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# Three-component reaction of azulene, aryl glyoxal and 1,3-dicarbonyl compound for the synthesis of various azulene derivatives†

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A three-component reaction of an azulene, an aryl glyoxal and a 1,3-dicarbonyl compound has been elaborated to access a series of azulene derivatives. Some of these azulene-containing adducts were further subjected to post-MCR transformations to assemble azulene–heterocycle conjugates.



## Introduction

Azulene is a bicyclic aromatic hydrocarbon with a deep blue colour and a dipole moment of about 1.08 D.[1] Such properties are in striking contrast with those of the isomeric naphthalene that is colourless and has a dipole moment of 0 D. The polarity of azulene and in turn the appearance of the blue colour can be explained by the charge-separated resonance structure in which the bicyclic core of azulene is regarded as a fusion of 6 π-electron cyclopentadienyl anion and 6 π-electron tropylium cation.

Owing to the unique structural and photophysical properties of the azulene core, a number of azulene-based advanced organic materials[2] has been developed targeting the applications in sensors,[3] bioimaging,[4] non-linear optics (NLO),[5] optoelectronics,[6] molecular electronics[7] and so on. Furthermore, azulene derivatives have been successfully incorporated in solar cells[8] and organic field-effect transistors (OFETs)[8c,d,9] demonstrating high potential for further exploration in this type of devices.

Consequently, this sparked a growing interest in the development of novel synthetic methodologies for azulene construction[10] and functionalization[11] with a special emphasis being given to the assembly of azulene-fused heterocycles,[12] azulene–heterocycle conjugates[13] and azulene-containing polymers.[8a,c,d,14]

Several recent methodologies for azulene functionalization involve one-pot and/or multicomponent approaches.[15] On the other hand, in recent years, a number of multicomponent transformations have been developed based on the ability of aryl glyoxals to react with 1,3-dicarbonyl compounds and additional nucleophiles resulting in the formation of structurally diverse (heterocyclic) adducts.[16] We decided to take an advantage of this strategy towards the synthesis of azulene derivatives through exploration of the nucleophilic potential of the five-membered ring of azulene core.

## Results and discussion

Knowing that the treatment of an aryl glyoxal **2** with a 1,3-dicarbonyl compound **3** results in the Knoevenagel condensation,[16] we envisaged that the presence of an azulene **1** would trigger the Michael addition of **1** onto the Knoevenagel adduct **A**. A subsequent proton transfer in the intermediate **B** would produce the desired azulene derivative **4** (Scheme 1). After conducting a brief screening of the reaction conditions (see ESI†), we were pleased to find that such a three-component transformation could be successfully accomplished at the elevated temperature of 80 °C using isopropanol as a solvent.

The scope of the resulting process is outlined in Scheme 1. In order to evaluate the reactivity of a 1,3-dicarbonyl component **3**, several barbituric acid derivatives and cyclic 1,3-diketones were reacted with unsubstituted azulene and phenyl glyoxal monohydrate resulting in the formation of products **4a–f** with the yields ranging from 37% to 91%. Interestingly, according to

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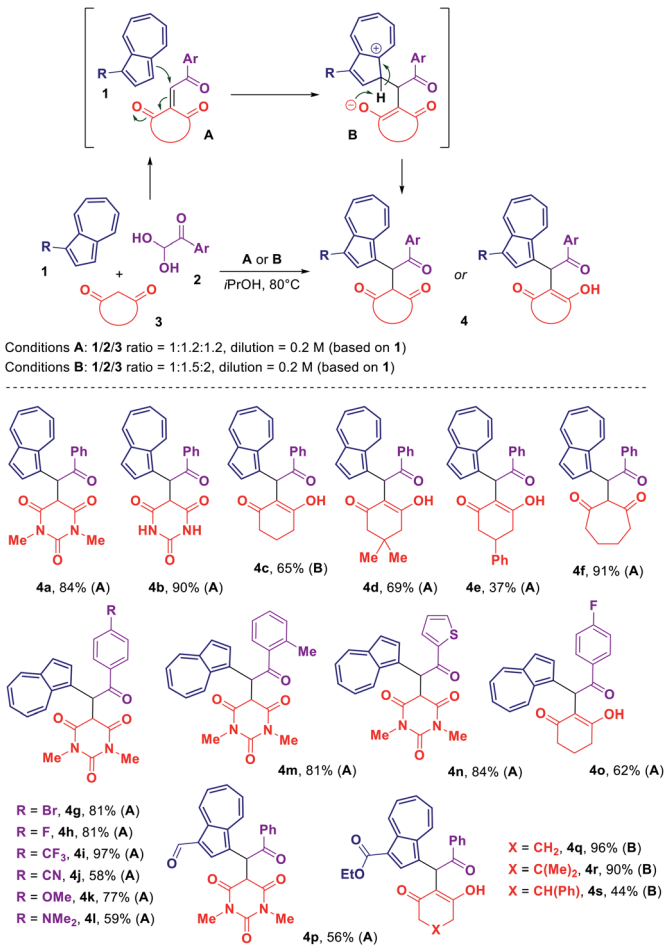
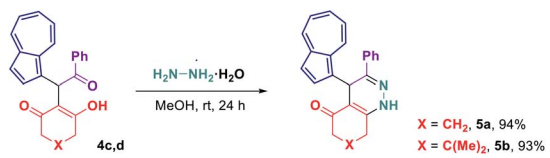



Scheme 1 Scope of the three-component reaction of azulene **1**, aryl glyoxal monohydrate **2** and 1,3-dicarbonyl compound **3**.



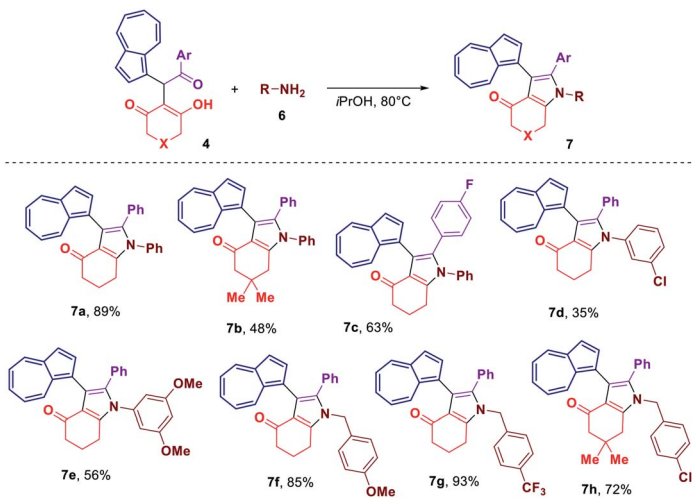

Scheme 2 Synthesis of azulene–tetrahydrocinnolin-5-one conjugates **5**.

NMR analysis, products **4a, b, f** derived from either barbituric acids or cycloheptane-1,3-dione were observed in a keto form in solution ($CDCl_3$ for **4a** and **4f**, $[D_6]$DMSO for **4b**). In contrast, products **4c–e** obtained using various cyclohexane-1,3-diones were observed in a enolized form, with the compound **4e** existing as a mixture of two interconvertible diastereomeric enol forms.

With respect to an aryl glyoxal component **2**, a number of variously substituted phenyl glyoxal monohydrates along with a heteroaromatic thiophen-2-yl glyoxal monohydrate have been tested allowing to acquire an array of azulene-containing adducts **4g–o** (Scheme 1). It was found that the presence of either electron-withdrawing or electron-donating substituent in the phenyl ring of glyoxal could be well tolerated.

Blocking one of the azulene's reactive positions with an electron-withdrawing group did not shut down the reactivity of the azulene core towards our transformation. Thus, we were able to prepare a series of 1,3-disubstituted azulene derivatives **4p–s** starting from either azulene-1-carbaldehyde or ethyl azulene-1-carboxylate.

Considering that some of the obtained azulene derivatives, such as for example **4c** and **4d** comprised a 1,4-diketo unit, we decided to probe their reactivity in the condensations with nitrogen nucleophiles towards the formation of azulene–heterocycle conjugates. To our delight, reacting **4c** and **4d** with hydrazine monohydrate in methanol at rt produced azulene–tetrahydrocinnoline conjugates **5a** and **5b** in high yields of 94% and 93%, respectively (Scheme 2). Encouraged by these results, we went on exploring the potential of our 1,4-diketones in a Paal–Knorr synthesis of pyrroles.[17] Gratifyingly, the treatment of **4c**, **4d** and **4o** with aniline in isopropanol at 80 °C allowed to prepare azulene–dihydroindol-4-one conjugates **7a–c** in moderate to good yields (Scheme 3). The molecular structure of representative azulene–dihydroindol-4-one derivative **7b** has been resolved through the X-ray crystallographic analysis (Fig. 1, see ESI† for details). The above synthetic strategy was also found to be amenable to a variation of an amine component **6**. Examining different aromatic and




Scheme 3 Synthesis of azulene–dihydroindol-4-one conjugates **7**.

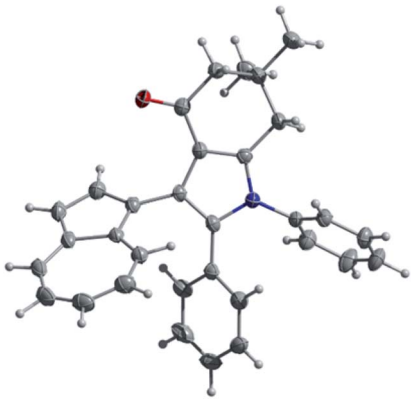
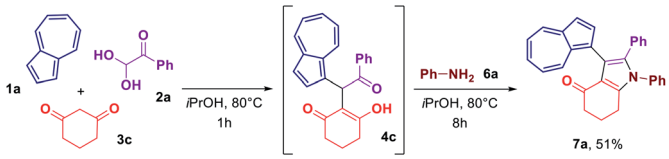


Fig. 1 Molecular structure of **7b**, showing thermal displacement ellipsoids at the 50% probability level. The dimethyl formamide (DMF) molecule acquired during the crystallization process and present in the crystal packing is not shown.

benzylic amines in the reactions with **4c** or **4d** delivered expected azulene-substituted dihydroindol-4-ones **7c–h** in up to 93% yield (Scheme 3).




Scheme 4 One-pot synthesis of azulene–dihydroindol-4-one conjugate **7a**.

In an attempt to streamline the access towards azulene–heterocycle conjugates, we have conducted a one-pot synthesis of compounds **7a** (Scheme 4). Reacting azulene (**1a**), phenyl glyoxal monohydrate (**2a**) and cyclohexane-1,3-dione (**3c**) in isopropanol at 80 °C for 1 h lead to the formation of acyclic adduct **4c**. Once the formation of **4c** was confirmed by the TLC analysis, the aniline (**6a**) was added and the reaction was continued for another 8 h allowing to obtain the desired azulene-substituted dihydroindol-4-one **7a** in 51% overall yield.

The optical properties of all acquired azulene derivatives **4**, **5** and **7** have been assessed by measuring their UV/Vis absorption

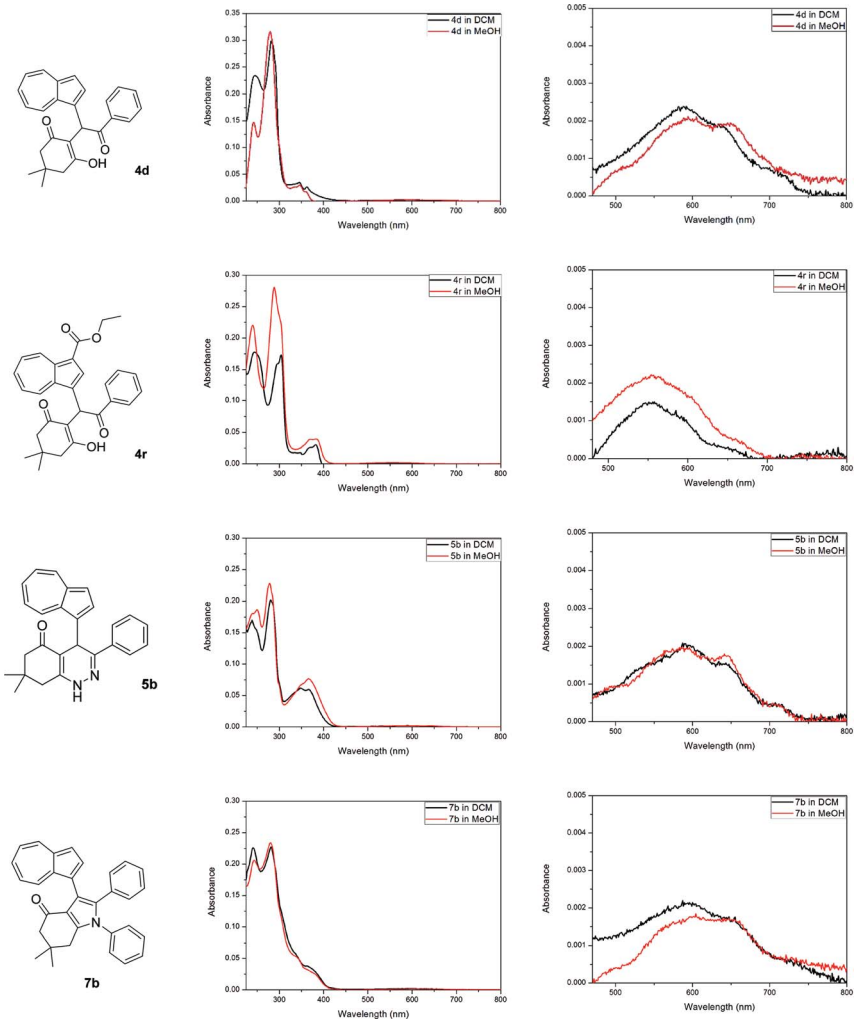



Fig. 2 UV/Vis absorption spectra of **4d**, **4r**, **5b** and **7b** measured in dichloromethane and in methanol (both at $c \cong 5 \times 10^{-6}$ M, left column); magnified visible region of UV/Vis absorption spectra of **4d**, **4r**, **5b** and **7b** (right column).

in dichloromethane and in methanol (both at $c \cong 5 \times 10^{-6}$ M, see ESI†).‡ The UV/Vis absorption spectra of representative azulene-containing products **4d**, **4r**, **5b** and **7b** are shown in Fig. 2. Similarly to most of simple azulene derivatives, all prepared compounds **4**, **5** and **7** were characterized by a strong absorbance in the UV region and a relatively weak absorbance in the visible region, with the latter being responsible for the colouration of their solutions.

## Conclusions

In conclusion, we have developed a novel multicomponent protocol for the azulene derivatization through the reaction with an aryl glyoxal and a 1,3-dicarbonyl compound. The scope of the process has been briefly explored resulting in generation of a small set of branched azulene-containing adducts. Some of these adducts could be further upgraded into azulene–heterocycle conjugates through the post-MCR condensations with nitrogen nucleophiles. Collectively, these methodologies provide a straightforward access to three distinct types of azulene derivatives.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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