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An efficient synthesis of novel dibenzoxdiazepine-fused heterocycles through a multicomponent reaction†

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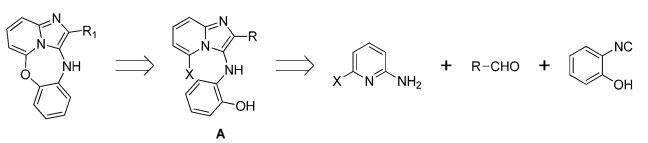
A one-pot synthesis of 6-oxa-2,2a[1],11-triazadibenzo[*cd*,*g*]azulenes by a three-component reaction of a 2-aminoheterocycle, aldehydes, and 2-isocyanophenyl acetate is presented. This efficient and green protocol has the advantages of environmental friendliness, high yields and operational simplicity. The atropisomeric properties of this unique structure were examined by ^{1}H NMR spectroscopy and X-ray structural analyses, and the barriers to their interconversion were clarified.

Polycyclic heterocycles are frequently found in natural products and pharmaceutical agents. Among them, functionalized dibenzoxazepines are a very important class of seven-membered rings and such structural units could widely exist in numerous medicinal heterocyclic molecules with promising biological and pharmaceutical activities.[1] These biological characteristics have stimulated organic researchers to explore synthetic methods for dibenzoxazepines and their structural analogues.[2] Recently, isocyanide-based multicomponent reactions (IMCR) followed by other synthetic transformations have emerged as a powerful tool for creating fused multicyclic skeletons. As a part of our program[3] to discover novel heterocycles as antitumor agents based on imidazo[1,2-*a*]pyridine ring system, which may be regarded as a privileged structure.[4] Following this strategy, our next challenge was the introduction of an additional benzoxdiazepine ring in the imidazo[1,2-*a*]pyridine framework to form the 6-oxa-2,2a,[1] 11-triazadibenzo[*cd*,*g*]azulene as shown in Scheme 1. We envisaged that this scaffold might be synthesized from halogen intermediate A, which itself could be prepared from 6-bromopyridin-2-amine, an aldehyde and 2-isocyanophenol *via* a Groebke–Blackburn–Bienaymé (GBB) reaction,[5] followed by *in situ* intramolecular cyclization to afford this polycyclic heterocycle (Scheme 1). To the best of our knowledge, this series of compounds has never been reported.

To test the hypothesis, we commenced the investigation with 6-bromopyridin-2-amine **1a** (0.2 mmol), benzaldehyde **2a** (0.2 mmol) and 2-isocyanophenyl acetate **3** (0.2 mmol)[6] as model substrates. The desired GBB condensation intermediate **4a** was afforded in 91% yield using catalyst-free and solvent-free conditions, which was recently developed by Sharada *et al.*[7] Subsequently, substrate **4a** was used for the optimization of the cyclization reaction conditions, including different catalysts and various solvents, and the results are summarized in Table 1. No reaction occurred in the absence of base (entry 1, Table 1). We envisaged that the acetyl group might be removed under basic condition. Various bases (entries 2–6, Table 1) were used in the intramolecular cyclization, however, we found that the acetyl group was easily transferred to the adjacent nitrogen to form the acetylamide **5a**. No deacetylated product **5a′** was observed in the reaction process. To our delight, the isolated yield of **5a** was enhanced further to 83% when the potassium carbonate was used as the base (entry 3, Table 1). Using weaker bases, such as sodium carbonate (entry 2, Table 1), sodium bicarbonate (entry 4, Table 1), potassium acetate (entry 5, Table 1), or stronger bases, such as sodium hydroxide (entry 6, Table 1) afford the product in lower yields compare to potassium carbonate. Moreover, no obvious improvement in the yield was observed when the solvent was switched to isopropanol and DMF (entries 7 and 8, Table 1). Next, typical Ullmann and Buchwald–Hartwig cross coupling reaction conditions were used and no significant improvement in the yield (entries 9 and



Scheme 1 Retro-synthetic approach for substituted 6-oxa-2,2a,[1] 11-triazadibenzo[*cd*,*g*]azulene.

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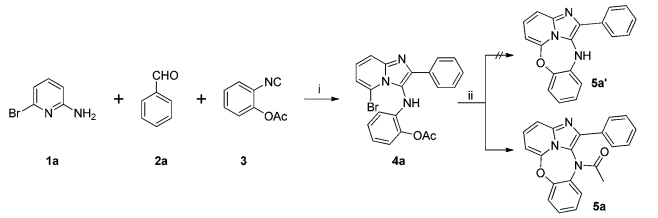
† Electronic supplementary information (ESI) available: General experimental procedures, compound characterization data, ^{1}H and ^{13}C NMR spectra of new compounds. CCDC [1007733, 1007734]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra09196e

Table 1 Optimization of reaction conditions[a]



Entry	Base	Additive	Solvent	Yield[b] (%)
1	None	None	Dioxane : H_2O(4 : 1)	0
2	Na_2CO_3	None	Dioxane : H_2O(4 : 1)	63
3	K_2CO_3	None	Dioxane : H_2O(4 : 1)	83
4	$NaHCO_3$	None	Dioxane : H_2O(4 : 1)	31
5	KOAc	None	Dioxane : H_2O(4 : 1)	40
6	NaOH	None	Dioxane : H_2O(4 : 1)	15
7	K_2CO_3	None	Isopropanol, reflux	70
8	K_2CO_3	None	DMF	78
9	K_2CO_3	CuI/TMEDA	Dioxane : H_2O(4 : 1)	70
10	K_2CO_3	$Pd(OAc)_2$/XPhos	Toluene	62

10, Table 1). The structure of **5a** was unambiguously established by X-ray crystallographic analysis (Fig. 1).

On the basis of the results obtained above, a plausible mechanism of this reaction is illustrated in Scheme 2. First, the reaction is expected to proceed *via* the *in situ* formation of A. The next step involves aminolysis of acetylphenol to form intermediate C. Finally, after intramolecular cyclization of C to afford the final product D.

With the optimal conditions established, we then investigated the scope of this method. The simplicity of a one-pot procedure is perfectly amenable to automation for combinatorial synthesis. Likewise, all the syntheses were performed on a parallel synthesizer (Radleys Discovery Technology, Carousel 12 Place Reaction Station) to give corresponding products **5a–t** (Table 2). First, we examined the reactions of various aldehydes **2a–q** with 6-bromopyridin-2-amine (**1a**) and 2-isocyanophenyl acetate (**3**), which proceeded smoothly and efficiently to

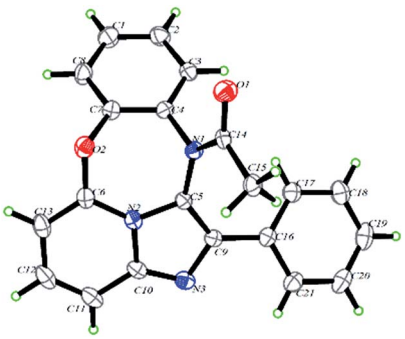
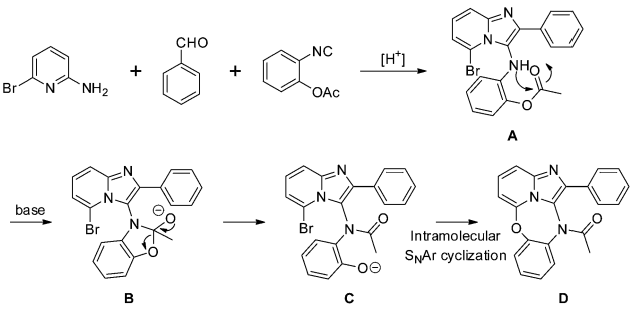


Fig. 1 X-ray structure of compound **5a**.[8]

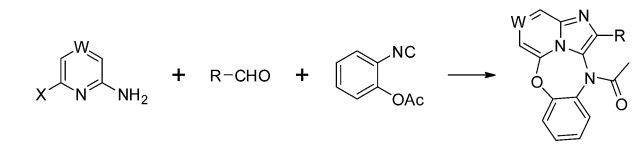


Scheme 2 The possible reaction mechanism.

produce the corresponding products (**5a–q**) in yields ranging from 36 to 65%. Moreover, we were pleased to find that the pyridine core could be successfully extended to pyrazine. For example, 6-chloropyrazin-2-amine (**1b**) smoothly reacted with benzaldehydes (**2a–c**) and 2-isocyanophenyl acetate (**3**) to give the expected product **5r–t** in around 42% yields (Table 2, entries 18–20).

While measuring the ^{1}H-NMR, we observed that compounds bearing the EWG substituted phenyl ring as the R substitution showed more complicated NMR signals compare to the EDG

Table 2 Scope of the one-pot reaction[a]



Entry	Cpds	R	Yield[b] (%)
1	**5a**	Ph (**2a**)	55%
2	**5b**	4-MeO-Ph (**2b**)	58%
3	**5c**	4-CF_3-Ph (**2c**)	62%
4	**5d**	4-Me-Ph (**2d**)	56%
5	**5e**	4-CN-Ph (**2e**)	65%
6	**5f**	4-Br-Ph (**2f**)	65%
7	**5g**	4-[1,1′-biphenyl] (**2g**)	51%
8	**5h**	2-Br-Ph (**2h**)	50%
9	**5i**	2-MeO-Ph (**2i**)	49%
10	**5j**	3,5-Difluor-Ph (**2j**)	49%
11	**5k**	2-Pyrrole (**2k**)	50%
12	**5l**	2-Thiophene (**2l**)	52%
13	**5m**	2-Furan (**2m**)	48%
14	**5n**	2-Pyridine (**2n**)	36%
15	**5o**	3-Pyridine (**2o**)	40%
16	**5p**	Cyclohexane (**2p**)	36%
17	**5q**	*n*-Propyl (**2q**)	56%
18	**5r**	Ph (**2a**)	40%
19	**5s**	4-MeO-Ph (**2b**)	44%
20	**5t**	4-CF_3-Ph (**2c**)	42%

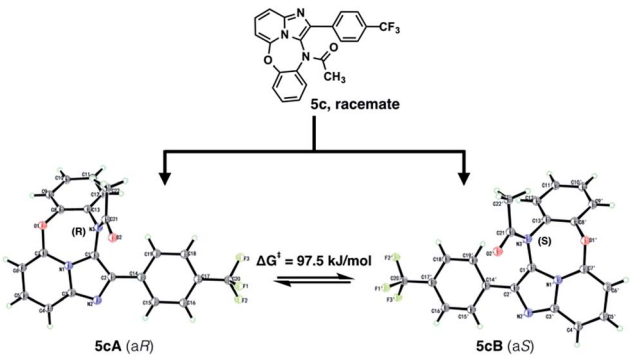


Fig. 2 X-ray analysis of atropisomer **5c**.

substituted compounds. We assumed this effect might be due to the atropisomer effect, which is very common for amide type of compound due to the pyramidal inversion. A variable-temperature 400 MHz ^{1}H NMR spectra in d^6-DMSO study of **5c** was carried out in order to verify the co-existence of two conformers (see ESI†). The acetyl dibenzoxdiazepine thus obtained were expected to exist as racemates of the atropisomers due to the axial chirality at aryl-N(C=O).[9] On the basis of its X-ray analysis, **5cA** was assigned to be (a*R*), and hence, **5cB** to be (a*S*) (Fig. 2).[7] We managed to obtain each enantiomer of **5c** using preparative chiral HPLC, however, racemization occurred immediately after separation, in the end we could only obtain each enantiomers at about 50% ee. We examined the stereochemical stability of the enantiomers (**5cA** and **5cB**) and found that it was estimated to be low: racemization occurred after storage for 2 h at 25 °C in EtOH. The activation free-energy barrier to rotation ($\Delta G^{\ddagger}$) was measured and calculated to be 97.5 kJ mol^{-1} (see ESI†).[10]

In summary, we have developed a clean and efficient method for the sequential synthesis of new functionalized 6-oxa-2,2a,[1] 11-triazadibenzo[*cd*,*g*]azulene derivatives, which were characterized by means of ^{1}H NMR, ^{13}C NMR, HRMS and X-ray. Easily available starting materials, metal catalyst-free conditions and good yields are the main advantages of this method. We hope that these stereochemical findings in acetyl dibenzoxazepine will assist in future drug design in which heterocyclic systems are utilized as the core structure for biologically active molecules.

Acknowledgements

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