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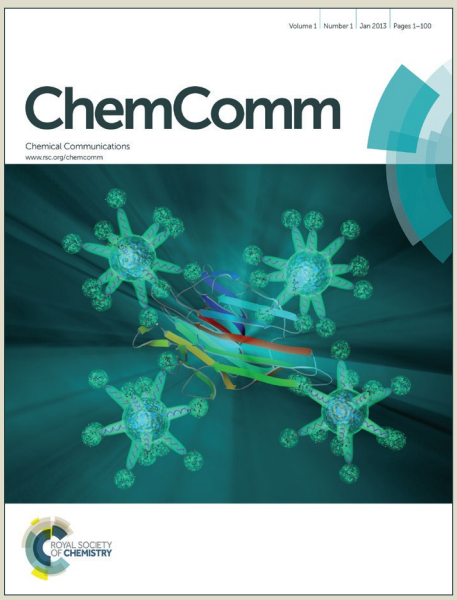

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Base-Promoted Synthesis of Multisubstituted Benzo[b][1,4]oxazepines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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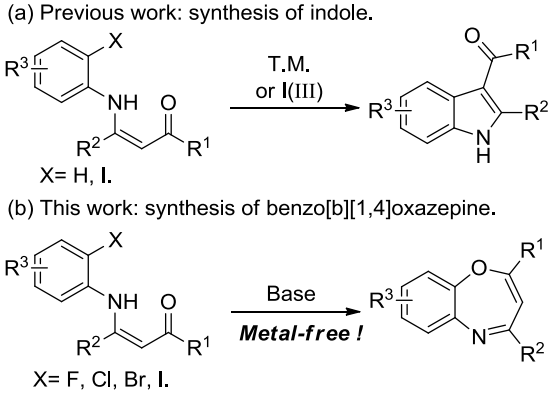
A novel protocol to synthesize multisubstituted benzo[b][1,4]oxazepines from *N*-(2-haloaryl)enaminones has been developed. In this procedure, only 2 equiv of Cs_2CO_3 was required. A variety of polysubstituted benzo[b][1,4]oxazepine derivatives were provided in up to 95% yield for 27 examples.

Fused oxazepine derivatives are receiving continuing attention owing to their promising biological and pharmaceutical activities,[1] including anti-inflammatory,[2] anti-tumor,[3] and anti-psychotic[4] activities. Consequently, exploring efficient methods to build such a structure and its analogues has attracted considerable attention from medicinal and organic chemists.[5] The conventional methods reported in literatures focus on the construction of dibenzoxazepines.[5] Direct synthesis of benzo[b][1,4]oxazepines remains rare. Only in 2012, Jiang group[6] reported a palladium-catalysed tandem reaction of *o*-aminophenols, bromoalkynes and isocyanides to produce 4-amine-benzo[b][1,4]oxazepines in good yields. Therefore, developing an efficient and clean procedure to benzo[b][1,4]oxazepines under mild reaction conditions remains highly desirable.

Recently, enaminone has emerged as a versatile synthetic intermediate for building various N-heterocycles due to the ambident nucleophilicity of enamine and the ambident electrophilicity of enone.[7-8] For instance, a variety of indoles could be synthesized by transition-metal or hypervalent iodine catalysed C-C bond coupling from *N*-aryl enaminones or *N*-(2-haloaryl) enaminones[9] (Scheme 1, a). Among the reported transition-metal catalysed processes, a study by Cacchi and co-workers caught our attentions.[9g] They found that a benzo[b][1,4]oxazepine derivative was formed in 36% yield as a by-product from the corresponding *N*-(2-bromophenyl) enaminone in presence of copper(I) iodide (5 mol%), 1,10-phenathroline (5 mol%), and an excess of potassium carbonate. In this process, an intramolecular Ullmann-type C-O coupling reaction may involve. Very recently, such Ullmann-type C-O coupling reactions have been extensively explored under basic conditions without any transition metals.[10] In 2010, Bolm[10a] and Ramón[10b] firstly reported the base-promoted intermolecular O-arylation of phenols with iodobenzenes for the synthesis of diaryl esters. At the same time, Bolm and coworkers[10a] developed an intramolecular O-arylation of *N*-(2-iodophenyl)benzamides for constructing the benzoxazole skeleton in KOH/DMSO system, which was further developed by the group of Peng and Chen[10c] in the system of K_2CO_3/DMSO. Fu group[10d, 10e] and our group[10g] recently reported the intramolecular O-arylation of 1-(2-haloaryl)-propane-1,3-diones for the synthesis of chromone and 3-allyl-chromone derivatives. Theoretically, the iminoenol tautomer of *N*-(2-haloaryl)enaminones may extensively exist under suitable basic condition,[11] which might be captured by the C-X bond via an intramolecular O-arylation to afford the benzo[b][1,4]oxazepines. In our continuing interest in enaminone chemistry,[12] here we report a novel protocol to substituted benzo[b][1,4]oxazepines from easily accessible *N*-(2-haloaryl)enaminones under mild conditions (Scheme 1, b).



Scheme 1. Enaminone-based synthesis of indole and benzo[b][1,4]oxazepines.

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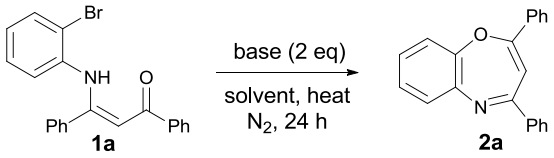
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

To verify this proposal, (*Z*)-3-((2-bromophenyl)amino)-1,3-diphenylprop-2-en-1-one **1a** was initially chosen as a model substrate to screen the reaction conditions. To our delight, the desired benzo[b][1,4]oxazepine **2a** was obtained in 56% yield in K_3PO_4/DMF system (entry 1). Then, other DMF-tailored heterogeneous base systems were next tested. As seen in Table 1, all the base/DMF systems tested could promote the formation of the desired benzo[b][1,4]oxazepine **2a** (entries 1-6), and the combination of Cs_2CO_3/DMF was found to be the most effective (yield of **2a** being 68%, entry 2). The effect of the solvent was subsequently investigated. DMF, DMAc, DMSO, and NMP turned out to be the better solvents with NMP being the best (92%, entry 9). Increasing or decreasing the reaction temperature led to a lower yield (entries 12-13). 2 Equiv of Cs_2CO_3 was crucial for complete conversion. When the loading of Cs_2CO_3 decreased to 1 equiv, the yield of the product was decreased to 75% (entry 14). To avoid the involvement of other metals in the reaction, Cs_2CO_3 (98% purity) was substituted by a sample with a purity of >99.99%, and the reaction provided a similar yield (90%, entry 15), indicating that this factor was irrelevant here. Finally, the standard reaction condition for the base-promoted synthesis of benzoxazepine derivatives was identified as follows: 2 equiv of Cs_2CO_3 as the additive and NMP as the solvent at 120 °C under nitrogen atmosphere.

With the optimized reaction conditions in hand, the generality and substrate scope were next investigated and illustrated in Scheme 2. The effect of the X substituent on the formation of the benzo[b][1,4]oxazepine was firstly investigated. As seen in Scheme 2, the yield of the product was slightly affected when the bromo group was changed to fluoro, chloro, or iodo group. Fluoro- and chloro-substituted substrates gave slightly lower yields (64% and 78%). Bromo- and iodo-substituted substrates performed better and led to **2a** in 91% and 88% yield, respectively. These observations showed that this base-promoted O-arylation reaction might not be a typical nucleophilic substitution reaction where the leaving group ability of the halide commonly showed a clear trend (F> Cl> Br> I).[13] When the halide substituent was replaced with methoxyl-, no desired product was obtained.[10e,10g] Owning to the steric hindrance, the 3-methyl substituted substrate gave a lower yield than the corresponding substrate with 4-methyl (**2b** *vs* **2c**). Other functional groups, including electro-donating and electro-withdrawing groups, were all tolerated and gave the corresponding benzo[b][1,4]oxazepines in 68-79% yields (**2d-2f**).

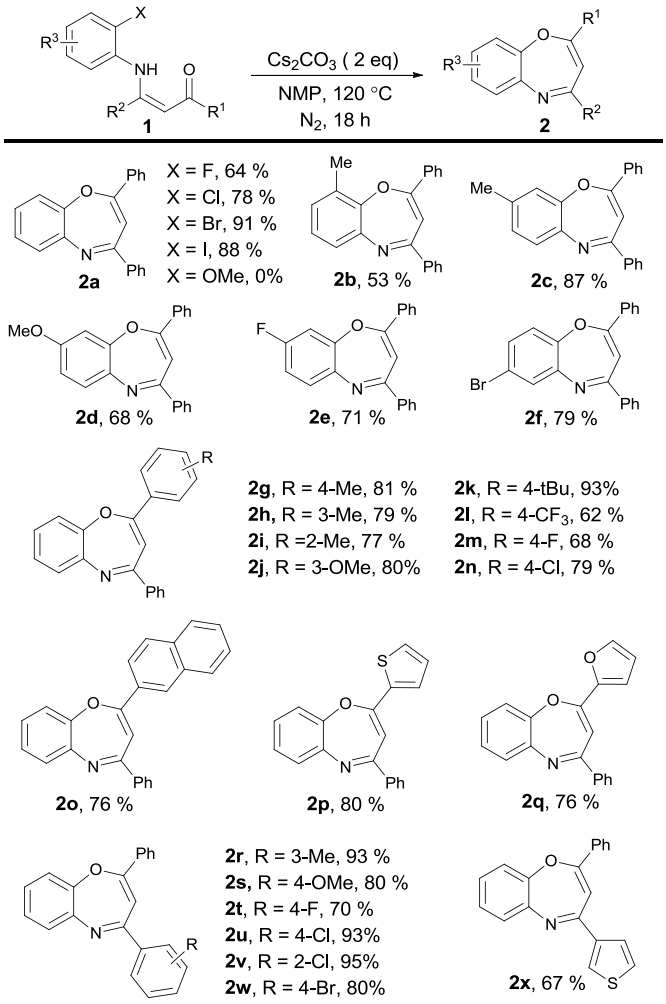
The scope of R^1 and R^2 were also investigated. When R^1 and R^2 were aryl groups, various substituents on R^1 and R^2 were well-tolerated. Substrates with an electrodonating group, such

Table 1. Screening the reaction parameters.[a]

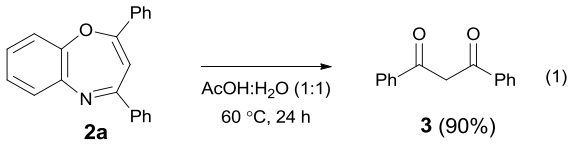


Entry	Base	Solvent	Temp (°C)	Yield (%)[b]
1	K_3PO_4	DMF	120	56
2	Cs_2CO_3	DMF	120	68
3	KOH	DMF	120	43
4	NaOH	DMF	120	24
5	NaOtBu	DMF	120	34
6	KOtBu	DMF	120	66
7	Cs_2CO_3	DMSO	120	55
8	Cs_2CO_3	DMAc	120	72
9	**Cs_2CO_3**	**NMP**	**120**	**92(91)**
10	Cs_2CO_3	CH_3CN	reflux	N.R.
11	Cs_2CO_3	Toluene	120	N.R.
12	Cs_2CO_3	NMP	110	77
13	Cs_2CO_3	NMP	130	81
14[c]	Cs_2CO_3	NMP	120	75
15[d]	Cs_2CO_3	NMP	120	90

[a] Reaction conditions: **1a** (0.2 mmol), and base (0.4 mmol) in solvent (2 mL) at corresponding temperature under N_2 atomsphere. [b] Yields were determined by GC, isolated yield in bracket. [c] 0.2 mmol of base was used. [d] Use highly pure Cs_2CO_3 (>99.99 purity from Alfa Aesar). DMF = N,N-dimethylformamide. DMSO = dimethylsulfoxide. NMP = N-methyl-2-pyrrolidone.



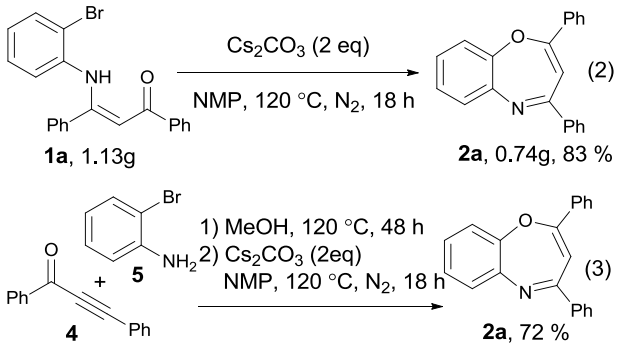
Scheme 2. Substrate scope, for **2b**-**2x**, X = Br.



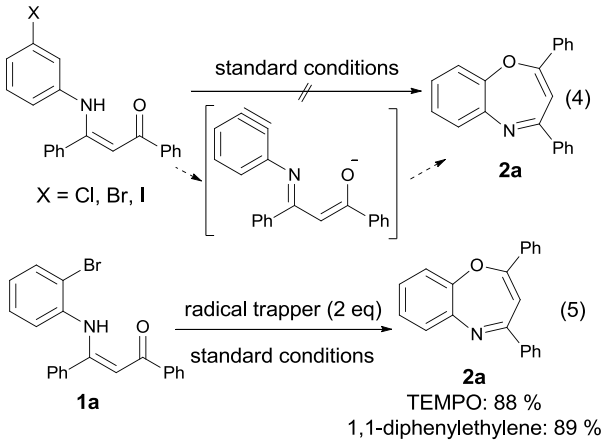
as methyl, methoxy, and *t*-butyl, or withdrawing group (−F and $-CF_3$) on R^1 or R^2 all proceeded efficiently. On the other hand, the steric hindrance on R^1 or R^2 did not influent this reaction obviously. The substrates with *ortho* substituents gave similar yields to the corresponding substrates with *para* substituents (**2i** vs **2g**, **2v** vs **2u**). Halogen, including F, Cl, and Br were totally well-tolerated (**2m-2n** and **2t-2w**, 68-95% yields), which makes this reaction particularly attractive for further transformation by transition metal-catalyzed coupling reactions. The fused aryl and heteroaryl groups, such as naphthyl, thienyl, and furanyl, were also suitable and provided the desired benzo[b][1,4]oxazepines in 67−80% yields. When R^1 or R^2 was an alkyl group, no desired product was obtained, may be because of the low stability of the corresponding products. As depicted in eq 1, when benzo[b][1,4]oxazepine **2a** was treated with water under mild acidic conditions, the hydrolytic product **3** was obtained in 90% yield from the hydrolysis of **2a**.

To prove the practicality of this base-promoted reaction, a gram-scale synthesis of the benzo[b][1,4]oxazepine **2a** was performed. When 1.13g of enaminone **1a** (3 mmol) was loaded, 0.74g of the desire product **2a** was obtained in 83% yield (Scheme 3, eq 2). To further make this reaction more attractive from a synthetic standpoint, we explored an "one-pot" strategy to directly synthesize the benzo[b][1,4]oxazepines from α,β-ynones and 2-*halo* anilines, avoiding the isolation of the enaminone intermediates. By adding NMP and Cs_2CO_3 to the crude mixture derived from the reaction of α,β-ynones **4** with 2-Bromoaniline **5** after evaporation of the volatile materials, benzo[b][1,4]oxazepine **2a** was isolated in a 72% overall yield (Scheme 3, eq 3).

To explore the reaction mechanism, some controlled experiments were carried out. As shown in Scheme 4, for substrates with halo substituents (Cl, Br, I) in the *meta*-position, no desire benzo[b][1,4]oxazepine was obtained, which makes an aryne mechanism[10a-c] unlikely (Scheme 4, eq 4). Combined



Scheme 3. Large-scale and "one-pot" synthesis of benzoxazepine **2a**.

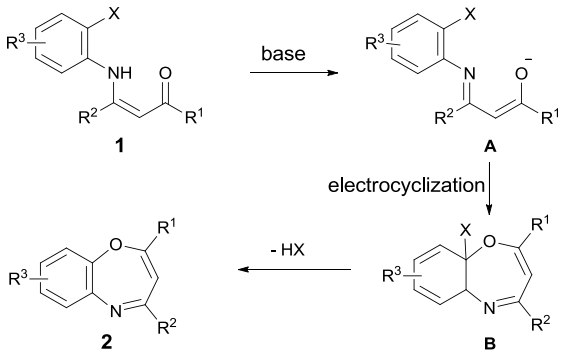


Scheme 4. Controlled experiments.

with the result of **2b** (53% yield, Scheme 2), an aryne involved path to the benzo[b][1,4]oxazepine derivatives could be excluded. On the other hand, the radical scavengers, TEMPO (2,2,6,6-tetramethylpiperidinooxy) and 1,1-diphenylethylene, did not influence this reaction obviously (Scheme 4, eq 5), which indicated that a radical pathway might not be involved in this reaction neither.

Based on the above observations and discussions on base-catalyzed/promoted coupling reaction in previous reports,[10e,10g] a tentative reaction mechanism for the formation of benzo[b][1,4]oxazepines **2** was proposed, as depicted in Scheme 5. The initial deprotonation of *N*-(2-haloaryl)enaminones **1** by Cs_2CO_3/NMP system generates the iminoenolate intermediates **A**. Then, an intramolecular electrocyclization of **A** gives intermediates **B**, and rearomatization of **B** by the elimination of HX provides the final benzo[b][1,4]oxazepine products **2**.

In conclusion, we have developed a simple and efficient methodology for the preparation of substituted benzo[b][1,4]oxazepines from readily available starting materials. The reaction was successful with a variety of *N*-(2-haloaryl)enaminones and smoothly converted to the desired benzo[b][1,4]oxazepine products in good to excellent yields. The intramolecular cyclization was promoted by the Cs_2CO_3/NMP system in absence of any transition metal and ligand. Benzo[b][1,4]oxazepine derivatives as effective pharmaceutical compounds with various biological activities



Scheme 5. Plausible reaction mechanism.

may be prepared by this method without the concern of potential metal contamination of the products.

This research was supported by NSF of China (21202048), Xiamen science and technology bureau (3502Z20150054), Xiamen Southern Oceanographic Center (15PYY052SF01), and Huaqiao University.

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