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SYNTHESIS OF MALEIMIDE-FUSED ACEHEPTYLENES FROM GUAIAZULENE

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Abstract – Maleimide-fused aceheptylenes were prepared using guaizulene as a starting material. The condensation reaction of 3,4-diformylguaiazulene derivative, which was prepared in three steps from guaiazulene, with maleimides in the presence of tri-*n*-butylphosphine and 1,8-diazabicyclo[5.4.0]undec-7-ene afforded the maleimide-fused aceheptylenes. Structural feature of the aceheptylenes prepared was revealed by ^{1}H NMR spectroscopy and nucleus-independent chemical shift calculations.

The maleimide substructure is widely observed in various natural products and pharmaceuticals.[1] Moreover, its exceptional electron mobility and fluorescence efficiency have attracted interest for its use in the field of organic electronics, such as n-type semiconductors and fluorescent materials.[2] Thus, numerous maleimide derivatives have been synthesized and their characteristic features have been investigated.

Aceheptylene is a tricyclic compound in which a cycloheptatriene is fused to an azulene framework. In the late 1950s to the early 1970s, Hafner *et al*. intensively developed synthetic methods of aceheptylene and its derivatives.[3] In the late 1970s to 1980s, the reactivity[4] and spectroscopic properties[5] of the aceheptylene derivatives were clarified by several researchers. However, despite the fact that various aceheptylene

derivatives have been synthesized, only one example of heterocycle-fused aceheptylene, shown in Figure 1, is described in the literature.[6]

In this paper, we describe the synthesis of maleimide-fused aceheptylenes using guaiazulene (**1**) as a starting material, as part of our efforts to develop a strategy for obtaining heterocycle-fused aceheptylene derivatives. The structural properties of the prepared aceheptylenes were verified by the analysis of ^{1}H NMR measurements and nucleus-independent chemical shift (NICS) calculations.

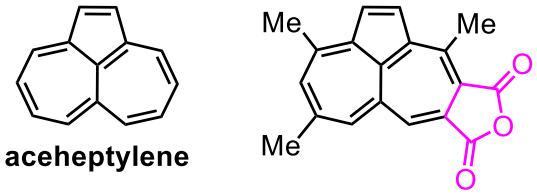
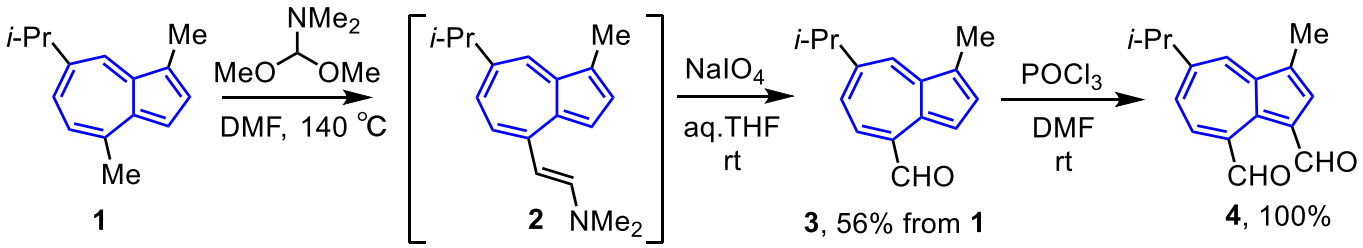


Figure 1. Structure of aceheptylene and heterocycle-fused aceheptylene derivative

We have previously reported the two-step procedure for the transformation of 2-methylazulene derivatives into 2-formylazulenes.[7] Recently, Lewis *et al*. extended our method to guaiazulene (**1**) and successfully prepared a 4-formylazulene derivative in the two-step procedure by the formal oxidation of the methyl group at the 4-position.[8] Accordingly, the preparation of the 4-formylazulene derivative, which serves as a precursor to maleimide-fused aceheptylenes, was conducted under the conditions described in the literature as illustrated in Scheme 1.

The synthetic pathway of 3,4-diformylazulene **4** from guaiazulene (**1**) is summarized in Scheme 1. The reaction of guaiazulene (**1**) with *N*,*N*-dimethylformamide dimethyl acetal (DMFDA) produced the enamine intermediate **2**, which was proved to be unstable and underwent decomposition during the purification process. Thus, the crude enamine product **2** was utilized in the subsequent oxidation reaction without further purification. The oxidation of the crude enamine **2** with $NaIO_4$ resulted in the formation of 4-formylazulene **3** in 56% yield as the two-step yield from **1**. Synthesis of 3,4-diformylazulene **4** was accomplished by the Vilsmeier reaction of **3** in a quantitative yield (100%).

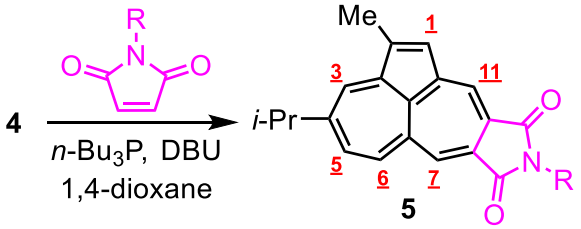


Scheme 1. Synthesis of 3,4-diformylazulene **4** from guaiazulene (**1**)

We have recently reported the successful application of a phosphine-mediated condensation reaction to the synthesis of the phthalimide-fused azulenes from 1,2-diformylazulenes and maleimides.[9] However, the reaction of **4** with maleimide in the presence of triphenylphosphine in *N*,*N*-dimethylformamide was found to yield a complex mixture instead of the desired maleimide-fused aceptylene **5**. Therefore, we explored the preparation of the aceheptylenes **5** by the procedure using trialkylphosphine and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) described by Saito and Yamaguchi *et al.*[10]

We found that the reaction of **4** with several maleimides in the presence of tri-*n*-butylphosphine (*n*-BuP_3) and DBU generated the products **5**. However, the reactivity was highly dependent on the substituent on the nitrogen atom of the maleimides, as evidenced by the results shown in Table 1. Maleimides incorporating an alkyl group substituted on the nitrogen atom underwent the reaction, affording **5a**–**5c** with 40–86% yields (Entries 1–3). In contrast, maleimides with phenyl, *para*-*n*-butylphenyl, or benzyl substituents on the nitrogen atom yielded complex mixtures, instead of the desired products (Entries 4–6). The reaction with maleimides possessing a phenethyl group produced **5d** in 42% yield, similar to use of the *N*-alkyl maleimides (Entry 7).

Table 1. Synthesis of maleimide-fused aceheptylenes **5**



Entry	R	Product, Yield [%]
1	Me	**5a**,[11] 86
2	Et	**5b**,[12] 66
3	*c*-hexyl	**5c**,[13] 40
4	Ph	0
5	*p*-(*n*-Bu)Ph	0
6	benzyl	0
7	phenethyl	**5d**,[14] 42

Previously, Hafner, Rabinovitz, and their colleagues determined through the analysis of ^{1}H NMR spectroscopy that heptalene moiety of aceheptylene does not possess aromaticity originating from its azulene substructure but serves as a non-aromatic cyclic polyolefin.[15] To examine the aromaticity of **5a**, a comparison of the chemical shifts in the ^{1}H NMR spectrum of **5a** with those of guaiazulene (**1**) was

conducted. Upon comparing the ^{1}H NMR spectra of **5a** and **1**, all signals of **5a** displayed a high field shift towards the olefinic region (δ_H = 5.8−7.4 ppm), whereas **1** exhibited proton signals in the typical aromatic region. These findings suggest that upon the fusion of cycloheptatriene to the azulene framework, the molecule loses its aromatic character and behaves as heptalene rather than azulene. The fusion of maleimide is also not effective in retaining the aromaticity of the azulene structure.

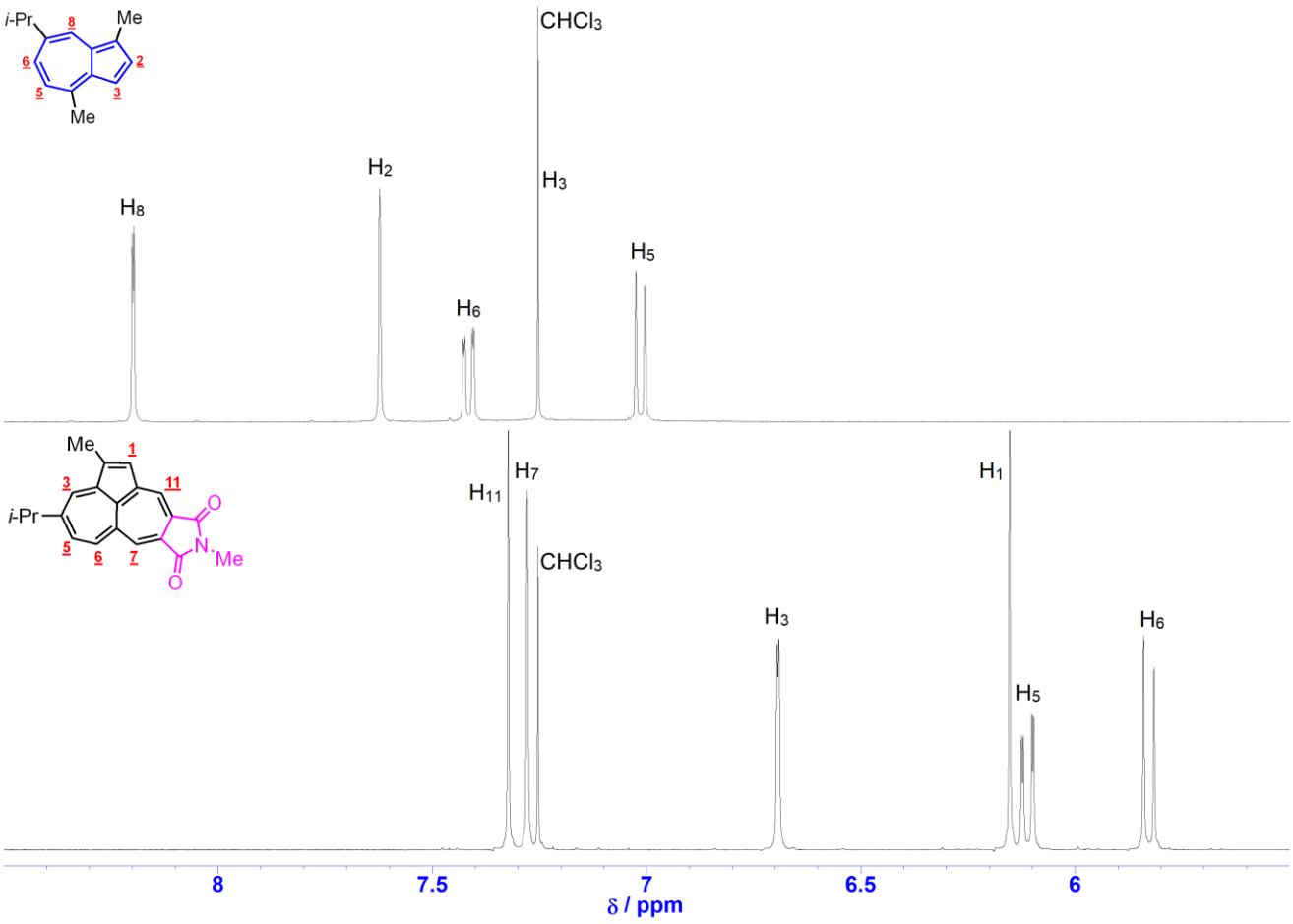
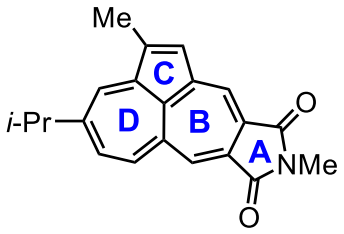


Figure 2. ^{1}H NMR spectra of **5a** and guaiazulene (**1**) in $CDCl_3$ (500 MHz)

To comprehend the aromaticity of each ring of **5a** from a theoretical perspective, calculations of the nucleus-independent chemical shift (NICS) were performed using the GIAO/HF/6-31G** level, as detailed in Table 2. The results indicate that, the five-membered ring C exhibits aromatic character, while the NICS values of the seven-membered rings, i.e., both B and D rings, exhibit notable downfield shifts, suggesting their anti-aromatic nature due to a 12π electron system. However, the calculations also showed that the ring D exhibits less anti-aromaticity than the ring B, indicating a slight contribution of azulene substructure in the fused ring structure of the rings C and D. The upfield shift of the H_1 , H_5 and H_6 proton signals observed

in the ^{1}H NMR spectrum is probably attributable to the paramagnetic ring current due to the adjacent heptalene moiety. The pronounced low-field shifts of the H_7 and H_{11} protons in the B ring should be attributed to the anisotropy of the carbonyl groups in the maleimide moiety. In conclusion, the NMR experiments and NICS calculations implied that aceheptylene **5a** possesses the structural properties of both azulene and heptalene units.

Table 2. The NICS values of **5a** at the GIAO/HF/6-31G**



Ring*	NICS(1)	NICS(0)	NICS(−1)
A	−3.65	−0.93	−3.65
B	5.96	10.70	5.96
C	−24.81	−25.83	−24.81
D	1.27	5.31	1.27

*Structure optimization was performed at B3LYP/6-31+G(d) level.

In summary, we have described a novel method for the synthesis of the maleimide-fused aceheptylenes, involving the reaction of a 3,4-diformylazulene derivative with several maleimides in the presence of tri-*n*-butylphosphine and DBU. The reactions of maleimides with alkyl or phenethyl substituents on the nitrogen atom resulted in the formation of the corresponding aceheptylene derivatives in good to moderate yields. Conversely, maleimides substituted with aryl or benzyl groups afford the complex mixtures, instead of the desired products. The structural feature of the maleimide-fused aceheptylenes prepared were elucidated, revealing that the compounds possess both aromatic and anti-aromatic properties, that is, contribution of azulene and heptalene structures.

ACKNOWLEDGEMENTS

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11. **5a**: *n*-Bu_3P (532 mg, 2.63 mmol) and DBU (4 mg, 0.023 mol) was added to a solution of **4** (312 mg, 1.30 mmol) and *N*-methylmaleimide (221 mg, 1.98 mmol) in 1,4-dioxane (7 mL) and the resulting mixture was stirred at 100 °C under an Ar atmosphere for 4 h. The reaction mixture was poured into water, extracted with $CHCl_3$ and washed with brine. The organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **5a** (353 mg, 86%). Mp 131–132 °C; IR (ATR): ν_{max} = 2956 (w),

1750 (s), 1698 (s), 1636 (m), 1604 (m), 1558 (w), 1541 (w), 1507 (w), 1486 (w), 1428 (m), 1378 (s),1365 (w), 1341 (w), 1320 (w), 1287 (w), 1258 (w), 1208 (w), 1164 (w), 1129 (w), 1113 (w), 1086 (w), 1056 (w), 1034 (w), 987 (w), 970 (w), 917 (w), 896 (w), 869 (w), 849 (w), 804 (w), 735 (s), 691 (w), 666 (w), 653 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.32 (s, 1H, H_{11}), 7.28 (s, 1H, H_7), 6.69 (d, *J* = 2.0 Hz, 1H, H_3), 6.15 (s, 1H, H_1), 6.11 (dd, *J* = 12.2, 2.0 Hz, 1H, H_5), 5.83 (d, *J* = 12.2 Hz, 1H, H_6), 3.04 (s, 3H, *N*-Me), 2.36 (sept, *J* = 6.9 Hz, 1H, *i*-Pr), 2.32 (s, 3H, Me), 1.10 (d, *J* = 6.9 Hz, 6H, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.47, 168.25, 154.15, 153.89, 143.16, 141.27, 136.72, 136.66, 135.84, 135.67, 134.33, 133.13, 132.45, 128.38, 128.07, 116.95, 36.59, 24.51, 22.63, 13.87 ppm.

12. **5b**: *n*-Bu_3P (69 mg, 0.343 mmol) and DBU (2 mg, 0.012 mol) was added to a solution of **4** (35 mg, 0.144 mol) and *N*-ethylmaleimide (35 mg, 0.278 mmol) in 1,4-dioxane (1 mL) and the resulting mixture was stirred at 100 °C under an Ar atmosphere for 4 h. The reaction mixture was poured into water, extracted with $CHCl_3$ and washed with brine. The organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **5b** (32 mg, 66%). Mp 182–184 °C; IR (ATR): ν_{max} = 2966 (w), 2871 (w), 2359 (w), 1753 (m), 1700 (s), 637 (w), 1617 (w), 1597 (m), 1525 (w), 1485 (w), 439 (w), 1401 (s), 1390 (w), 1369 (m), 1339 (w), 1319 (w), 1284 (w), 1241(w), 1211 (w), 1141 (w), 1106 (w), 1083 (w),1062 (w), 1040 (w), 1020 (w), 983 (w), 934 (w), 894 (w), 853 (w), 828 (w),815 (w), 742 (s), 681 (w), 663 (w), 654 (w), 634 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.34 (s, 1H, H_{11}), 7.30 (s, 1H, H_7), 6.70 (d, *J* = 2.0 Hz, 1H, H_3), 6.17 (s, 1H, H_1), 6.11 (dd, *J* = 12.2, 2.1 Hz, 1H, H_5), 5.84 (d, *J* = 12.3 Hz, 1H, H_6), 3.60 (q, *J* = 7.2 Hz, 3H, *N*-Et), 2.36 (sept, *J* = 6.9 Hz, 1H, *i*-Pr), 2.33 (s, 3H, Me), 1.19 (t, *J* = 7.2 Hz, 3H, *N*-Et), 1.10 (d, *J* = 6.9 Hz, 6H, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.27, 168.01, 154.27, 153.96, 143.14, 141.31, 136.84, 136.74, 135.77, 135.69, 134.35, 133.16, 132.32, 128.29, 128.21, 117.10, 36.61, 33.40, 22.63, 13.87, 13.61 ppm.
13. **5c**: *n*-Bu_3P (39 mg, 0.191 mol) and DBU (1 mg, 0.060 mol) was added to a solution of **4** (17 mg, 0.069 mmol) and *N*-cyclohexylmaleimide (19 mg, 0.108 mol) in 1,4-dioxane (1 mL) and the resulting mixture was stirred at 100 °C under an Ar atmosphere for 4 h. The reaction mixture was poured into water, extracted with $CHCl_3$ and washed with brine. The organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **5c** (11 mg, 40%). Mp 251–252 °C; IR (ATR): ν_{max} = 2930 (w), 2859 (w), 2360 (w), 2341 (w), 1748 (s), 1703 (s), 1643 (w), 1605 (w), 1486 (w), 1459 (w), 1419 (w), 1395 (w), 1364 (s), 1318 (w), 1303 (w), 1288 (w), 1254 (w), 1200 (w), 1167 (w), 1112 (m), 1093 (w), 1070 (w), 1052 (w), 1033 (w), 1011 (w), 962 (w), 929 (w), 894 (m), 832 (w), 820 (w), 808 (w), 797 (w), 739 (s), 661 (w), 634 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.31 (s, 1H, H_{11}), 7.28 (s, 1H,

H_7), 6.68 (d, *J* = 2.0 Hz, 1H, H_3), 6.12 (s, 1H, H_1), 6.08 (dd, *J* = 12.2, 2.0 Hz, 1H, H_5), 5.82 (d, *J* = 12.2 Hz, 1H, H_6), 4.01–3.96 (m, 1H, *c*-hexyl), 2.36 (sept, *J* = 6.9 Hz, 1H, *i*-Pr), 2.33 (s, 3H, Me), 2.17–2.08 (m, 2H, *c*-hexyl), 1.83–1.80 (m, 2H, *c*-hexyl), 1.66–1.60 (m, 3H, *c*-hexyl), 1.34–1.30 (m, 1H, *c*-hexyl), 1.28–1.21 (m, 3H, *c*-hexyl), 1.10 (d, *J* = 6.9 Hz, 6H, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.11, 154.44, 143.00, 141.25, 136.62, 135.60, 134.41, 133.21, 131.99, 128.45, 127.92, 117.12, 51.27, 36.58, 29.44, 26.02, 25.20, 22.60, 13.89 ppm.

14. **5d**: *n*-Bu_3P (136 mg, 0.673 mol) and DBU (4 mg, 0.023 mol) was added to a solution of **4** (77 mg, 0.318 mol) and *N*-phenethylmaleimide (100 mg, 0.496 mol) in 1,4-dioxane (1 mL) and the resulting mixture was stirred at 100 °C under an Ar atmosphere for 4 h. The reaction mixture was poured into water, extracted with $CHCl_3$ and washed with brine. The organic layer was dried with Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by column chromatography on silica gel with $CHCl_3$ as an eluent to give **5d** (53 mg, 42%). Mp 206–207 °C; IR (ATR): ν_{max} = 2961 (w), 2359 (m), 2342 (w), 1749 (m), 1697 (s), 1638 (w), 1622 (w), 1598 (m), 1431 (m), 1372 (s), 1336 (w), 1271 (w), 1173 (w), 1119 (m), 1085 (w), 1056 (w), 1021 (w), 1005 (w), 988 (w), 925 (w), 890 (w), 837 (w), 822 (w), 807 (w), 737 (s), 654 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ_H = 7.32 (s, 1H, H_{11}), 7.31–7.28 (m, 3H, H_7, *m*-Ph), 7.23–7.19 (m, 3H, *o*,*p*-Ph), 6.70 (d, *J* = 2.0 Hz, 1H, H_3), 6.14 (s, 1H, H_1), 6.11 (dd, *J* = 12.2, 2.0 Hz, 1H, H_5), 5.83 (d, *J* = 12.2 Hz, 1H, H_6), 3.78 (t, *J* = 7.9 Hz, 2H, CH_2), 2.90 (t, *J* = 7.9 Hz, 2H, CH_2), 2.36 (t, *J* = 6.9 Hz, 1H, *i*-Pr), 2.33 (s, 3H, Me), 1.10 (d, *J* = 6.9 Hz, 6H, *i*-Pr) ppm; ^{13}C NMR (125 MHz, $CDCl_3$) δ_C = 168.17, 167.94, 154.30, 154.01, 143.23, 141.33, 138.22, 136.84, 136.68, 135.83, 135.68, 134.40, 133.25, 132.34, 128.94, 128.61, 128.32, 128.23, 126.67, 116.89, 39.78, 36.61, 34.28, 22.62, 13.88 ppm.

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