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## Introduction

Azulene is a bicyclic aromatic hydrocarbon with a deep blue colour and a dipole moment of about 1.08 D.<sup>1</sup> 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  $\pi$ -electron cyclopentadienyl anion and 6  $\pi$ -electron tropylum cation.

Owing to the unique structural and photophysical properties of the azulene core, a number of azulene-based advanced organic materials<sup>2</sup> has been developed targeting the applications in sensors,<sup>3</sup> bioimaging,<sup>4</sup> non-linear optics (NLO),<sup>5</sup> optoelectronics,<sup>6</sup> molecular electronics<sup>7</sup> and so on. Furthermore, azulene derivatives have been successfully incorporated in solar cells<sup>8</sup> and organic field-effect transistors (OFETs)<sup>8c,d,9</sup> 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<sup>10</sup> and functionalization<sup>11</sup> with a special emphasis being given to the assembly of azulene-fused heterocycles,<sup>12</sup> azulene-heterocycle conjugates<sup>13</sup> and azulene-containing polymers.<sup>8a,c,d,14</sup>

Several recent methodologies for azulene functionalization involve one-pot and/or multicomponent approaches.<sup>15</sup> 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.<sup>16</sup> 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,<sup>16</sup> 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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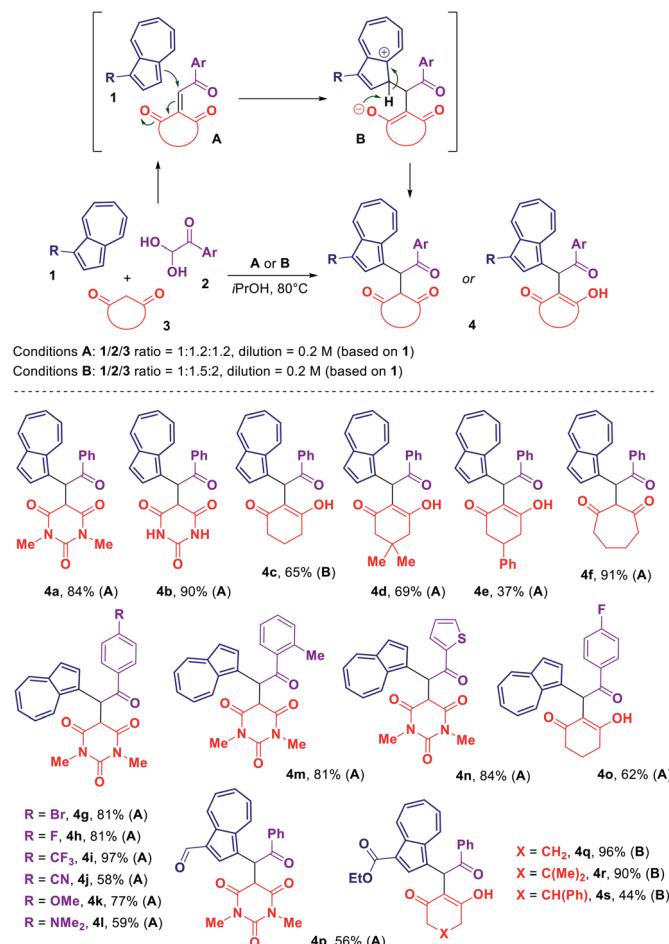
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† Electronic supplementary information (ESI) available: Detailed experimental procedures, products characterization, X-ray crystallographic data and copies of UV/vis absorption and NMR spectra. CCDC 1974555. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra00356e

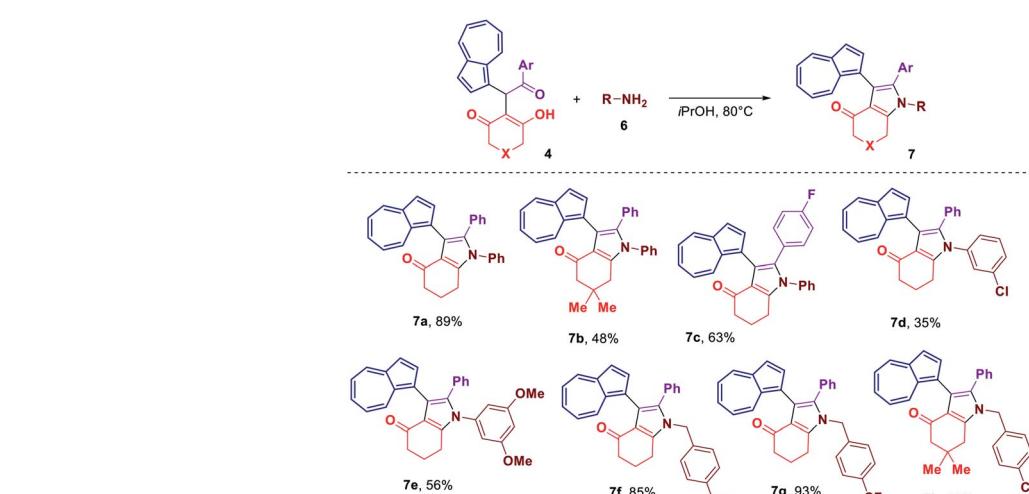




Scheme 1 Scope of the three-component reaction of azulene 1, aryl glyoxal monohydrate 2 and 1,3-dicarbonyl compound 3.



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



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

NMR analysis, products **4a, b, f** derived from either barbituric acids or cycloheptane-1,3-dione were observed in a keto form in solution ( $\text{CDCl}_3$  for **4a** and **4f**,  $[\text{D}_6]\text{DMSO}$  for **4b**). In contrast, products **4c-e** obtained using various cyclohexane-1,3-diones were observed in an 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-tetrahydrocinnolin 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.<sup>17</sup> 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



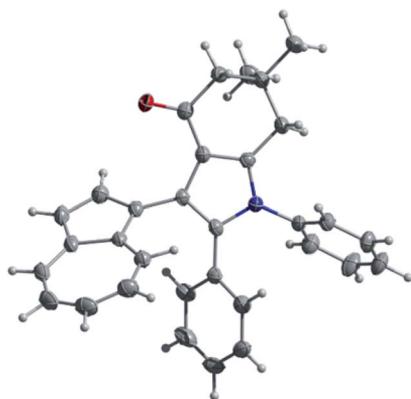
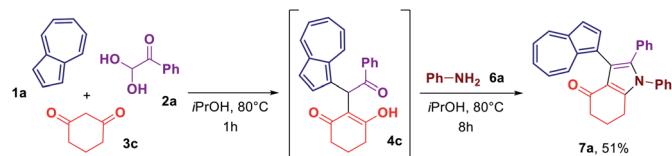


Fig. 1 Molecular structure of **7b**, showing thermal displacement ellipsoids at the 50% probability level. The dimethyl formamide (DMF) molecule acquired during the crystallization process and present in the crystal packing is not shown.

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

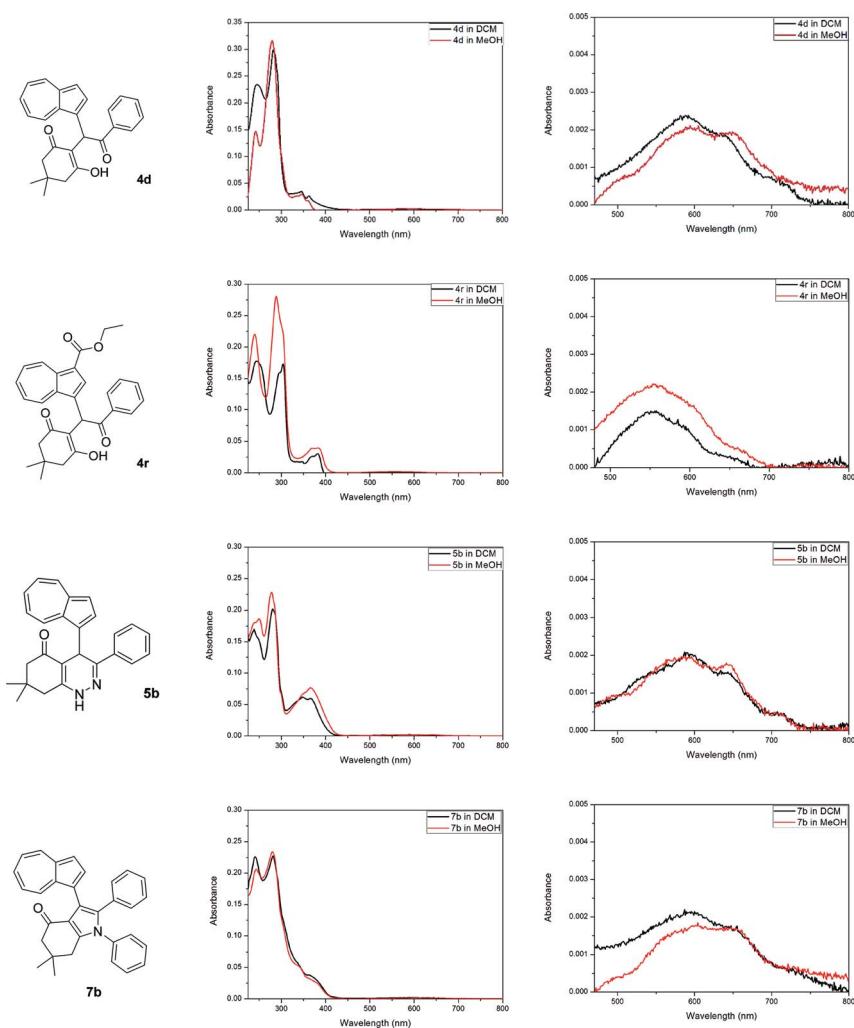


Fig. 2 UV/Vis absorption spectra of **4d**, **4r**, **5b** and **7b** measured in dichloromethane and in methanol (both at  $c \approx 5 \times 10^{-6}$  M, left column); magnified visible region of UV/Vis absorption spectra of **4d**, **4r**, **5b** and **7b** (right column).



in dichloromethane and in methanol (both at  $c \approx 5 \times 10^{-6}$  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.

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## Notes and references

- (a) D. M. Lemal and G. D. Goldman, *J. Chem. Educ.*, 1988, **65**, 923; (b) A. G. Anderson Jr and B. M. Steckler, *J. Am. Chem. Soc.*, 1959, **81**, 4941.
- (a) A. E. Ion, A. Dogaru, S. Shova, A. M. Madalan, O. Akintola, S. Ionescu, M. Voicescu, S. Nica, A. Buchholz, W. Plass and M. Andruh, *CrystEngComm*, 2018, **20**, 4463; (b) F. Wang, T. T. Lin, C. He, H. Chi, T. Tang and Y.-H. Lai, *J. Mater. Chem.*, 2012, **22**, 10448; (c) K. Kurotobi, K. S. Kim, S. B. Noh, D. Kim and A. Osuka, *Angew. Chem., Int. Ed.*, 2006, **45**, 3944.
- (a) T. Tang, T. Lin, F. Erden, F. Wang and C. He, *J. Mater. Chem. C*, 2018, **6**, 5153; (b) E. H. Ghazvini Zadeh, A. W. Woodward, D. Richardson, M. V. Bondar and K. D. Belfield, *Eur. J. Org. Chem.*, 2015, 2271; (c) E. Amir, R. J. Amir, L. M. Campos and C. J. Hawker, *J. Am. Chem. Soc.*, 2011, **133**, 10046; (d) H. Salman, Y. Abraham, S. Tal, S. Meltzman, M. Kapon, N. Tessler, S. Speiser and Y. Eichen, *Eur. J. Org. Chem.*, 2005, 2207.
- (a) P. M. Gosavi, Y. S. Moroz and I. V. Korendovych, *Chem. Commun.*, 2015, **51**, 5347; (b) Y. S. Moroz, W. Binder, P. Nygren, G. A. Caputod and I. V. Korendovych, *Chem. Commun.*, 2013, **49**, 490; (c) W. Pham, R. Weissleder and C.-H. Tung, *Angew. Chem., Int. Ed.*, 2002, **41**, 3659; (d) L. C. Murfin, M. Weber, S. J. Park, W. T. Kim, C. M. Lopez-Alled, C. L. McMullin, F. Pradaux-Caggiano, C. L. Lyall, G. Kociok-Köhn, J. Wenk, S. D. Bull, J. Yoon, H. M. Kim, T. D. James and S. E. Lewis, *J. Am. Chem. Soc.*, 2019, **141**, 19389.
- (a) L. Cristian, I. Sasaki, P. G. Lacroix, B. Donnadieu, I. Asselberghs, K. Clays and A. C. Razus, *Chem. Mater.*, 2004, **16**, 3543; (b) P. G. Lacroix, I. Malfant, G. Iftime, A. C. Razus, K. Nakatani and J. A. Delaire, *Chem.-Eur. J.*, 2000, **6**, 2599.
- (a) T. Shoji, K. Miura, T. Araki, A. Maruyama, A. Ohta, R. Sekiguchi, S. Ito and T. Okujima, *J. Org. Chem.*, 2018, **83**, 6690; (b) T. Shoji and S. Ito, *Chem.-Eur. J.*, 2017, **23**, 16696; (c) H. Xin and X. Gao, *ChemPlusChem*, 2017, **82**, 945; (d) J.-X. Dong and H.-L. Zhang, *Chin. Chem. Lett.*, 2016, **27**, 1097.
- (a) G. Yang, S. Sangtarash, Z. Liu, X. Li, H. Sadeghi, Z. Tan, R. Li, J. Zheng, X. Dong, J. Liu, Y. Yang, J. Shi, Z. Xiao, G. Zhang, C. Lambert, W. Hong and D. Zhang, *Chem. Sci.*, 2017, **8**, 7505; (b) F. Schwarz, M. Koch, G. Kastlunger, H. Berke, R. Stadler, K. Venkatesan and E. Lörtscher, *Angew. Chem., Int. Ed.*, 2016, **55**, 11781.
- (a) E. Puodziukynaite, H.-W. Wang, J. Lawrence, A. J. Wise, T. P. Russell, M. D. Barnes and T. Emrick, *J. Am. Chem. Soc.*, 2014, **136**, 11043; (b) H. Nishimura, N. Ishida, A. Shimazaki, A. Wakamiya, A. Saeki, L. T. Scott and Y. Murata, *J. Am. Chem. Soc.*, 2015, **137**, 15656; (c) J. Yao, Z. Cai, Z. Liu, C. Yu, H. Luo, Y. Yang, S. Yang, G. Zhang and D. Zhang, *Macromolecules*, 2015, **48**, 2039; (d) H. Xin, C. Ge, X. Jiao, X. Yang, K. Rundel, C. R. McNeill and X. Gao, *Angew. Chem., Int. Ed.*, 2018, **57**, 1322.
- (a) E. C. P. Smits, S. Setayesh, T. D. Anthopoulos, M. Buechel, W. Nijssen, R. Coehoorn, P. W. M. Blom, B. de Boer and D. M. de Leeuw, *Adv. Mater.*, 2007, **19**, 734; (b) P. H. Wöbkenberg, J. G. Labram, J.-M. Swiecicki, K. Parkhomenko, D. Sredojevic, J.-P. Gisselbrecht, D. M. de Leeuw, D. D. C. Bradley, J.-P. Djukic and T. D. Anthopoulos, *J. Mater. Chem.*, 2010, **20**, 3673; (c) Y. Yamaguchi, Y. Maruya, H. Katagiri, K.-i. Nakayama and Y. Ohba, *Org. Lett.*, 2012, **14**, 2316; (d) Y. Yamaguchi, K. Ogawa, K.-i. Nakayama, Y. Ohba and H. Katagiri, *J. Am. Chem. Soc.*, 2013, **135**, 19095; (e) Y. Yamaguchi, M. Takubo, K. Ogawa, K.-i. Nakayama, T. Koganezawa and H. Katagiri, *J. Am. Chem. Soc.*, 2016, **138**, 11335; (f) H. Xin, C. Ge, L. Fu, X. Yang and X. Gao, *Chin. J. Org. Chem.*, 2017, **37**, 711; (g) H. Xin, C. Ge, X. Yang, H. Gao, X. Yang and X. Gao, *Chem. Sci.*, 2016, **7**, 6701–6705; (h) H. Xin, J. Li, C. Ge, X. Yang, T. Xue and X. Gao, *Mater. Chem. Front.*, 2018, **2**, 975.
- (a) D. D. Nolting, M. Nickels, R. Price, J. C. Gore and W. Pham, *Nat. Protoc.*, 2009, **4**, 1113; (b) N. R. Kumar,

‡ UV/Vis absorption of **7b** was measured only in methanol due to poor solubility in dichloromethane.



A. R. Agrawal and S. S. Zade, *Chem.-Eur. J.*, 2019, **25**, 14064; (c) H. Langhals and M. Eberspächer, *Synthesis*, 2018, **50**, 1862; (d) V. Claus, M. Schukin, S. Harrer, M. Rudolph, F. Rominger, A. M. Asiri, J. Xie and A. S. K. Hashmi, *Angew. Chem., Int. Ed.*, 2018, **57**, 12966.

11 (a) M. Fujinaga, K. Suetake, K. Gyoji, T. Murafuji, K. Kurotobi and Y. Sugihara, *Synthesis*, 2008, 3745; (b) J. Dubovik and A. Bredihhin, *Synthesis*, 2015, **47**, 538; (c) A. Székely, Á. Péter, K. Aradi, G. L. Tolnai and Z. Novák, *Org. Lett.*, 2017, **19**, 954; (d) T. Shoji, T. Araki, N. Iida, Y. Kobayashi, A. Ohta, R. Sekiguchi, S. Ito, S. Mori, T. Okujima and M. Yasunami, *Eur. J. Org. Chem.*, 2018, 1145; (e) X. Shi, A. Sasimal, J.-F. Soulé and H. Doucet, *Chem.-Asian J.*, 2018, **13**, 143.

12 (a) C. Kogawa, A. Fujiwara, R. Sekiguchi, T. Shoji, J. Kawakami, M. Okazaki and S. Ito, *Tetrahedron*, 2018, **74**, 7018; (b) T. Shoji, T. Araki, N. Iida, K. Miura, A. Ohta, R. Sekiguchi, S. Ito and T. Okujima, *Org. Chem. Front.*, 2019, **6**, 195; (c) T. Shoji, K. Miura, A. Ohta, R. Sekiguchi, S. Ito, Y. Endo, T. Nagahata, S. Mori and T. Okujima, *Org. Chem. Front.*, 2019, **6**, 2801; (d) H. Xin, J. Li, X. Yang and X. Gao, *J. Org. Chem.*, 2020, **85**, 70.

13 (a) A. C. Razus, L. Birzan, A. Corbu, O. Zaharia and C. Enache, *ARKIVOC*, 2006, (xii), 121; (b) T. Shoji, S. Takagaki, M. Tanaka, T. Araki, S. Sugiyama, R. Sekiguchi, A. Ohta, S. Ito and T. Okujima, *Heterocycles*, 2017, **94**, 1870; (c) T. Shoji, M. Tanaka, S. Takagaki, K. Miura, A. Ohta, R. Sekiguchi, S. Ito, S. Mori and T. Okujima, *Org. Biomol. Chem.*, 2018, **16**, 480.

14 (a) F. Wang, Y.-H. Lai and M.-Y. Han, *Macromolecules*, 2004, **37**, 3222; (b) X. Wang, J. K.-P. Ng, P. Jia, T. Lin, C. M. Cho, J. Xu, X. Lu and C. He, *Macromolecules*, 2009, **42**, 5534; (c) K. Tsurui, M. Murai, S.-Y. Ku, C. J. Hawker and M. J. Robb, *Adv. Funct. Mater.*, 2014, **24**, 7338.

15 (a) N. Takenaga, K. Fukazawa, M. Maruko and K. Sato, *Heterocycles*, 2015, **90**, 113; (b) C. F. Gers, J. Rosellen, E. Merkul and T. J. J. Müller, *Beilstein J. Org. Chem.*, 2011, **7**, 1173.

16 (a) J. Khalafy, M. Rimaz, M. Ezzati and R. H. Prager, *Bull. Korean Chem. Soc.*, 2012, **33**, 2890; (b) G.-H. Ma, X.-J. Tu, Y. Ning, B. Jiang and S.-J. Tu, *ACS Comb. Sci.*, 2014, **16**, 281; (c) V. A. Peshkov, A. A. Peshkov, O. P. Pereshivko, K. Van Hecke, L. L. Zamigaylo, E. V. Van der Eycken and N. Yu. Gorobets, *ACS Comb. Sci.*, 2014, **16**, 535; (d) H. Wei, B. Li, G. Wang, K. Van Hecke, O. P. Pereshivko and V. A. Peshkov, *Synthesis*, 2016, **48**, 1734; (e) X. Yang, L. Zheng, Z. Chen and W. Zhong, *Synth. Commun.*, 2018, **48**, 929; (f) X. Chang, X. Zhang and Z. Chen, *Org. Biomol. Chem.*, 2018, **16**, 4279; (g) M. Saroha and J. M. Khurana, *New J. Chem.*, 2019, **43**, 8644; (h) V. G. Melekhina, V. S. Mityanov, B. V. Lichitsky, A. N. Komogortsev, A. N. Fakhrutdinov, E. D. Daeva and M. M. Krayushkin, *Tetrahedron Lett.*, 2019, **60**, 1745; (i) B. V. Lichitsky, A. D. Tretyakov, A. N. Komogortsev, V. S. Mityanov, A. A. Dudinov and M. M. Krayushkin, *Chem. Heterocycl. Compd.*, 2019, **55**, 156.

17 A. Balakrishna, A. Aguiara, P. J. M. Sobral, M. Y. Wani, J. Almeida e Silva and A. J. F. N. Sobral, *Catal. Rev.: Sci. Eng.*, 2019, **61**, 84.

