic ring,[12] we used the pyridine N-oxides in order to activate the *o*-H of pyridines to facilitate the subsequent C−H insertion step (Scheme 1).[13] We first studied the reaction conditions with substrate **1b** to investigate the effects of different catalysts, ligands, bases, solvents and temperatures for the preparation of **5** and subsequently **6** upon reduction of the N-oxides. The results are shown in Table 1.



Scheme 1. Planned for the synthesis of pyridine-fused indolizinone derivatives.

After an extensive survey of reaction conditions, we

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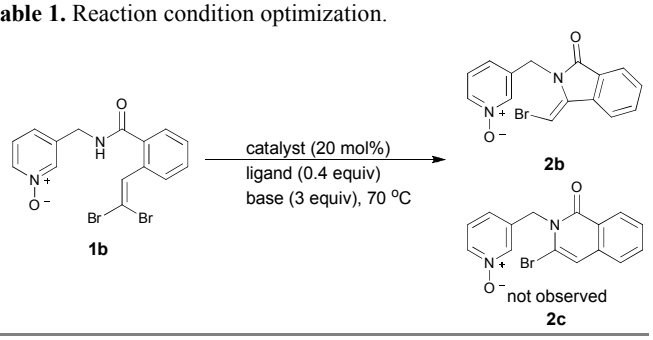
† *Electronic Supplementary Information (ESI) available: General procedures, spectral data and other supplementary information. See DOI: 10.1039/c000000x/*

couldn't obtain the desired product by using various Pd or Cu catalysts. Quite surprisingly, compound **2b** rather than the expected compound **2c** was formed in moderate yield (Table 1, entry 6) and the structure of this intermediate was confirmed by two-dimensional NMR NOE spectroscopy experiment. Later, we found that the yield of **2b** increased significantly when only base was added to the reaction (entry 13). Although the desired indolizinone compound **5** couldn't be afforded in this condition, a trace amount of another structurally rare type of indolizinone structure **3b** was obtained instead when Pd catalysts were present. We then started to investigate the reaction conditions of transforming **2b** into the indolizinone compound **3b** separately and the results are summarized in Table 2. After we screened several reaction parameters, the reaction system with $Pd(OAc)_2$ (10 mol%), P(2-MeOPh)$_3$ (20 mol%), and K_2CO_3 (3.0 equiv) in toluene was found to be most efficient (Table 2, entry 5). Finally we combined these two steps into a one-pot process. After the intramolecular amination addition reaction completed with mild base under 70°C, we added catalyst and ligand into the reaction mixture for the direct arylation while raising the temperature to 120°C for the C−H insertion reaction. The desired compound **3b** was afforded in good yield through this sequential one-pot process. **3b** was hydrogenated by Raney Ni to afford compound **3a** in excellent yield (Scheme 2).

With this optimized reaction conditions in hand, we set to investigate the generality of this one-pot reaction for various pyridinyl heterocycles (Table 3). In the case of unoxidized pyridinyl substrate, the reaction underwent smoothly but two isomers **3a** and **4** from *o* and *p* insertions were obtained in 30% and 60% of yields respectively. We started by introducing substitutions on pyridine to study the substitution effects. Methyl substituted pyridinyl compounds were well tolerated (**3c**, **3d**). We extended the linker between the pyridine and the nitrogen atom, and the pyridine-fused six-membered ring was formed in 63% under this standard condition (**3e**). A limitation of this protocol was observed for substrate **1f**, as the *m*-H of the pyridine couldn't be activated under the standard conditions with only the intermediate **2f** obtained.

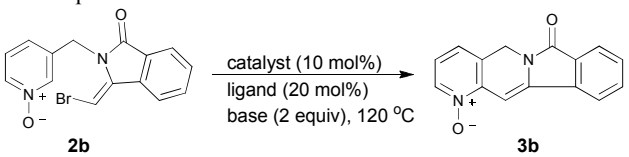
Table 1. Reaction condition optimization.



Entry	Catalyst	Ligand	Base	Solvent	Yield [%][c]
1[b]	$Pd(OAc)_2$	$PtBu_3$-HBF_4	K_2CO_3	toluene	trace
2[b]	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	toluene	trace
3[b]	$Pd_2(dba)_3$	P(2-MeOPh)$_3$	Cs_2CO_3	toluene	trace
4	CuI	phen	Cs_2CO_3	toluene	54
5	CuI	phen	K_3PO_4	toluene	73
6	CuI	phen	K_2CO_3	toluene	77[d]
7	CuI	L-proline	K_2CO_3	toluene	6.5
8	CuCl	phen	K_2CO_3	toluene	65
9	CuBr	phen	K_2CO_3	toluene	45
10	CuI	phen	K_2CO_3	THF	42
11	CuI	phen	K_2CO_3	1,4-Dioxane	64
12	CuI	phen	K_2CO_3	CH_3CN	17
13[e]			K_2CO_3	toluene	99[d]

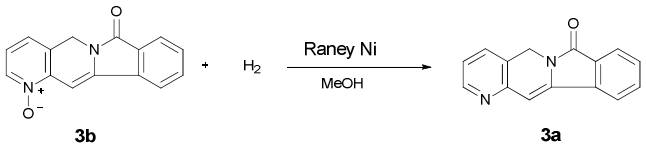
[a] Reaction were carried out under an argon atmosphere. [b] catalyst (10 mol%), ligand (20 mol%), 120°C. [c] Yields of compound **2b**, determined by NMR adding mesitylene as the internal standard. [d] Yield of isolated product. [e] Without catalyst and ligand and react in the air.

Table 2. Optimization of C-H activation conditions.[a]



Entry	Catalyst	Ligand	Base	Yield [%][b]
1	$Pd(OAc)_2$	PCy_3	K_2CO_3	54
2	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	37
3	$Pd(OAc)_2$	PCy_3	K_3PO_4	61
4	$Pd(OAc)_2$	$PtBu_3 \cdot HBF_4$	K_2CO_3	11
5	$Pd(OAc)_2$	P(2-MeOPh)$_3$	K_2CO_3	91[c]
6	$Pd(OAc)_2$	Diethyl phosphite	K_2CO_3	8
7	$Pd(OAc)_2$	P(2-MeOPh)$_3$	K_2CO_3	0[d]
8	$Pd(OAc)_2$	PPh_3	K_2CO_3	79
9	$Pd(OAc)_2$	JohnPhos	K_2CO_3	39
10	$Pd(OAc)_2$	P(2-MeOPh)$_3$	K_3PO_4	74
11	$Pd_2(dba)_3$	P(2-MeOPh)$_3$	K_2CO_3	40

[a] Reactions were carried out under an argon atmosphere. [b] Yields were determined by NMR adding mesitylene as the internal standard. [c] Yield of isolated product. [d] 1 equiv of Bu_4NBr was added.



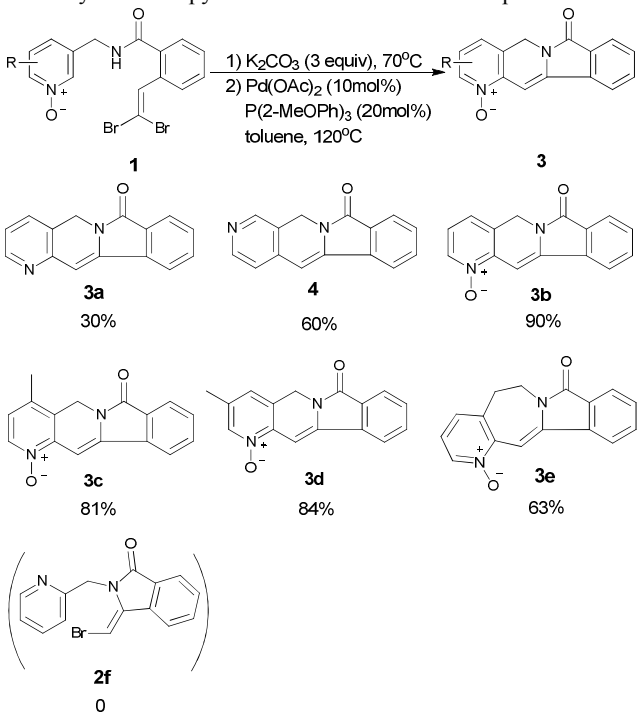
Scheme 2. Reduction of indolizinone *N*-oxide.

We then expanded the method to other aromatics. Benzene and substituted benzenes were chosen as the substrates first. We found that the reaction was sluggish in the amination addition step and complete conversion could not be reached even after several days. We reasoned that it may due to the lack of basicity of K_2CO_3. We then added 1 eq. of KOtBu to the reaction mixture, the amination addition step was finished in about one hour and the desired products were afforded readily. Benzene with various of functional group substitutions were well tolerated including both electron-donating and electron-withdrawing groups. Besides benzene aramatics, other aromatic rings including furan, thiophene, indol, quinolone, naphthalene moieties were applied to the reaction and the desired product were obtained in moderate to good yields. The results were summarized in Table 4.

A tentative mechanism of the reaction is depicted in Scheme 3. The first step involves a simple elimination reaction to form the acetylene bromide followed by a 5-exo intramolecular N-ncleophilic addition as previously reported.[14] The monobromo olefinic compound intermediate **2b** was isolated and its structure was

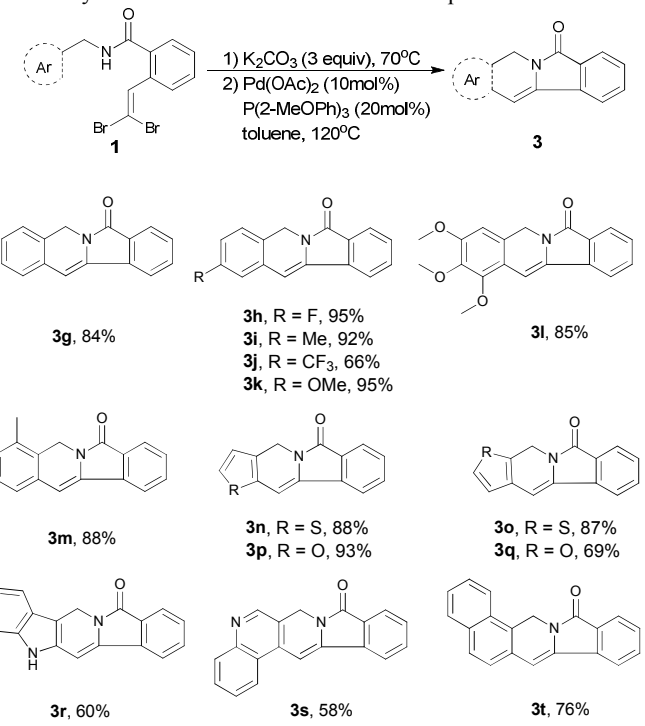
confirmed. This monobromo intermediate undergoes C−Br bond insertion with Pd followed by intramolecular C−H activation and insertion to give the indolidizines.[15]

Table 3. Synthesis of pyridine-fused indolizinone compounds.[a]



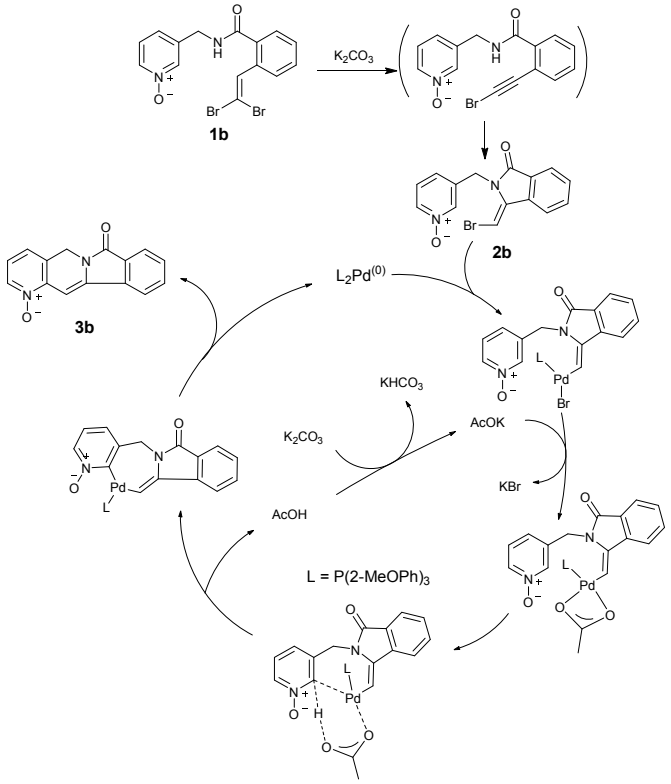
[a] Yield of isolated product.

Table 4. Synthesis of Various Indolizinone Compounds.[a]



[a] Yield of isolated product.

In summary, we have developed an efficient and practical intramolecular N-nucleophilic addition and direct C−H arylation process using *gem*-dibromoolefinsfor the synthesis of uncommon indolizinone scaffold. This reaction process is applicable to various aromatic rings with various substitutions, and a series of novel indolizinone compounds were obtained in good yields. The method provides an entry into the efficient preparations of uncommon indolizinone structures.



Scheme 3. A proposed mechanism for this sequential addition and cross-coupling process.

Typical Experimental Proccess

3-((2-(2,2-dibromovinyl)benzamido)methyl)pyridine *N*1-oxide (**1b,** 100 mg, 0.24 mmol, 1.0 equiv) was dissolved in toluene and K_2CO_3 (100 mg, 0.74 mmol, 3.0 equiv) was added. The mixture was stirred at 70 °C for 5h. Then $Pd(OAc)_2$ (5.4 mg, 0.024 mmol, 10 mol%) and P(2-MeOPh)$_3$ (17 mg, 0.048 mmol, 20 mol%) were added. The reaction mixture was stirred under an argon atmosphere at 120 °C for 12 h. The resulting mixture was concentrated in vacuo and purified by column chromatography on silica gel to give the product **3b** (55 mg, 90 %).

Acknowledgement: The research was supported in part by Foshan municipal funds for scientific and technological innovation projects (2013HK100012), Guangzhou Science and Technology Project (2014J4100222), Chinese NSFC grant (Nos.21402205).

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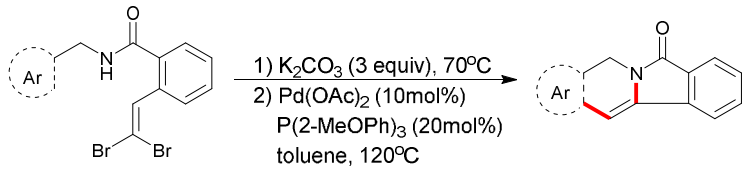

A rare type of indolizinones is constructed from an Intramolecular one-pot process of gem-dibromoolefins.