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Palladium-catalyzed nucleophilic allylic substitution of Morita–Baylis–Hillman adducts with enamines: Synthesis of 1,5-dicarbonyl compounds

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ABSTRACT

An efficient nucleophilic allylic substitution of a variety of Morita–Baylis–Hillman adducts with enamines catalyzed by $Pd(OAc)_2$ in the presence of $ZnBr_2$ as a promoter is described in the present study. The reaction gives S_N2-type 1,5-dicarbonyl compounds that may subsequently undergo an intramolecular conjugate addition onto the enone moiety affording the corresponding 1,4-adducts. All the synthesized compounds have been isolated in moderate to good yields and fully characterized.

1. Introduction

1,5-Diketones are useful precursors to various substituted anilines [1] and heterocyclic compounds including pyridine derivatives [2–5], dihydropyridines [5,6], and pyrazolo[1,5-*a*] pyrimidines [7]. Moreover, 1,5-diketones with abstractable γ-hydrogen atoms were shown to be highly photoactive cage molecules for the release of fragrances [8]. These dicarbonyl compounds were also used for the synthesis of bicyclic ethers via their annulation reaction with bis (trimethylsilyl) enol ethers [9] and pinacol coupling through their reductive dimerization [10].

Michael addition of ketone enolates or their surrogates onto α,β-enones is one of the common methods for the synthesis of 1,5-diketones [11–13]. These compounds can also be prepared by a cross-coupling reaction of aryl methyl ketones with either aromatic aldehydes [14] or acetohydrazones [15], as well as by dimerization of α,β-enones in the presence of a quaternary ammonium salt as a phase-transfer catalyst [16]. In addition, the cross-metathesis of olefins was found to be a rapid access to such dicarbonyl derivatives [1,3]. In another synthetic protocol, Zard et al. reported a free radical approach for the synthesis of 1,5-diketones from alkenylacylphosphonates and keto-xanthates [2].

On the other hand, during the last decades, the nucleophilic behavior of enamines has been explored in palladium-catalyzed nucleophilic substitution of allylic compounds. Indeed, the reaction of allylic acetates with enamines worked well in the presence of Pd(II)/metallocene-based ligands, affording the corresponding allylation products [17]. Such a nucleophilic allylic substitution was used to prepare γ,δ-unsaturated ketones through the reaction of allylic benzotriazoles with

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1631-0748/

enamines under the action of Pd(0)/PPh_3 in the presence of $ZnBr_2$ [18].

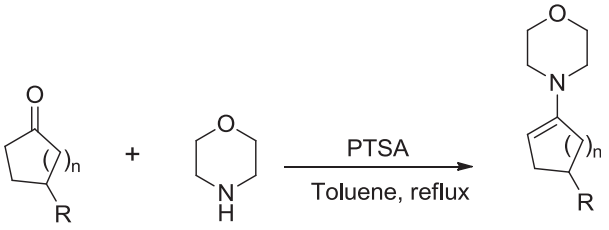
Furthermore, it was shown that the one-pot reaction of functionalized acyclic Morita–Baylis–Hillman (MBH) acetates with various enamino β-ketoesters in the presence of NaH afforded a series of trisubstituted 2-pyridones [19,20]. Nevertheless, it is worth noting that up to now, no Pd-catalyzed nucleophilic reaction of enamines with acyclic or cyclic MBH adducts has been reported. In our previous studies on the MBH chemistry, we have reported a Pd-free Tsuji-Trost–type reaction of MBH alcohols or acetates with β-dicarbonyl compounds, affording γ,δ-unsaturated 1,5-diketones [21,22]. In continuation of our interest in the allylic substitution of MBH derivatives with various nucleophiles [23,24], we report herein the first examples of a Pd-catalyzed allylic nucleophilic substitution of both cyclic and acyclic MBH adducts, as functionalized allylic substrates, with ketoenamines, providing a new series of saturated and γ,δ-unsaturated 1,5-dicarbonyl compounds.

2. Results and discussion

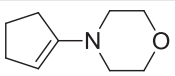
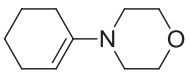
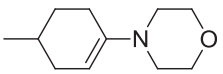
For this purpose, we have initially prepared the enamines **2a**–**c** in 60–70% yields (Table 1) from the reaction of cyclic ketones **1a**–**c** with morpholine using conventional reaction conditions [25].

Next, upon treatment of the enamine **2a** with the MBH acetate **3a** [21], at room temperature (rt), under solvent-free conditions, and without any additive, the starting materials were recovered within 48 h (Table 2, entry 1). The same result was also obtained when toluene was used as a solvent in the same reaction at rt or at reflux for 72 h (Table 2, entries 2 and 3). Interestingly, in dichloromethane at rt, the 1,5-dicarbonyl compound **4a** was obtained, within 72 h, but in only 30% yield (Scheme 1, Table 2, entry 4). To improve the reaction yield and reduce the reaction time, our subsequent experiment was conducted in refluxing dichloromethane. Under these conditions, the 1,5-keto ester **4a** was produced in the same yield within 72 h (Scheme 1, Table 2, entry 5).

Table 1
Synthesis of enamines **2a**–**c** from the reaction of ketones **1a**–**c** with morpholine.[a]



1a, **2a**, n=1, R=H — **2a**
1b, **2b**, n=2, R=H — **2b**
1c, **2c**, n=2, R=CH_3 — **2c**

Entry	Enamine 2	Reaction time (days)	Yield 2 (%)[b]
1	**2a** 	3	60
2	**2b** 	4	70
3	**2c** 	1	65

[a] The reaction was performed using ketones **1a**–**c** (1 equiv), morpholine (1.5 equiv), *p*-toluenesulfonic acid (2 equiv) in toluene.
[b] Isolated yield.

Table 2
Optimization of the reaction conditions for the synthesis of **4a** from the reaction of **2a** with **3a**.[a]

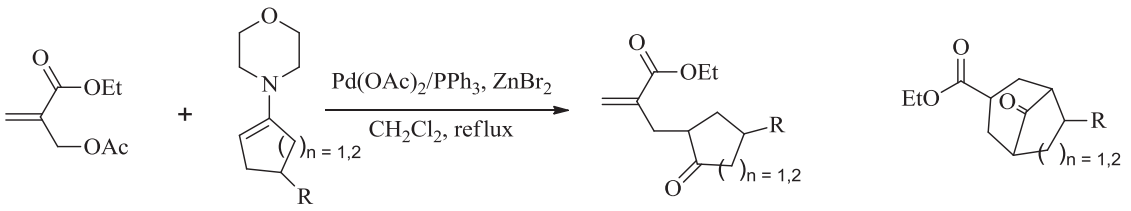
Entry	*T* (°C)	Solvent	Time (h)	Yield **4a**[b] (%)
1	rt	None	48	–
2	rt	Toluene	72	–
3	110	Toluene	72	–
4	rt	CH_2Cl_2	72	30
5	40	CH_2Cl_2	72	30

[a] The reaction was performed using the acetate **3a** (1 equiv) and enamine **2a** (5 equiv) in CH_2Cl_2.
[b] Isolated yield.

Taking into account the low yields of the compound **4a** and long reaction times recorded in the previous preliminary attempts, we therefore decided to explore a new synthetic approach for **4a** under catalytic conditions. In this context, we reacted, under the established conditions, the enamine **2a** (5 equiv) with the MBH acetate **3a** (1 equiv) in the presence of $Pd(OAc)_2$ (0.04 equiv)/PPh_3 (0.16 equiv) and $ZnBr_2$ (2.66 equiv) as a Lewis acid in refluxing dichloromethane. The conversion of the substrate **3a** was complete within 6 h, yielding exclusively, after hydrolysis of the reaction mixture, the unsaturated 1,5-keto ester **4a** in 70% yield (Scheme 1, Table 3, entry 1). Under the same conditions, the allylic nucleophilic substitution of the substrate **3a** was also successfully performed with enamines **2b** and **2c**, affording similarly the corresponding S_N2 and/or S_N2'-type products **4b** and **4c** in 80 and 68% yield, respectively (Scheme 1, Table 3, entries 2 and 3).

Next, to establish the substrate scope, we selected the cyclic MBH derivatives **3b**–**d** bearing three different leaving groups (LG = OAc, OMe, OEt), and we explored their behavior toward the nucleophilic enamines **2**. First, upon treatment of allylic acetate **3b** or allylic ethers **3c** and **3d** with enamine **2a**, under the previous conditions (MBH adduct (1 equiv), ketoenamine (5 equiv), $Pd(OAc)_2$ (0.04 equiv), PPh_3 (0.16 equiv), and $ZnBr_2$ (2.66 equiv) in CH_2Cl_2), the reaction worked well. Nevertheless, the expected S_N2-type product **4d** was not isolated but we exclusively obtained the same compound **5d**, in 75–80% yields (entries 4–6). This derivative was presumably formed through an in situ intramolecular Michael addition on the enone moiety of its precursor **4d** (Scheme 2, Table 3, entries 4–6). The best yield (80%) and the shorter reaction time (24 h) were achieved with the allylic acetate **3b** that was found to be the most reactive.

It is noteworthy that the monitoring of the reaction progress by thin layer chromatography, from the beginning of our experiment, showed only the formation of the compound **5d** with no trace of its precursor **4d** (Table 3,



Scheme 1. Synthesis of ketoesters **4a**–**c** from acyclic MBH **3a** and enamines **2a**–**c**.

Table 3
Synthesis of 1,5-dicarbonyl compounds **4** and **5** through the reaction of substrates **3a**–**e** with enamines **2a**–**c**.[a]

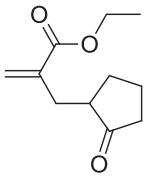
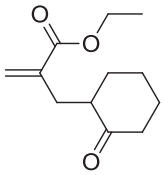
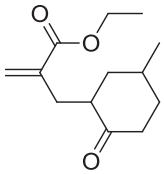
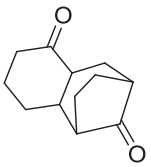
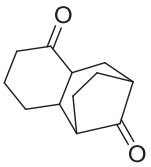
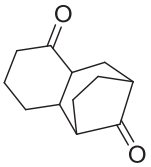
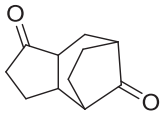
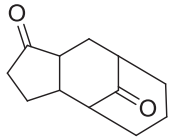
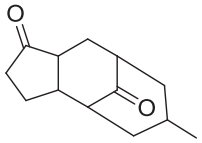
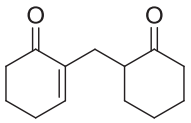
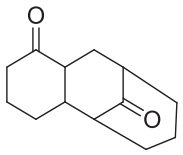
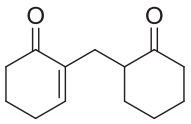
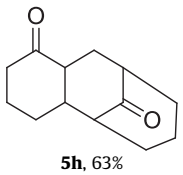
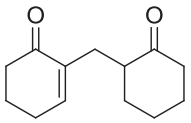
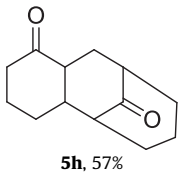
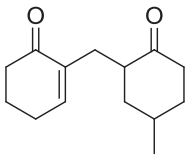
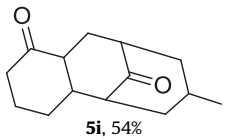
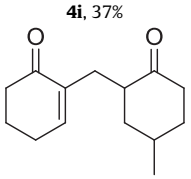
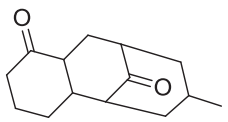
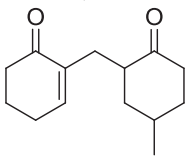
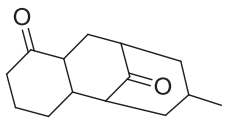
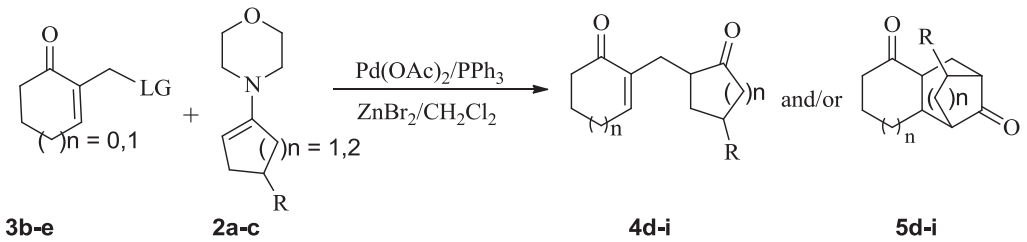
Entry	3	2	Time (h)	Product **4** and/or **5**[b]	Ratio **4**:**5**
1	**3a**	**2a**	6	 **4a**, 70%	**4a**/**5a** = 100:0
2	**3a**	**2b**	4	 **4b**, 80%	**4b**/**5b** = 100:0
3	**3a**	**2c**	4	 **4c**, 68%	**4c**/**5c** = 100:0
4	**3b**	**2a**	24	 **5d**, 80%	**4d**/**5d** = 0:100
5	**3c**	**2a**	48	 **5d**, 75%	**4d**/**5d** = 0:100
6	**3d**	**2a**	24	 **5d**, 75%	**4d**/**5d** = 0:100

Table 3 (*continued*)

Entry	3	2	Time (h)	Product 4 and/or 5[b]	Ratio 4:5
7	**3e**	**2a**	37	 **5e**, 60%	**4e**/**5e** = 0:100
8	**3e**	**2b**	32	 **5f**, 64%	**4f**/**5f** = 0:100
9	**3e**	**2c**	40	 **5g**, 57%	**4g**/**5g** = 0:100
10	**3b**	**2b**	7	 **4h**, 27%  **5h**, 60%	**4h**/**5h** = 31:69
11	**3c**	**2b**	28	 **4h**, 26%  **5h**, 63%	**4h**/**5h** = 29:71
12	**3d**	**2b**	12	 **4h**, 35%  **5h**, 57%	**4h**/**5h** = 38:62
13	**3b**	**2c**	24	 **4i**, 37%  **5i**, 54%	**4i**/**5i** = 40:60
14	**3c**	**2c**	28	 **4i**, 28%  **5i**, 65%	**4i**/**5i** = 30:70
15	**3d**	**2c**	24	 **4i**, 27%  **5i**, 64%	**4i**/**5i** = 30:70

[a] The reaction was performed using MBH adducts **3** (1 equiv), ketoenamine **2** (5 equiv), $Pd(OAc)_2$ (0.04 equiv), PPh_3 (0.16 equiv), and $ZnBr_2$ (2.66 equiv) in refluxing CH_2Cl_2.

[b] Isolated yield.



n = 1, **3b**, LG = OAc, **3c**, LG = OMe, **3d**, LG = OEt
n = 0, **3e**, LG = OAc

Scheme 2. Allylic substitution of MBH adducts **3b**–**e** with enamines **2a**–**c**.

entries 4–6), suggesting that the conversion of this intermediate into **5d** was kinetically faster than that of substrates **3b**–**d** into the intermediate **4d**.

Correlatively, an interesting example on Michael–Stork addition of enamine **2a** to allenyl ketones and esters was previously reported by Lepore et al. [26]. They showed that a Michael addition onto the title substrates provided an iminium ion intermediate, which could further undergo hydrolysis to afford the 1,4-adducts **6**. Alternatively, the corresponding enamines can undergo an intramolecular cyclization to yield the bicyclic compounds **7** (Scheme 3).

Furthermore, we explored the scope of this allylic nucleophilic substitution reaction involving the five-membered MBH acetate **3e** with enamines **2a**–**c**. Under the previous conditions ($Pd(OAc)_2/ZnBr_2$), adducts **5e**–**g** were exclusively obtained in 57–64% yields (Scheme 2, Table 3, entries 7–9).

Finally, the nucleophilic allylic substitution of substrates **3b**–**d** with six-membered enamines **2b** and **2c** has been investigated (Scheme 2, Table 3, entries 10–15). We observed that these substrates did not have the same behavior toward the five-membered enamine **2a** (vide supra) and the six-membered enamines **2b** and **2c** (Scheme 2, Table 3, entries 10–15). Indeed, the reaction with enamine **2a** gave exclusively the adduct **5d** (Scheme 2, Table 3, entries 4–6), whereas the use of **2b** and **2c** gave predominantly adducts **5h** and **5i** along with their corresponding precursors **4h** and **4i** (Scheme 2, Table 3, entries 10–15) in high overall yields.

Compounds **5h** and **5i** and the corresponding precursors **4h** and **4i** were easily separated by column chromatography (petroleum ether/ether = 60:40) and fully characterized. Polycyclic compounds **5d**–**i** were unequivocally elucidated by ^1H NMR and high-resolution mass spectra (HRMS).

It is notable that, under the catalysis of both Pd(0) and $ZnBr_2$, we did not observe any S_N2' product along with the S_N2-type products **4d**–**i** using cyclic MBH adducts **3b**–**e** and enamines **2a**–**c**. We believe that this allylic substitution is under thermodynamic control, affording exclusively the α-products [27,28].

To explain the formation of the 1,5-dicarbonyl compounds **4** and **5**, we propose an initial departure of the leaving group on adducts **3**, which would be assisted by the Lewis acid $ZnBr_2$ [29–31]. Indeed, the resulting intermediate **7** undergoes an oxidative addition to Pd(0) to form a cationic Π–allyl Pd(II) complex **8** (i) that is further attacked by the enamines **2**, yielding an iminium intermediate **9** (ii). After that, there is either the hydrolysis of the intermediate **9** to give the δ-diketones **4** (iii), or alternatively the carbanion derived from the tautomeric form **9′** of **9** undergoes an intramolecular Michael addition on the enone moiety to finally provide, after hydrolysis, the δ-diketones **5** (iv) (Scheme 4).

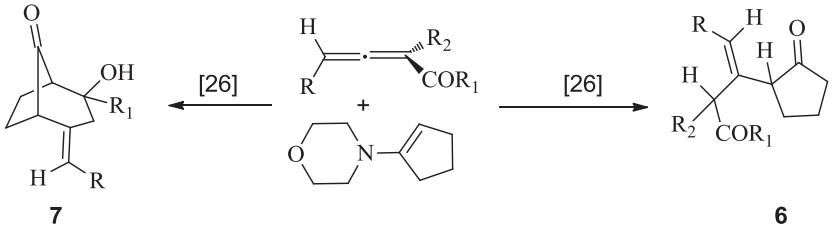
3. Conclusion

We have reported the first examples of an efficient $ZnBr_2$-promoted Pd-catalyzed allylic substitution reactions of cyclic and acyclic MBH adducts with cyclic ketoenamines in refluxing dichloromethane. These reactions afford a series of S_N2-type unsaturated 1,5-dicarbonyl compounds, which can further undergo an intramolecular Michael addition on the enone moiety, yielding the corresponding 1,4-adducts. All the newly synthesized compounds were isolated in moderate to good yields and fully characterized.

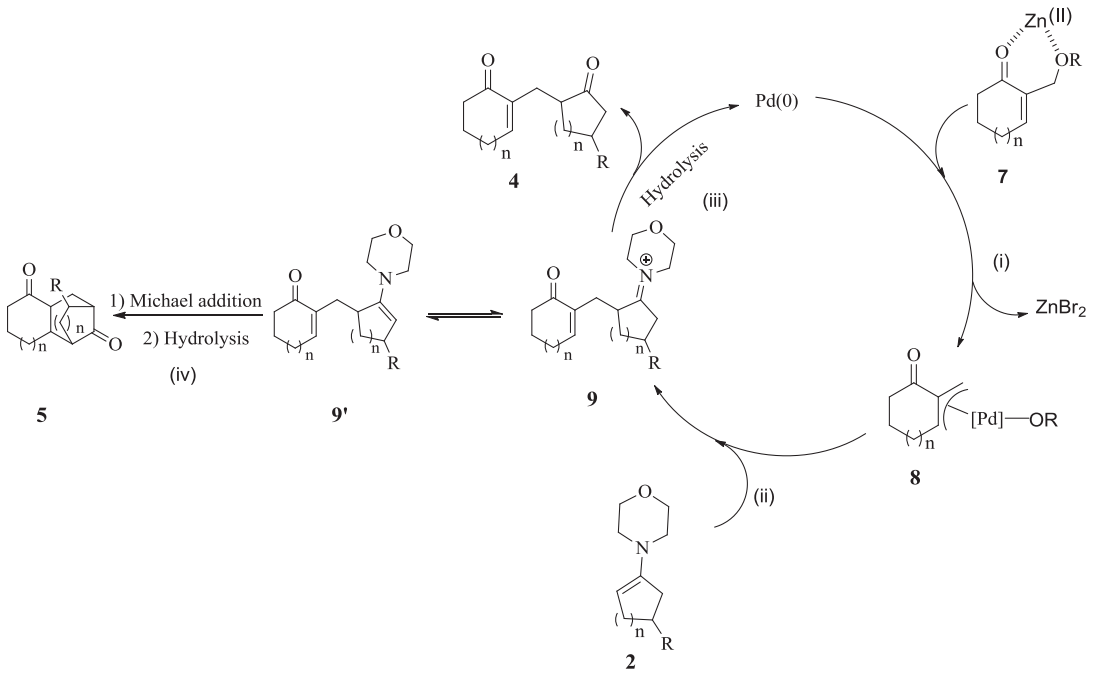
4. Experimental section

4.1. General comments

^1H NMR and ^{13}C NMR spectra were recorded either on a 300 MHz Bruker for ^1H or 75 MHz in $CDCl_3$, using tetramethylsilane as an internal standard (chemical shifts in



Scheme 3. Michael–Stork addition of an enamine to allenyl ketones and esters.



Scheme 4. Proposed reaction mechanism for 1,5-dicarbonyl compounds **4** and **5**.

δ values and J in Hz). HRMS were recorded as ESI-HRMS on an Auto Spec Ultima/micromass mass spectrometer. Mass spectra (EI) were obtained at 70 eV on a Hewlett–Packard HP-5890. Analytical thin layer chromatography was performed using Fluka Kieselgel 60 F_{254} precoated silica gel plates. Visualization was achieved by UV light (254 nm). Flash chromatography was performed using silica gel 60 and a gradient solvent system (petroleum ether/ether). Compounds **3** and enamines **2** were prepared according to the literature methods [21,25].

4.2. General procedure for the synthesis of 1,5-dicarbonyl compounds *4a–i* and *5a–i*

Under nitrogen, a mixture of MBH acetate **3** (1.5 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol), PPh_3 (63 mg, 0.24 mmol), and $ZnBr_2$ (0.90 g, 4 mmol) was refluxed in CH_2Cl_2 (10 mL) for 15 min. Then the solution of enamine **2** (7.5 mmol) in CH_2Cl_2 (5 mL) was added, and the reaction mixture was refluxed for 4–48 h. After evaporation of CH_2Cl_2, water (10 mL) was added with NaOH (1 M, 30 mL), and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The organic phase was washed with a saturated solution of ammonium chloride (10 mL) and dried over magnesium sulfate. After removal of the solvent, the residue was subjected to column chromatography (petroleum ether/ether = 60:40) to produce pure unsaturated 1,5-dicarbonyl compounds **4a–i** and **5a–i**.

4.3. Ethyl 2-((2-oxocyclopentyl)methyl)acrylate (*4a*)

Yield 70%; colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.19 (d, J = 3 Hz, 1H), 5.59 (d, J = 3 Hz, 1H), 4.21 (q, J = 7.5 Hz, 2H), 2.91–2.85 (m, 1H), 2.38–2.34 (m, 2H), 2.33–2.21 (m, 4H), 1.99–1.86 (m, 1H), 1.54–1.50 (m, 1H), 1.32 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.5, 166.9, 138.9, 126.1, 60.7, 48.1, 37.8, 32.1, 29.7, 20.6, 14.2. MS (*m/z*), 55 (53), 68 (50), 96 (100), 151 (21), 168 (51), 196 (M^+, 39); HRMS calcd for $C_{11}H_{16}O_3^+$ $[M-H]^+$ 195.1021, found 195.1020.

4.4. Ethyl 2-((2-oxocyclohexyl)methyl)acrylate (*4b*)

Yield 80%; colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.19 (d, J = 3 Hz, 1H), 5.57 (d, J = 3 Hz, 1H), 4.20 (q, J = 7.5 Hz, 2H), 2.36–2.32 (m, 4H), 2.12–2.08 (m, 2H), 1.89–1.85 (m, 4H), 1.74–1.68 (m, 1H), 1.30 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.1, 166.9, 138.4, 126.6, 60.5, 49.1, 41.8, 33.5, 31.8, 27.9, 26.9, 14.0. MS (*m/z*), 55 (39), 67 (34), 97 (41), 136 (100), 165 (32), 210 (M^+, 8); HRMS calcd for $C_{12}H_{18}O_3^+$ $[M+H]^+$ 211.1327, found 211.1325.

4.5. Ethyl 2-((5-methyl-2-oxocyclohexyl)methyl)acrylate (*4c*)

Yield 68%; colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.20 (s, 1H), 5.56 (d, J = 3 Hz, 1H), 4.20 (q, J = 8 Hz, 2H), 2.87–2.80 (m, 1H), 2.71–2.67 (m, 1H), 2.42–2.27 (m, 3H), 2.14–2.04 (m, 2H), 1.70 (t, J = 6 Hz, 2H), 1.65–1.55 (m, 1H), 1.30 (t, J = 8 Hz, 3H), 1.08 (d, J = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 213.3, 166.8, 138.3, 126.4, 60.7, 46.5, 39.3, 37.9, 34.2, 32.9, 26.6, 19.5, 14.1. MS (*m/z*), 55 (89), 67 (42), 136 (28), 151 (100), 179 (62), 224 (M^+, 10); HRMS calcd for $C_{13}H_{20}O_3^+$ $[M+H]^+$ 225.1484, found 225.1486.

4.6. Decahydro-1H-5,8-methanobenzo[7]annulene-1,10-dione (*5d*)

Yield 80% from (6-oxocyclohex-1-en-1-yl)methyl acetate **3b**, 75% from 2-(methoxymethyl)cyclohex-2-enone **3c**,

and 75% from 2-(ethoxymethyl)cyclohex-2-enone **3d**; white solid; mp 128–130 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.66–2.57 (m, 1H), 2.40–2.32 (m, 3H), 2.19–1.92 (m, 7H), 180–1.60 (m, 4H), 1.25–1.16 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.4, 210.6, 51.4, 49.2, 47.1, 43.4, 41.3, 34.7, 29.7, 26.0, 23.1, 18.5. MS (*m*/*z*), 96 (48), 110 (40), 164 (31), 192 (M^+, 100); HRMS calcd for $C_{12}H_{16}O_2^+$ $[M+H]^+$ 193.1229, found 193.1230.

4.7. Octahydro-4,7-methanoazulene-1,9(2H)-dione (**5e**)

Yield 60%; white solid; mp 122–126 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.37–2.00 (m, 4H), 1.81–1.43 (m, 4H), 1.39 –1.23 (m, 4H), 0.91–0.83 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 220.8, 220.7, 47.1, 46.8, 38.0, 30.2, 30.1, 29.9, 29.7, 29.6, 20.7. MS (*m*/*z*), 150 (100), 178 (M^+, 60); HRMS calcd for $C_{11}H_{14}O_2^+$ $[M+H]^+$ 179.1072, found 179.1071.

4.8. Decahydro-1H-4,8-methanocyclopenta[8]annulene-1,10-dione (**5f**)

Yield 64%; white solid; mp 119–121 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.04–2.95 (m, 1H), 2.82–2.74 (m, 1H), 2.43 –2.31 (m, 3H), 2.19–2.05 (m, 9H), 1.77–1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.3, 219.2, 50.3, 47.4, 45.7, 45.2, 36.9, 35.1, 34.3, 32.2, 27.0, 20.1. MS (*m*/*z*), 96 (48), 110 (40), 164 (31), 192 (M^+, 100); HRMS calcd for $C_{12}H_{16}O_2^+$ $[M+H]^+$ 193.1229, found 193.1241.

4.9. 6-Methyldecahydro-1H-4,8-methanocyclopenta[8] annulene-1,10-dione (**5g**)

Yield 57%; white solid; mp 120–123 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.47–2.42 (m, 1H), 2.26–1.96 (m, 4H), 1.94 –1.83 (m, 4H), 1.76–1.27 (m, 6H), 0.96 (d, J = 9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.2, 213.0, 51.8, 47.8, 47.5, 46.8, 37.9, 34.5, 34.1, 33.6, 27.9, 24.5, 20.0. MS (*m*/*z*) 96 (90), 110 (88), 164 (89), 206 (M^+, 98); HRMS calcd for $C_{13}H_{18}O_2^+$ $[M+H]^+$ 207.1385, found 207.1389.

4.10. 2-((2-Oxocyclohexyl)methyl)cyclohex-2-enone (**4h**)

Yield 27% from (6-oxocyclohex-1-en-1-yl)methyl acetate **3b**, 26% from 2-(methoxymethyl)cyclohex-2-enone **3c**, and 35% from 2-(ethoxymethyl)cyclohex-2-enone **3d**; colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.79 (t, J = 4.5 Hz, 1H), 1.76–1.70 (m, 1H), 2.60–2.50 (m, 1H), 2.43–2.28 (m, 6H), 2.08–1.95 (m, 5H), 1.86–1.81 (m, 1H), 1.68–1.59 (m, 2H), 1.21–1.36 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 212.9, 199.7, 147.8, 137.5, 49.2, 42.2, 38.5, 34.0, 30.3, 28.1, 26.3, 25.0, 23.0. MS (*m*/*z*) 55 (100), 67 (71), 95 (52), 110 (31), 122 (83), 206 (M^+, 92); HRMS calcd for $C_{13}H_{18}O_2^+$ $[M+H]^+$ 207.1385, found 207.1389.

4.11. Decahydro-5,9-methanobenzo[8]annulene-1,11(2H)-dione (**5h**)

Yield 60% from (6-oxocyclohex-1-en-1-yl)methyl acetate **3b**, 57% from 2-(methoxymethyl)cyclohex-2-enone **3c**, and 63% from 2-(ethoxymethyl)cyclohex-2-enone **3d**; white solid; mp 113–116 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.44–3.35 (m, 1H), 2.58–2.53 (m, 2H), 2.46–2.22 (m, 4H), 2.15–1.98 (m, 7H), 1.74–1.54 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.2, 213.0, 51.8, 47.8, 47.5, 46.8, 37.9, 34.5, 34.1, 33.6, 27.9, 24.5, 20.0. MS (*m*/*z*): 55 (77), 95 (52), 110 (34), 150 (34), 178 (21), 206 (M^+, 100); HRMS calcd for $C_{13}H_{18}O_2^+$ $[M+H]^+$ 207.1385, found 207.1383.

4.12. 2-((5-Methyl-2-oxocyclohexyl)methyl)cyclohex-2-enone (**4i**)

Yield 37% from (6-oxocyclohex-1-en-1-yl)methyl acetate **3b**, 28% from 2-(methoxymethyl)cyclohex-2-enone **3c**, and 27% from 2-(ethoxymethyl)cyclohex-2-enone **3d**; colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.80 (t, J = 4.5 Hz, 1H), 2.77–2.37 (m, 2H), 2.34–2.31 (m, 6H), 2.02–1.92 (m, 7H), 1.90–1.28 (m, 1H), 0.96 (d, J = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 220.9, 199.7, 147.8, 137.5, 47.9, 42.1, 41.6, 38.5, 36.1, 31.9, 30.2, 26.2, 23.0, 21.2. MS (*m*/*z*), 55 (79), 110 (47), 203 (88), 220 (M^+, 100); HRMS calcd for $C_{14}H_{20}O_2^+$ $[M+H]^+$ 221.1542, found 221.1544.

4.13. 7-Methyldecahydro-5,9-methanobenzo[8]annulene-1,11(2H)-dione (**5i**)

Yield 54% from (6-oxocyclohex-1-en-1-yl)methyl acetate **3b**, 65% from 2-(methoxymethyl)cyclohex-2-enone **3c**, and 64% from 2-(ethoxymethyl)cyclohex-2-enone **3d**; white solid; mp 106–108 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.46–3.38 (m, 1H), 2.56–2.23 (m, 7H), 2.18–2.12 (m, 4H), 1.69–1.40 (m, 4H), 1.35–1.17 (m, 1H), 0.89 (d, J = 6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 219.4, 212.9, 51.9, 48.4, 47.8, 45.8, 43.2, 42.8, 37.4, 33.6, 27.6, 26.4, 24.4, 22.4. MS (*m*/*z*), 55 (100), 110 (77), 163 (42), 220 (M^+, 59); HRMS calcd for $C_{14}H_{20}O_2^+$ $[M+H]^+$ 221.1542, found 221.1546.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.crci.2016.11.011.

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