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Direct aromatization of chlorohydroazulenones with triflic anhydride: access to chloroazulenyl triflates

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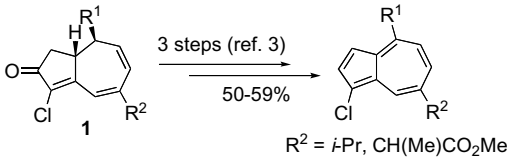
ABSTRACT

A direct and efficient aromatization of chlorohydroazulenones has been achieved by using triflic anhydride and then lutidine or tropylium cation to afford selectively chloroazulenes and chloroazulenyl triflates, respectively.

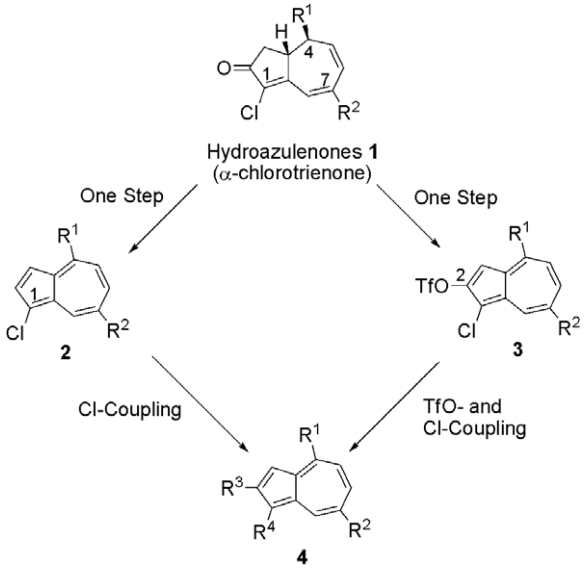
Azulenes constitute a class of polycyclic nonbenzenoid aromatic hydrocarbons that have long interested chemists for not only their remarkable blue colors but also their unusual electronic[1a–c] and biological properties.[1d,e] These important compounds are used in areas as varied as pharmaceuticals,[1f–h] cosmetics,[1i] and new molecular materials.[1j,k] Many approaches have been developed to access this family of aromatics, but low yields are not uncommon and many substitution patterns are still difficult to access among the polysubstituted azulenes.[2] We recently have described a new, flexible, and efficient approach to polysubstituted natural and non-natural azulenes through a 3-step reduction-elimination-aromatization sequence from hydroazulenones **1** (Scheme 1).[3]

Herein, we present a new direct access to polysubstituted azulenes through an unusually direct aromatization (without a dehydrogenation step) to obtain various 1-chloroazulenes (Scheme 2). This direct access to 1-chloroazulenones suppressed the 2-step reduction-elimination sequence. Hydroazulenones **1** are easily obtained by a [2+2] cycloaddition/ring expansion/elimination sequence[4] (Scheme 3).

This improvement provides selective access to chloroazulenes, precursors of natural compounds, and in addition to novel chloroazulenyl triflates converted to azulene **4** by selective



Scheme 1. Synthesis of polysubstituted chloroazulenes by 3-step reduction-elimination-aromatization sequence from chlorohydroazulenones **1**.



Scheme 2. Synthesis of azulenes from hydroazulenones **1**.

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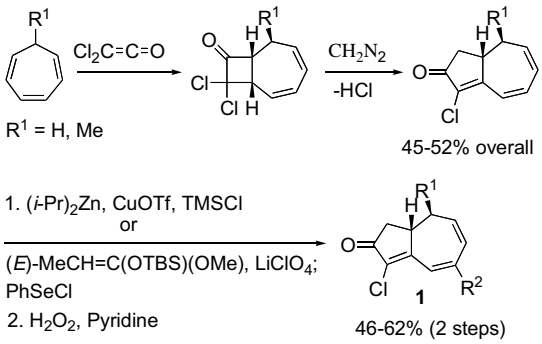


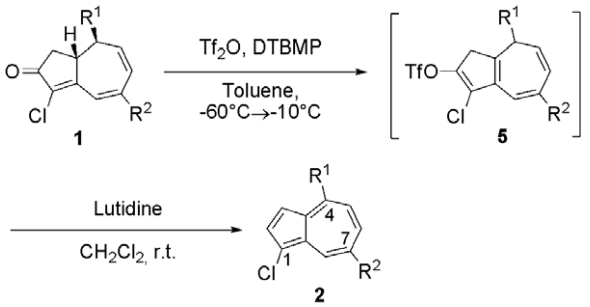
Scheme 3. Synthesis of chlorohydroazulenones **1**.

cross-coupling reactions (Scheme 2). This new direct aromatization with triflic anhydride is a very higher flexible and efficient approach to polysubstituted azulenes.

Takase et al.[5] have demonstrated by UV spectroscopy that 2-hydroxyazulenes exist in solution predominately as their ketonic form, the aromaticity energy gain being insufficient to favor the enolic form. Taking this into account, a direct aromatization of the α-chlorotrienone **1** (R^1 = Me, R^2 = H) was previously achieved in our group by trapping of the enolic form with acetic anhydride and dehydrogenation on 10% Pd/C, but elevated temperature was required, and the reaction was insufficient (only 50% yield).[3] As a result, we have sought a new more efficient aromatization procedure to obtain under mild conditions polysubstituted azulenes from the α-chlorotrienones **1**.

Initial studies were performed by exposing compound **1** (R^1 = Me, R^2 = H) to Eaton's reagent,[6] previously used by Scott et al.[7] to effect direct dehydration of a bicyclic trienone. Unfortunately, these conditions only provided traces of an unseparable azulene mixture and considerable degradation. Methanesulfonic anhydride afforded no azulenic products at all. Finally, triflic anhydride in CH_2Cl_2 was found to give encouragingly a mixture of two azulenes, **2** and **3** (R^1 = Me, R^2 = H) in 26% and 10% yields, respectively. By decreasing the reaction temperature and adding a non-nucleophilic base such as 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), it was possible to isolate and characterize[8] the unstable tetraene triflate **5b** as a reaction intermediate (Table 1). During their study, Scott et al.[7] assumed that enol derivatives such as **5** would readily isomerize via sequential hydrogen shifts and would eventually aromatize by loss of HX. Therefore, lutidine was added to the isolated **5b** to generate the chloroazulene **2b** as the unique

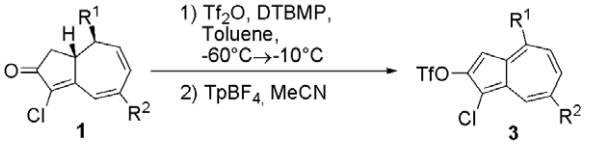
Table 1
Direct synthesis of 1-chloroazulenes **2** from α-chlorotrienones **1**



Chlorotrienone	R^1	R^2	Yield[a] (%)	Product (via **5**)
1a	H	H	42	**2a** (**5a**)
1b	Me	H	81	**2b** (**5b**)
1c	Me	*i*-Pr	73	**2c** (**5c**)
1d	Me	CH_3–CH–CO_2Me	85	**2d** (**5d**)

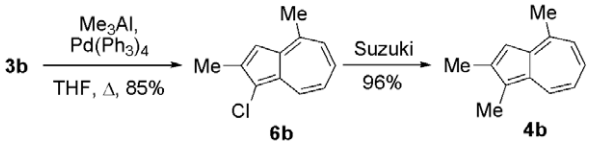
[a] Yields obtained after purification on silica gel.

Table 2
Direct synthesis of 1-chloroazulen-2-yl triflates **3** from α-chlorotrienone **1**



Chlorotrienone	R^1	R^2	Yield (%)	Product
1a	H	H	44[a] (44)[b]	**3a**
1b	Me	H	69[a] (64)[b]	**3b**
1c	Me	*i*-Pr	76	**3c**
1d	Me	CH_3–CH–CO_2Me	75	**3d**

[a] Yields obtained after purification on silica gel chromatography.
[b] Yields for one-step transformation.



Scheme 4. Synthesis of 1,2,4-trimethylazulene **4b.**

product in excellent yield.[9] Various trienones **1** were submitted to this methodology to provide the corresponding chloroazulenes **2** as the sole products. These precursors of natural and non-natural azulenes[3] are thus obtained now in good to excellent yields (Table 1).[10]

Next, the selective formation of 1-chloroazulen-2-yl triflates **3** was investigated. Azulenes display usual polarity (dipole moment),[11] which reflects their tropylium cation-cyclopentadienyl anion character. Our approach was to generate by hydride abstraction the tropylium cation, which by proton loss would be exposed to aromatize to afford the desired azulenes **3**. Indeed, addition of tropylium cation[12] ($TpBF_4$) provided the more stable (delocalized) tropylium derivatives, which rapidly aromatized.[13] The substituted azulenes **3a–d** could thus be obtained in good to excellent yields in only one[14] or two steps from the α-chlorotrienones **1** (Table 2).

These chloro-trifates **3** can be selectively coupled by using trialkyl aluminium reagents[15] to introduce a methyl group at C-2. For example, **3b** was transformed into chloroazulene **6b** in 85% yield. This in turn can be engaged in a Suzuki cross-coupling[16] to afford new non-natural 1,2,4-trimethylazulene **4b** in 96% yield (Scheme 4).[17]

This improved preparation of chloroazulenes translates into an improved synthesis of natural azulenes. For example, azulene itself can now be synthesized in just 4 steps and in 17.4% overall yield[18] from inexpensive cycloheptatriene and 1,4-dimethylazulene in 5 steps and in 34% overall yield[19] from the tropylium cation. In addition, this new and unusually direct aromatization also leads to a new type of azulene, activated toward coupling at both C-1 and C-2. These derivatives should prove interesting for the synthesis of novel azulenes by different cross-coupling reactions.

Finally, this new direct aromatization technique appears to be applicable for accessing benzene derivatives, and is still under investigation.

Acknowledgments

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8. The ^{1}H NMR data demonstrate that the structure of the tetraene triflates **5** results of a 1,5-shift of hydrogen. Synthesis of tetraene **5b**: To a stirred solution of trienone **1b** (200 mg, 1.03 mmol) and 2,6-di-*tert*butyl-4-methylpyridine (DTBMP) (634 mg, 3.09 mmol) in 20 mL of anhydrous toluene at −60 °C was added dropwise triflic anhydride (0.35 mL, 2.06 mmol). The resulting solution was allowed to warm to −10 °C and was then diluted with pentane and filtrated over celite with pentane–ether (10:3) to recover the DTBMP. The organic layer was washed with HCl (recover DTBMP), $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. The crude tetraene triflate **5b** (ca. 1.03 mmol) was used in the next step without further purification. ^{1}H NMR: δ ppm (300 MHz, $CDCl_3$): 6.76 (d, J = 11.1 Hz, 1H), 6.65 (dd, J = 11.1, 5.9 Hz, 1H), 6.10 (dd, J = 9.9, 5.8 Hz, 1H), 5.22 (dd, J = 9.9, 5.8 Hz, 1H), 3.40 (AB, δ_A = 3.38, δ_B = 3.43 ppm, J_{AB} = 24 Hz, 2H), 2.53–2.65 (m, 1H), 1.27 (d, J = 7.3 Hz, 3H).
9. By addition of lutidine to the reaction mixture containing **5b** at –10 °C, the yield of isolated chloroazulene **2b** was 33%.
10. Direct purification of the intermediates **5** over basic alumina afforded the corresponding chloroazulenes as unique product, but in lower yields (61% for **2b**).
    Synthesis of azulene **2b**: (By one step) The crude tetraene **5b** (ca. 1.03 mmol) obtained after aqueous work-up was then directly purified over basic alumina to afford 111 mg (61%) of chloroazulene **2b**. (By two steps) To a stirred solution of isolated tetraene **5b** (ca. 1.03 mmol) in 20 mL of dichloromethane was added lutidine (0.23 mL, 2.06 mmol) at 0 °C. The resulting solution was stirred at rt overnight and diluted with pentane. The organic layer was then washed with NaH_2PO_4, water, and brine, and dried over anhydrous Na_2SO_4. Purification by dry silica gel column chromatography with pentane gave 146 mg (81%) of chloroazulene **2b** (see Ref. 3).
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12. The yields were identical using triphenylcarbenium, but the purification was more difficult.
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14. Chloroazulenyl triflates can also be obtained in one pot by treatment with triflic anhydride, followed by the addition of a solution of $TpBF_4$ in acetonitrile (44% and 64%, respectively, for **3a** and **3b**).
    Synthesis of azulene **3b**: (By one step) A solution of tropylium cation (274 mg, 1.54 mmol) in 10 mL of acetonitrile was directly added to the reaction mixture containing the crude tetraene **5b** (ca. 0.51 mmol) at −10 °C. The reaction mixture was then stirred for 24 h at rt. The reaction mixture was diluted with pentane–EtOAc (10:2) and the organic layer was washed with HCl (recover DTBMP), $NaHCO_3$, water, and brine, and dried over anhydrous Na_2SO_4. Purification by dry silica gel column chromatography with pentane–EtOAc (10:1) gave 107 mg (64%) of azulene **3b**. (By two steps) To a solution of isolated tetraene **5b**, obtained after aqueous work-up, in 15 mL of acetonitrile at room temperature was added tropylium cation. The reaction mixture was stirred for 24 h and 115 mg (69%) of azulene **3b** was obtained following the same procedure described for the one-pot reaction. ^{1}H NMR: δ ppm (300 MHz, $CDCl_3$): 8.47 (d, J = 10.2 Hz, 1H), 7.67 (t, J = 9.9 Hz, 1H), 7.34 (d, J = 10.2 Hz, 1H), 7.32 (t, J = 9.9 Hz, 1H), 7.23 (s, 1H), 2.89 (s, 3H); ^{13}C NMR: δ ppm (75 MHz, $CDCl_3$): 150.4, 147.8, 138.7, 136.2, 133.7, 131.7, 129.5, 124.3, 119.0 (q, J_{C-F} = 321 Hz), 106.0, 103.3, 24.5; MS (ESI): [M+H$^+$] = 325; HRMS calcd for $C_{12}H_9ClF_3S$ [M+H$^+$] 324.9908, found 324.9916.
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17. *1,2,4-Trimethylazulene* **(4b)**: Blue crystals, mp: 47–48 °C. Anal. Calcd (%) for $C_{13}H_{14}$: C, 91.71; H, 8.29. Found: C, 91.37; H 8.45. ^{1}H NMR: δ ppm (300 MHz, $CDCl_3$): 8.15 (d, J = 9.9 Hz, 1H), 7.39 (t, J = 10.0 Hz, 1H), 7.21 (s, 1H), 7.08–6.99 (m, 2H), 2.85 (s, 3H), 2.58 (s, 3H), 2.54 (s, 3H); ^{13}C NMR: δ ppm (75 MHz, $CDCl_3$): 146.8, 143.5, 137.0, 134.6, 131.9, 125.9, 124.2, 120.6, 115.6, 24.4, 15.2, 10.5; MS (ESI): [M+H$^+$] = 171; HRMS calcd for $C_{13}H_{15}$ [M+H$^+$] 171.1168, found 171.1166.
    1-Chloro-2,4-dimethylazulene **(6b)**: ^{1}H NMR: δ ppm (400 MHz, $CDCl_3$): 8.31 (d, J = 9.6 Hz, 1H), 7.48 (t, J = 10.0 Hz, 1H), 7.21–7.12 (m, 3H), 2.85 (s, 3H), 2.62 (s, 3H); ^{13}C NMR: δ ppm (100 MHz, $CDCl_3$): 145.3, 144.1, 136.0, 135.9, 133.9, 132.7, 127.3, 122.2, 116.7, 114.2, 24.0, 14.8; MS (ESI): [M+H$^+$] = 191; HRMS calcd for $C_{12}H_{12}Cl$ [M+H$^+$] 191.0622, found 191.0620.
18. Chlorotrienone **1a** is obtained in 2 steps from cycloheptatriene in 45% overall yield. Chlorine reduction in **2a** is achieved in 92% yield (see Ref. 3).
19. Chlorotrienone **1b** is obtained from the tropylium cation in 43% overall yield (see Ref. 4b). Chlorine/methyl exchange in **2b** is achieved in 98% to give the 1,4-dimethylazulene (see Ref. 3).