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Directed *ortho* Lithiation of Sulfonylazulenes. An Efficient Method to Introduce Substituents at the 2-position of Azulene

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Abstract

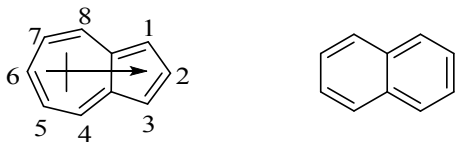
2-Lithioazulenes were successfully synthesized from 1-azulenyl *p*-tolyl sulfone **3** and *N, N*-diethyl 1-azulenylsulfonamide **4** by using directed *ortho* metallation with a directing sulfonyl group. Proton abstraction at the 2-position of azulenes was done by using lithium 2,2,6,6-tetramethylpiperidide (LTMP). The azulenyllithiums thus obtained from **3** and **4** were effectively transformed into 2-substituted azulenes in moderate to good yields by trapping with electrophiles.

Key words: Azulenes, alternant and nonalternant hydrocarbons, directed *ortho* metallation, sulfonyl group.

I. **Introduction**

Azulene is a nonalternant hydrocarbon and an isomer of alternant naphthalene. Both of these molecules exhibit physical and chemical properties quite different from each other. Naphthalene is colorless whereas azulene is deep blue due to the charge transfer with its dipole moment vector towards the five-membered ring (Chart-1). Furthermore, compared to naphthalene azulene has high electron affinity[1], low ionization potential[2,3] and in particular low aromatic resonance energy.[4]

Chart-1 Nonalternant and alternant hydrocarbons



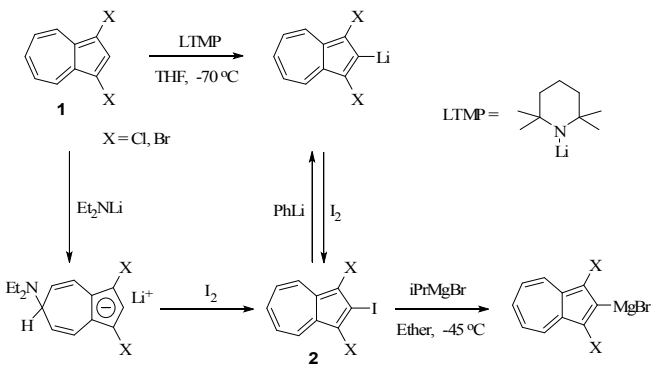
Azulene
(Nonalternant)

Naphthalene
(Alternant)

Due to the polarization of the π-electron, azulene suffers from nucleophilic addition at the 4,6,8-positions[5] and undergoes electrophilic substitution at the 1,3-positions[6], but does not show any reactivity at the 2-, 5- and 7-positions at all[7]. For this reason, azulene derivatives bearing a substituent at the 2-, 5-, or 7-position have been produced by the straightforward construction of the azulene skeleton introducing the substituent at the early stage of each method.

In contrast to the well-established research fields of benzenoid hydrocarbons, no metallated species such as lithium and Grignard derivatives appeared in azulene chemistry. Recently, we have reported a versatile method to generate 2-lithioazulenes from 1,3-dihaloazulenes by direct proton abstraction using lithium 2,2,6,6-tetramethylpiperidide (LTMP) (Scheme 1).[8] These azulenyllithiums are useful intermediates for the synthesis of 2-substituted azulenes by trapping with various electrophiles. Furthermore, the corresponding Grignard reagents as well as the lithium reagents were found to be generated through halogen–metal exchange reaction of 1,3-dihalo-2-iodoazulenes. These findings revealed that the electron-withdrawing groups effectively stabilize the anionic species of azulene to facilitate the deprotonation or halogen–metal exchange.

Scheme 1



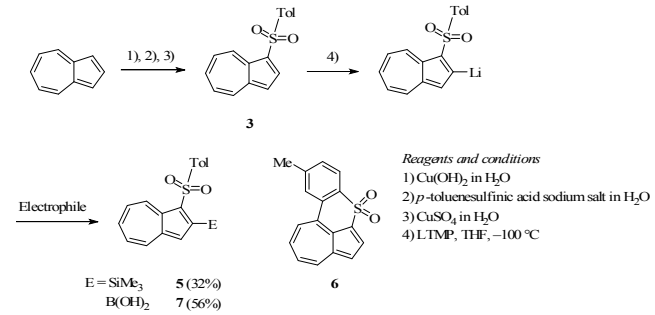
The directed *ortho* metallation is one of the most powerful methods for the elaboration of complex aromatic compounds.[9] The deprotonation of *ortho* proton is possible by strong bases to give an *ortho*-lithiated species. This species, upon treatment with electrophilic reagents, yields 1,2-disubstituted products. Although a number of *ortho* directing groups have been investigated, most of the studies have been concentrated on the examples of benzenes, ferrocenes, and heterocycles.[10] If a strong *ortho* directing group such as a sulfonyl substituent featuring strong electron-withdrawing properties is introduced into 1-position of azulene skeleton in place of the two halogen atoms of **1**, it is expected to facilitate the lithiation at the 2-position of azulene. In this paper, we report an efficient method to introduce substituents at the 2-position of azulene based on sulfonyl directed lithiation.

II. **Results and Discussion**

1-Azulenyl *p*-tolyl sulfone (**3**) was synthesized by the coupling reaction of azulene with sodium *p*-toluenesulfonate in the presence of copper salts (Scheme 2).[11] On the basis of

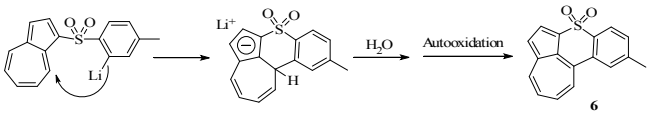
the sulfonyl group, the 2-position of azulene is considered as *ortho*-position.

Scheme 2



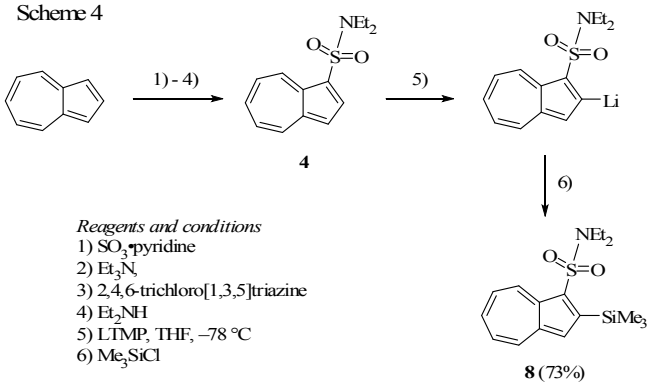
When a solution of LTMP (1.5 equiv) in THF was added to **3** in the same solvent at –70 °C, the colour of the solution of **3** immediately changed from violet to reddish-violet. After 10 min, quenching by chlorotrimethylsilane at the same temperature gave the desired 2-substituted product **5**, although the yield was very low (5%), along with cyclic azulenyl sulfone **6** (2%) and unidentifiable tarry substances. Formation of **6** suggests that the concomitant lithiation of the *p*-tolyl group proceeds and the probable mechanism of the formation of **6** is shown in scheme 3.

Scheme 3



In order to improve the yield, LTMP was added at –100 °C and the resulting solution was treated immediately with an electrophile. As expected, the yield of **5** increased to 32% and a little formation of the **6** was detected. When the 2-lithioazulene was allowed to react with boron triisopropoxide, the corresponding substituted product **7** was obtained in 56% yields. The low efficiency of trapping with electrophiles indicates that, in contrast to the lithiated species of aryl sulfones, the lithiated azulenyl sulfone is very reactive even if generated at –100 °C.[12] The two chlorine atoms of **1** seem to strongly stabilize the lithiated species compared to the sulfonyl group of **3**. In contrast, lithiation of **4**[13] gave a stable 2-lithioazulene at –78 °C by using LTMP. Thus, trimethylsilyl group was introduced into the 2-position to give **8** in 73% yield (Scheme 4).

Scheme 4



In conclusion, the present work demonstrates a convenient route for the synthesis of 2-substituted azulenes using sulfonyl substituent as a directing metalation group (DMG), which has been considered to require many reaction steps when the conventional method is used. We believe that this method is expected to have broad synthetic utility and undoubtedly will contribute to the development of the chemistry of azulene.

III. **Experimental Section**

General Comments. All reactions were carried out under argon unless otherwise noted. THF, dioxane and diethyl ether were distilled from calcium hydride under nitrogen before use. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a BRUKER AVANCE 400S spectrometer with TMS as an internal standard and coupling constants (*J*) were reported in Hertz (Hz). IR spectra were obtained as KBr pellets on a Nicolet Impect 410 spectrophotometer.

*Preparation of **3***. A solution of azulene (10 mmol in 15 mL acetonitrile) was added drop–wise into freshly prepared $Cu(OH)_2$ solution (5 mmol in 10 mL dist. water). To this solution, *p*-toluensulfonic acid sodium salt (10 mmol in 10 mL dist. water) and $CuSO_4$ (20 mmol in 10 mL dist. water) were added sequentially. The reaction mixture was then allowed to react for 4 h at 35 °C and then acetonitrile was evaporated. The resultant aqueous solution was extracted with chloroform (7 mL × 3) and the combined extracts were dried over anhydrous sodium sulfate and evaporated to leave a residue, which was chromatographed on silica gel using hexane–AcOEt (3:1) to give **3**.

*1-(p-Tolylsulfonyl)azulene (**3**)*. Violet powder; yield 84% ; mp 143-145 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.24 (3H, s), 7.22 (2H, d, *J* 8.2, ArH), 7.33 (1H, d, *J* 4.2, AzH), 7.50 (1H, t, *J* 10.0, AzH), 7.59 (1H, t, *J* 10.0, AzH), 7.86 (1H, t, *J* 10.0, AzH), 7.87 (2H, d, *J* 8.2, ArH), 8.32 (1H, d, *J* 4.2, AzH), 8.49 (1H, d, *J* 10.0, AzH), 9.33 (1H, d, *J* 10.0, AzH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.37, 117.40, 124.08, 126.52, 127.47, 127.73, 129.56, 136.56, 137.23, 138.89, 139.49, 139.87, 141.34, 142.99, 144.23; IR: 1579, 1395, 1290, 1136, 740 cm^{-1}.

*Preparation of **4***. A mixture of azulene (5 mmol) and sulfur trioxide pyridine complex (5.5 mmol) in dioxane or THF (25 mL) was stirred for 24 h at 50 °C. To this solution, triethylamine (7 mmol) and 2,4,6-trichloro[1,3,5]triazine (7 mmol) were added sequentially. The reaction mixture was then allowed to react for 12 h at 35 °C. The solvent was evaporated and thus the residue obtained was chromatographed over silica gel using hexane–AcOEt (2:1) to give 1-azulenesulfonylchloride, which was then disolved in ether (20 mL), added diethylamine (10 mmol) and stirred for 5 min. at 0 °C. The mixture was evaporated to give pure **4**.

*N,N-Diethyl 1-azulene-sulfonamide (**4**).*Violet powder; yield 34%; mp 53-55 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (6H, t, *J* 7.0), 3.27 (4H, q, *J* 7.0), 7.33 (1H, d, *J* 4.2), 7.49 (1H, t, *J* 10.0), 7.55 (1H, t, *J* 10.0), 7.85 (1H, t, *J* 10.0), 8.17 (1H, d, *J* 4.2), 8.50 (1H, d, *J* 10.0), 9.29 (1H, d, *J* 10.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.9, 41.5, 116.7, 122.8, 126.6, 126.8, 136.5, 136.6, 138.0, 139.1, 139.6, 143.0; IR: 1399, 1330, 1299, 1200, 1017, 943, 780, 697, 524 cm^{-1}.

General Procedure for the Formation of Azulenyllithium and the Reaction with Electrophiles. A typical example is exemplified by the reaction with chlorotrimethylsilane electrophile. A solution of lithium 2,2,6,6-tetramethylpiperidide (ca. 1.5 mmol) prepared from 2,2,6,6-tetramethylpiperidine (1.5 mmol) and BuLi (1.5 mmol) in THF (5 mL) at –100 °C was added to a solution of 1-azulenyl *p*-tolyl sulfone (1.0 mmol) in THF (5 mL) at the same temperature. The color of the solution immediately turned from violet to reddish-violet showing the formation of azulenyllithium. To this solution was added chlorotrimethylsilane (1.0 mmol) immediately and the resulting solution was stirred for 5 min. The reaction was quenched at –70 °C with brine (10 mL) and the mixture was extracted with ethyl acetate (7 mL × 3) and the combined extracts were dried over anhydrous sodium sulfate and evaporated to leave a residue, which was chromatographed over silica gel using hexane–AcOEt (3:1) to give **5**.

*1-(p-Tolylsulfonyl)-2-trimethylsilylazulene (**5**)*. Violet powder; yield 32%; mp 129-131 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.50 (9H, s), 2.33 (3H, s), 7.18 (2H, d, *J* 8.2), 7.48 (1H, t, *J* 10.0), 7.49 (1H, t, *J* 10.0), 7.54 (1H, s), 7.69 (2H, d, *J* 8.2), 7.82 (1H, t, *J* 10.0), 8.46 (1H, d, *J* 10.0), 9.18 (1H, d, *J* 10.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.5, 21.4, 126.0, 126.4, 127.3, 127.6, 129.3, 136.3, 138.8, 139.9, 140.0, 142.2, 142.5, 143.8, 155.8; IR: 1407, 1315, 1294, 1247, 1185, 1138, 1082, 842, 670, 539 cm^{-1}.

*10-Methyl-7-thia-naphtho[3,2,1-cd]azulene 7,7-dioxide (**6**)*. Blue powder; yield 2%; mp 250−251 °C, ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.54 (3H, s), 7.46 (1H, d, *J* 4.4), 7.54 (1H, dd, *J* 8.0), 7.61 (1H, t, *J* 10.0), 8.00 (1H, t, *J* 10.0), 8.17 (1H, s), 8.30 (1H, d, *J* 8.0), 8.40 (1H, d, *J* 4.4), 8.45 (1H, d, *J* 10.0), 8.58 (1H, d, *J* 10.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.9, 120.4, 124.6, 124.7, 127.9, 128.2, 130.6, 131.8, 132.9, 133.0, 136.1, 137.7, 138.4, 139.7, 142.2, 145.0; IR: 1385, 1270, 1258, 1202, 1132, 797, 610, 540 cm^{-1}.

*1-(Tolylsulfonyl)-2-azulenylboronic acid (**7**)*. Violet powder; yield 56%; mp 170−172 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.33 (3H, s), 6.84 (2H, s), 7.21 (2H, d, *J* 8.3, ArH), 7.54 (1H, t, *J* 9.6, AzH), 7.63 (1H, t, *J* 10.1, AzH), 7.78 (2H, d, *J* 8.3, ArH), 7.92 (1H, t, *J* 9.6, AzH), 7.94 (1H, s), 8.55 (1H, d, *J* 9.4, AzH), 9.61 (1H, d, *J* 10.2, AzH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.1, 121.5, 126.2, 126.9, 128.0, 128.3, 129.8, 135.6, 137.3, 139.4, 140.4, 141.4, 143.1, 144.2; IR: 1453, 1416, 1348, 1328, 1275, 1129, 1080, 744, 665, 562 cm^{-1}.

*1-(N,N-Diethylaminosulfonyl)-2-trimethylsilylazulene (**8**)*. Dark violet powder; yield 74%; mp 77−78 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.47 (9H, s), 1.04 (6H, t, *J* 7.1), 3.30 (4H, q, *J* 7.1), 7.46 (1H, t, *J* 7.2), 7.48 (1H, s), 7.50 (1H, t, *J* 7.7), 7.82 (1H, t, *J* 9.9), 8.44 (1H, d, *J* 9.5), 9.00 (1H, d, *J* 10.0); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 0.2, 13.1, 40.1, 125.5, 126.6, 127.0, 127.2, 136.1, 138.3, 138.5, 139.7, 143.2, 155.8; IR: 1577, 1463, 1404, 1346, 1241, 1181, 834, 693, 530 cm^{-1}.

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1. Becker, R. S. and E. Chen, 1966. Extension of Electron Affinities and Ionization Potentials of Aromatic Hydrocarbons. *J. Chem. Phys.* ***45***, 2403–2410.
2. Huebner, R. H., W. F. Frey and R. N. Compton, 1973. Threshold electron excitation of azulene. *Chem. Phys. Lett.* ***23***, 587–591.
3. Clark, P. A., F. Brogli and E. Heilbronner, 1972. The π-Orbital Energies of the Acenes. *Helv. Chim. Acta*, ***55***, 1415–1428.
4. Dewar, M. J. S. and C. D. Llano, 1968. Ground states of conjugated molecules. XI. Improved treatment of hydrocarbons. *J. Am. Chem. Soc.* ***91***, 789–795.
5. (a) Hafner, K. and H. Weldes, 1957. Zur Kenntnis Der Azulene II. Die Substitution Von Azulenen Mit Metallorganischen Verbindungen. *Justus Liebigs Ann. Chem.* ***606***, 90–99.

   (b) McDonald, R. N., H. E. Petty, N. L. Wolfe and J. V. Paukstelis, 1974. Nonbenzenoid aromatic systems. X. Formation, nuclear magnetic resonance spectral identification, and reactions of both Meisenheimer type and methyleneazulenate anions. *J. Org. Chem.* ***39***, 1877–1887.
6. Anderson Jr., A. G., J. A. Nelson and J. J. Tazuma, 1953. Azulene. III. Electrophilic Substitution. *J. Am. Chem. Soc.* ***75,*** 4980–4989.
7. (a) Nozoe, T., S. Seto, S. Matsumura and Y. Murase, 1962. The Synthesis of Azulene Derivatives from Troponoids. *Bull. Chem. Soc. Jpn.* ***35***, 1179–1188.

   (b) McDonald, R. N, J. M. Richmond, J. R. Curtis, H. E. Petty and T. L. Hoskins, 1976. Nonbenzenoid aromatic systems. XII. Synthesis of 2-, 3-, and 6-substituted 2-(1-azulyl)ethanols and their tosylate esters. *J. Org. Chem.* ***41***, 1811–1821.
8. Kurotobi, K., H. Tabata, M. Miyauchi, A. F. M. M. Rahman, K. Migita, T. Murafuji, Y. Sugihara, H. Shimoyama and K. Fujimori, 2003. The First Generation of Azulenyl-Lithium and -Magnesium: A Novel, Versatile Method of Introducing a Substituent at the 2-Position of an Azulene Skeleton. *Synthesis*, ***1***, 30–34.
9. (a) Gilman, H. and R. L. Bebb, 1939. Relative Reactivities of Organometallic Compounds. XX. Metalation. *J. Am. Chem. Soc.* ***61***, 109–112.

   (b) Wittig, G. and G. Fuhrman, 1940. Über das Verhalten der halogenierten Anisole gegen Phenyl-lithium (V. Mitteil. über die Reaktionsweise des Phenyl-lithiums), *Chem. Ber.* ***73***, 1197–1218.

   (c) Puterbaugh, W. H. and C. R. Hauser, 1964. Metalation of *N*-Methylbenzamide with Excess *n*-Butyllithium. Condensations with Electrophilic Compounds to Form ortho Derivatives. Cyclizations. *J. Org. Chem.* ***29***, 853–856.

   (d) Omae, I., 1979. Organometallic intramolecular-coordination compounds containing a nitrogen donor ligand. *Chem. Rev.* ***79***, 287–321.
10. (a) Snieckus, V., 1990. Directed ortho metalation. Tertiary amide and O-carbamate directors in synthetic strategies for polysubstituted aromatics. *Chem. Rev.* ***90***, 879–933.

    (b) Murafuji, T., K. Satoh, Y. Sugihara and N. Azuma, 1998. The First X-ray Structure Determination of an Optically Pure Bismuthane. *Organometallics*, ***17***, 1711–1715.

11. Nefedov, V. A. and L. V. Kryuchkova, 1977. Oxidative Substitution XII. Direct synthesis of sulfones. *J. Org. Chem.*(USSR) ***13***, 1601–1604.

12. Suzuki, H. and T. Murafuji, 1992. A new general method for the synthesis of chiral triarylbismuthines based on the intramolecular coordination by a sulfonyl group. *J. Chem. Soc., Chem. Commun.* ***16***, 1143–1144.

13. Tomiyama, T., M. Yokota, S. Wakabayashi, K. Kosakai and T. Yanagisawa, 1993. Design, synthesis, and pharmacology of 3-substituted sodium azulene-1-sulfontes and related compounds: non-prostanoid thromboxane A2 receptor antagonists. *J. Med. Chem.* ***36***, 791–800.