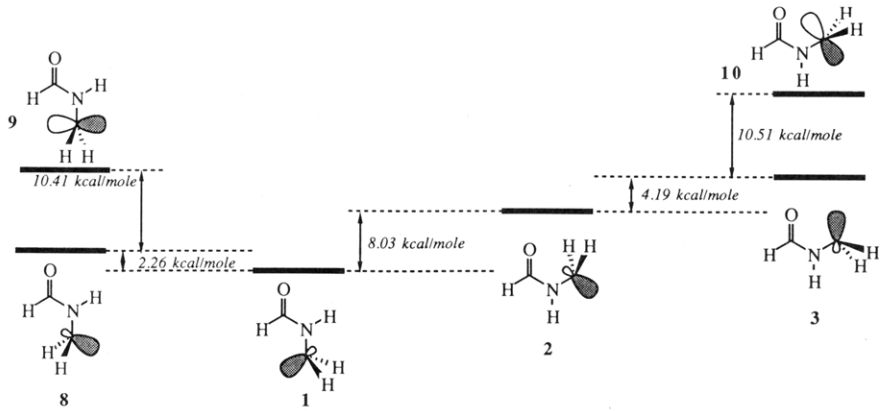

Figure 2. Relative energies of *N*-methylformamide anion geometries (fully optimized using 6-31G* basis set).

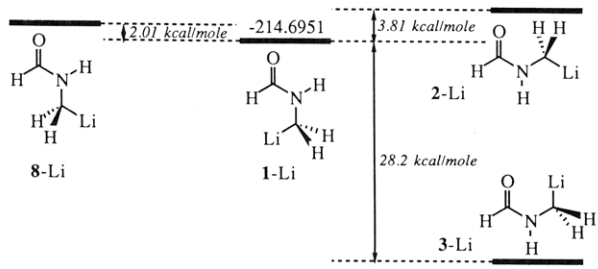

Figure 3. Relative energies of *N*-methylformamide lithium (fully optimized using 6-31G* basis set).

nomenon is readily accounted for by the relative energies and stereoelectronic arguments presented by Bach.[4] The former effect has been postulated to result from the chelation of the lithium by the amide carbonyl. If chelation is important, the energy gained would have to be substantial in order to explain the chemistry, since **3** is 10–12 kcal/mol less stable than **1**, and the calculated difference for the corresponding esters **6** and **7** (13 kcal/mol)[3] is probably not enough.

The total energy difference between **1**, **8**, and **2** (6-31G* level) is about 8 kcal/mol but decreases to less than 4 kcal/mol when a lithium cation is added. The lowering of energy of **3**-Li, relative to the other lithiated species, is dramatic: the difference between the anti and syn isomers (**1**-Li and **3**-Li) is 28 kcal/mol. Considering that for the free anions **3** is 12 kcal/mol less stable than **1**, the 28 kcal/mol difference between **3**-Li and **1**-Li is remarkable. The energy difference is considerably larger than the calculated difference for the two ester anions **6** and **7**.[3] It is likely that the major reason for the larger effect in the amide anions is the larger dipole and hence greater charge on oxygen created by delocalization of the amide nitrogen lone pair.

The geometries of the lithiated species (Table 2, supplementary material) are quite similar, with the exception of **3**-Li, for which the N–C^2–Li bond angle is compressed to 93°. The fact that the oxygen is responsible for this bond angle compression is seen from the Li–O bond distance of 1.86 Å.[11] Note, however, that the effect of chelation has little effect on the C=O and C^1–N bond lengths: the C=O bond is 1.20 Å for **1**-Li, **2**-Li, and **8**-Li, and 1.23 Å for **3**-Li; the C^1–N bond lengths are 1.33 Å for **1**-Li, 1.34 Å for **2**-Li and 8-Li, and 1.31 Å for **3**-Li. Otherwise, the stereoelectronic effects that dictate anion geometry[4] appear to be fully operative here.[12]

(11) In an effort to discount "overchelation" by the lithium in **3**-Li, attempts were made to calculate the relative energies of **3**-Li and **1**-Li, each solvated by three water molecules. No conclusions could be drawn due to lack of convergence in these attempts.

Summary

A new low-energy geometry for *N*-methylformamide anion has been calculated, and the barrier to in-plane inversion is estimated to be 10 kcal/mol for both the syn and anti amide geometries. The presence of a lithium cation drastically changes the relative energy of one of the four isomeric *N*-methylformamide anion structures. Specifically: the isomer **3**, which models chemically important species such as piperidine amide anions, is 12 kcal/mol higher in energy than its isomer **1**, when calculated with the 6-31G* basis set. In the presence of a lithium ion, **3**-Li is 28 kcal/mol more stable than **1**-Li. We attribute this relative energy change to chelation of the lithium by the carbonyl oxygen. It therefore seems most appropriate to call these species "dipole-stabilized organometallics."

Acknowledgment. We thank the National Institutes of Health, Grant No. GM-37985, for financial support.

Registry No. **3**-Li, 120446-29-9; $HCONHCH_2^-$, 78715-78-3.

Supplementary Material Available: Table 2, containing the geometries of all the calculated structures (1 page). Ordering information is given on any current masthead page.

(12) Semiempirical (MNDO) calculations on lithiated aminooxazolines also show a preference for maintaining a relatively flat chelated metallocycle: see ref 7. For an X-ray crystal structure of a pivaloylisoquinoline Grignard with a flat metallocyclic ring, see: Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1–13.

Nucleophilic Reaction of Azulene Derivatives with Some Ketone Enolates

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While general nucleophilic aromatic substitution occurs by addition–elimination mechanisms,[1] photoinduced $S_{RN}1$ reaction of haloarenes is known to proceed by an electron transfer from the nucleophile, and hence no extra acti-

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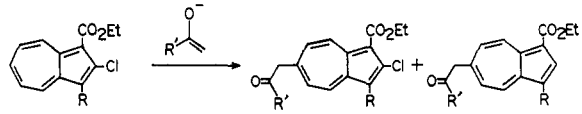
Table I. Reaction of Azulenes with Ketone Enolates

entry	azulenes	ketones	reaction conditions[a]	product (yield, %) 4-substituted	6-substituted
1	1	^{t}BuCOMe	−60 °C, 10 min	–	**2a** (23), **3a** (45)
2		Me_2CO	0 °C, 20 min	–	**2b** (22), **3b** (22)
3		$MeCOCH_2CO_2Me$	0 °C, 2 h[b]	–	**3c** (29)
4	4	^{t}BuCOMe	−35 °C, 30 min	–	**5a** (73)
5	6	^{t}BuCOMe	0 °C, 2 h	**8a** (37)	**9a** (37)
6		$PhCMe_2COMe$	rt,[c] 8 h	–	**9d** (41)
7		Et_2CO	rt, 3 h	no reaction	
8		$^i Pr_2CO$	rt, 3 h	no reaction	
9	7	^{t}BuCOMe	0 °C, 2 h	**10a** (8)	**11a** (23)

[a] KO^{t}Bu/THF. [b] NaH–BuLi/THF. [c] Rt = room temperature.

vating group is required on the aromatic ring. Therefore, the photoinduced $S_{RN}1$ reaction has been the subject of intensive investigations[2] since its discovery by Kim and Bunnett.[3] Azulene is known to have almost the same electron affinity to anthracene,[4] accordingly haloazulenes are expected to be susceptibile to the photoinduced $S_{RN}1$ reaction as are haloanthracenes.[5]

In our continuous effort to develop the synthetic application of this unique reaction,[6] we examined the reactivity of 2-haloazulenes with a simple ketone enolate under the typical $S_{RN}1$ reaction conditions (irradiation in liquid ammonia). The product obtained, however, is not the one expected for this reaction but 6-substituted azulene, and it is found that the reaction is completed before photoirradiation.



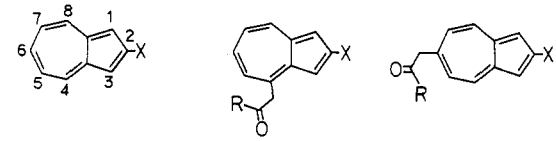
1 R = CO_2Et **2a-b** R = CO_2Et **3a-c** R = CO_2Et
4 R = H **5a** R = H

(a: R′ = t-Bu, b: R′ = Me, c: R′ = CH_2CO_2Me)

Generally two types of reactions on azulenes with carbon nucleophiles have been known. One is the formal $S_{RN}1$ type displacement reaction of a halogeno substituent with reagents such as $^-CH(CO_2R)_2$,[7] $^-CH(CN)(CO_2R)$,[7] $^-CH(CN)_2$,[8] and ^-CN.[7,9] Prerequisite for the former three cases is an electron-withdrawing substituent at 1- or 3-position. The other is addition of the reagents at the 4- or 6-position with the formation of dihydroazulenes. A wide variety of carbon nucleophiles [RLi,[10,11] RMgX,[12] RC≡CLi,[13] $^-CH_2PO(OR)_2$, $^-CH(SR)_2$, $^-CH(CN)(NR_2)$,[14] $^-C(SR)_3$[15]] has been reported to give the product by the second type of addition reaction. However, to our surprise, no such report of the reaction with a simple ketone enolate on azulenes has been given so far.[16] In this paper we describe the convenient synthesis of 6-substituted azulenes by the reaction with ketone enolates as new nucleophiles.

The reaction of diethyl 2-chloroazulene-1,3-dicarboxylate (**1**)[7] with pinacolone in the presence of KO^{t}Bu in liquid NH_3 or in THF gave a mixture of 6-substituted azulene derivatives (**2a** and **3a**) after the oxidation with chloranil (Table I). The yield of products was better in THF than in liquid NH_3. The position of the substituent of **2a** and **3a** was determined on the basis of the ^{1}H NMR spectra, which showed symmetrical signals due to the aromatic protons at δ 7.52 and 9.41 (each 2 H, d, J = 11 Hz) (**2a**) and at δ 7.56 and 9.69 (each 2 H, d, J = 11 Hz) (**3a**). The presence of a signal due to the C_2 proton at δ 8.80 (1 H, s) confirmed the dechlorinated structure (**3a**). Other results are summarized in Table I.

While nucleophilic substitution at the C_2 position of **1** with methyl acetoacetate monoanion has been reported,[7] its dianion attacks only at the C_6 position (entry 3). The monoester (**4**)[7] also reacts with pinacolone enolate to give a single 6-substituted product (**5a**) (entry 4). Regiospecific attack of nucleophiles on the 6-position of the azulene nucleus is found as long as at least one ester carbonyl group is present on C_1 or C_3 of azulene (**1** and **4**). On the other hand, the absence of the ester carbonyl on the azulene nucleus [2-chloroazulene (**6**) or azulene itself (**7**)] afforded a mixture of 4- (**8a** and **10a**) and 6-substituted azulene derivatives (**9a** and **11a**) in 1:1 to 1:3 ratios (entries 5 and 9). It is noted that even in the latter case the preferential attack at the C_6 position was observed when a more bulky ketone was used (entry 6). The use of the secondary or tertiary (diethyl or diisopropyl) ketone gave none of the substituted products under the same conditions (entries 7 and 8).



6 X = Cl **8a** X = Cl **9a,d** X = Cl
7 X = H **10a** X = H **11a** X = H

(a: R = t-Bu, d: R = CMe_2Ph)

The regioselectivity found in the reaction is worthy to discuss in detail. It is known that while hard nucleophiles attack preferentially at the 4-position of the azulene ring (charge control), soft nucleophiles react at the 6-position (orbital control).[14] From this criterion, simple ketone enolates are classified to be rather soft nucleophiles for azulenes, and hence orbital interaction predominates over charge interaction in this reaction. According to Klop-

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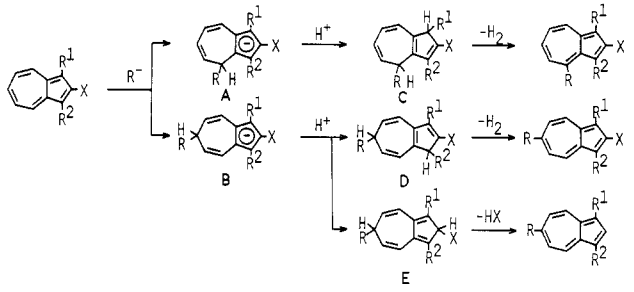
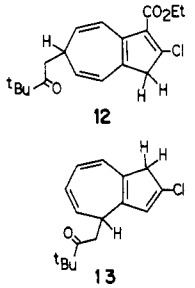
Scheme I



man's interpretation[17] for the HSAB principle,[18] the orbital interaction energy can be expressed in second-order perturbation term as

$$\Delta E = \frac{(C_a C_b \beta)^2}{|E_a - E_b|}$$

where E_a and E_b are frontier orbital energies of the nucleophile and an azulene, and C_a and C_b are AO (atomic orbital) coefficients in their orbitals. From MO calculations (CNDO/S) it is found that there is no sizable difference in the AO coefficients between 1 and 7 (1, C_4 = −0.426, C_6 = 0.510; 7, C_4 = −0.432, C_6 = 0.516). Therefore the denominator contributes to the difference in selectivity. The energy level of the LUMO in 1 (−2.3406 eV) is lower than that of 7 (−2.0653 eV), thus the energy difference between the HOMO of the acetone enolate[19] (−3.6996 eV) is smaller in 1 than in 7. The orbital interaction energy of 1 is therefore larger than 7. The observed high selectivity for 1 can then be successfully explained by the larger contribution of the orbital interaction term in 1 than in 7.



12

13

Dihydroazulenes were isolated as intermediates by careful workup of the reaction mixture under argon in the reaction of monoester 4 and 2-chloroazulene with pinacolone. On the basis of ^{1}H NMR spectral data (see the Experimental Section), the structures of these intermediates were elucidated to be the 3,6- and the 1,4-dihydro derivatives (**12** and **13**), respectively. They were converted to the corresponding azulene derivatives (**12**, **5a**; **13**, **8a**) by treatment with chloranil. These results support the mechanisms summarized in Scheme I. The nucleophile attacks at the 4- or 6-position of the azulene nucleus. The resulting cyclopentadienyl anion (A or B) is then protonated to produce the corresponding dihydro derivative (C or D). The dechlorinated products (**3a–c**) are probably formed by dehydrochlorination of the 2,6-dihydro intermediate (E).

Experimental Section

General. ^{1}H NMR spectra were recorded on Hitachi R-22 (90 MHz) spectrometers. Chemical shifts are reported in δ (ppm downfield from Me_4Si) using the following abbreviations: s, singlet; br s, broad singlet; d, doublet; t, triplet; q, quartet; m, multiplet. All melting points are uncorrected. IR spectra were recorded on a Hitachi 260-10 spectrometer. Column chromatography was performed using Merck silica gel (70–230 mesh).

Reaction of Diethyl 2-Chloroazulene-1,3-dicarboxylate (1) with Pinacolone Enolate. To a cooled solution (−60 °C) of 1 (50 mg, 0.16 mmol) and pinacolone (0.10 mL, 0.60 mmol) in dry THF (5 mL) was added KO^{t}Bu (67 mg, 0.60 mmol). After stirring for 10 min at −60 °C, the mixture was acidified with dilute hydrochloric acid and extracted with benzene. The organic extract was washed with water, dried (Na_2SO_4), and concentrated. The residue that contained dihydroazulene derivatives was then oxidized with chloranil in benzene. The mixture was concentrated to dryness and chromatographed on silica gel (10% ethyl acetate in benzene eluent) to give diethyl 6-(3,3-dimethyl-2-oxobutyl)-azulene-1,3-dicarboxylates (**2a** and **3a**) (ca. 1:2 mixture based on the ^{1}H NMR spectral data, 43 mg, 68%). Further purification using HPLC (SI60-5, 7.5 × 300 mm column, 10% acetone in hexane eluent) afforded the authentic samples. **2a** as red needles: mp 143–145 °C (EtOH); IR (KBr) 1692, 1667 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.24 (9 H, s, $C(CH_3)_3$, 1.46 (6 H, t, J = 7, ethyl CH_3), 4.10 (2 H, s, $COCH_2$), 4.48 (4 H, q, J = 7, ethyl CH_2), 7.52 (2 H), d, J = 11, H5,7), 9.41 (2 H, d, J = 11, H4,8). Anal. Calcd for $C_{22}H_{25}ClO_5$: C, 65.26; H, 6.22; Cl, 8.76. Found: C, 65.03; H, 6.41; Cl, 8.95. **3a** as red needles: mp 146–148 °C (EtOH); IR (KBr) 1677 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25 (9 H, s, $C(CH_3)_3$, 1.44 (6 H, t, J = 7, ethyl CH_3), 4.13 (2 H, s, $COCH_2$), 4.43 (4 H, q, J = 7, ethyl CH_2), 7.56 (2 H, d, J = 11, H5,7), 8.80 (1 H, s, H2), 9.69 (2 H, d, J = 11, H4,8). Anal. Calcd for $C_{22}H_{26}O_5$: C, 71.33; H, 7.08. Found: C, 71.42; H, 7.29.

Reaction of 1 with Acetone Enolate. A mixture of 1 (53 mg, 0.17 mmol), acetone (0.04 mL, 0.52 mmol), and KO^{t}Bu (58 mg, 0.52 mmol) in dry THF (5 mL) was stirred for 20 min at 0 °C. After the usual workup, the crude product was oxidized with chloranil and chromatographed on silica gel (10% ethyl acetate in benzene eluent) to give diethyl 6-(2-oxopropyl)azulene-1,3-dicarboxylates (**2b** and **3b**) (ca. 1:1 mixture based on the ^{1}H NMR spectral data, 25 mg, 44%). Further purification using HPLC (SI60-5, 7.5 × 300 mm column, 15% acetone in hexane eluent) afforded the authentic samples. **2b** as orange needles: mp 145–146 °C (EtOH); IR (KBr) 1712, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47 (6 H, t, J = 7, ethyl CH_3), 2.27 (3 H, s, $COCH_3$), 4.02 (2 H, s, $COCH_2$), 4.50 (4 H, q, J = 7, ethyl CH_2), 7.57 (2 H, d, J = 11, H5,7), 9.44 (2 H, d, J = 11, H4,8). Anal. Calcd for $C_{19}H_{19}ClO_5$: C, 62.90; H, 5.28; Cl, 9.77. Found: C, 62.52; H, 5.15; Cl, 10.12. **3b** as red needles: mp 163–164 °C (EtOH); IR (KBr) 1712, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.44 (6 H, t, J = 7, ethyl CH_3), 2.26 (3 H, s, $COCH_3$), 4.04 (2 H, s, $COCH_2$), 4.44 (4 H, q, J = 7, ethyl CH_2), 7.59 (2 H, d, J = 11, H5,7), 8.82 (1 H, s, H2), 9.72 (2 H, d, J = 11, H4,8). Anal. Calcd for $C_{19}H_{20}O_5$: C, 69.50; H, 6.14. Found: C, 69.27; H, 6.28.

Reaction of 1 with Methyl Acetoacetate Dianion. To the solution of methyl acetoacetate dianion, prepared from methyl acetoacetate (0.26 mL, 2.42 mmol), NaH (60%, 191 mg), and n-BuLi (2.4 mmol) in dry THF (20 mL) was added 1 (249 mg, 0.81 mmol) at 0 °C. The mixture was stirred for 2 h at the same temperature. After the usual workup, the crude product was oxidized with chloranil and chromatographed on silica gel (30% ethyl acetate in benzene eluent) to give diethyl 6-(3-(methoxycarbonyl)-2-oxopropyl)azulene-1,3-dicarboxylate (**3c**) (91 mg, 29%) as red needles: mp 161–162 °C (EtOH); IR (KBr) 1747, 1700, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (6 H, t, J = 7, ethyl CH_3), 3.53 (2 H, s, $COCH_2$), 3.72 (3 H, s, CO_2CH_3), 4.17 (2 H, s, $COCH_2$), 4.40 (4 H, q, J = 7, ethyl CH_2), 7.58 (2 H, d, J = 11, H5,7), 8.80 (1 H, s, H2), 9.72 (2 H, d, J = 11, H4,8). Anal. Calcd for $C_{21}H_{23}O_7$: C, 65.27; H, 5.74. Found: C, 65.55; H, 5.81.

Reaction of Ethyl 2-Chloroazulene-1-carboxylate (4) with Pinacolone Enolate. A mixture of 4 (53 mg, 0.23 mmol), pi-

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(19) Geometry of acetone enolate is obtained from the crystallographic analysis of pinacolone enolate (Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1986**, *108*, 462).

nacolone (0.08 mL, 0.68 mmol), and KO^{t}Bu (76 mg, 0.68 mmol) in dry THF (5 mL) was stirred for 30 min at −35 °C. After the addition of water, the mixture was extracted with benzene under argon. The organic extract was concentrated, and the residue was purified by column chromatography on silica gel (benzene eluent) to give 3,6-dihydroazulene derivative **12** as a colorless oil: ^{1}H NMR (CCl_4) δ 1.11 (9 H, s, $C(CH_3)_3$), 2.26–2.48 (1 H, m, H6), 2.75 (2 H, d, J = 7, $COCH_2$), 3.50 (2 H, s, H2), 4.99 (1 H, dd, J = 4, 10, H5 or H7), 5.06 (1H, dd, J = 4, 10, H5 or H7), 6.22 (1 H, d, J = 10, H4), 6.73 (1 H, d, J = 10, H8). This dihydro compound (**12**) and the other fractions containing **12** were oxidized with chloranil and chromatographed on silica gel (benzene eluent) to give ethyl 2-chloro-6-(3,3-dimethyl-2-oxobutyl)azulene-1-carboxylate (**5a**) (54.6 mg, 73%) as red needles: mp 115–116 °C (hexane); IR (KBr) 1707, 1672 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (9 H, s, $C(CH_3)_3$), 1.43 (3 H, t, J = 7, ethyl CH_3), 3.82 (2 H, s, $COCH_2$), 4.36 (2 H, q, J = 7, ethyl CH_2), 7.00 (1 H, s, H3), 6.95–7.30 (2 H, m, H4,5), 8.01 (1 H, d, J = 11, H7), 9.30 (1 H, d, J = 11, H8). Anal. Calcd for $C_{19}H_{21}ClO_3$: C, 68.56; H, 6.36; Cl, 10.65. Found: C, 68.37; H, 6.34; Cl, 10.64.

Reaction of 2-Chloroazulene (6) with Pinacolone Enolate. A mixture of **6** (105 mg, 0.65 mmol), pinacolone (0.26 mL, 2.1 mmol), and KO^{t}Bu (230 mg, 2.0 mmol) in dry THF (10 mL) was stirred for 2 h at 0 °C. After the addition of water, the mixture was extracted with benzene under argon atmosphere. The organic extract was concentrated, and the residue was purified by column chromatography on silica gel (50% benzene in hexane eluent) to give 1,4-dihydro derivative **13** as a colorless oil: ^{1}H NMR (CCl_4) δ 0.98 (9 H, s, $C(CH_3)_3$), 2.41 (2 H, d, J = 7, $COCH_2$), 3.20 (2 H, s, H1), 3.64 (1 H, br q, J = 7, H4), 5.45 (1 H, dd, J = 8, 10, H5), 5.9–6.3(2 H, m, H6, 7), 6.19 (1 H, br s, H3), 6.48 (1 H, d, J = 10, H8). Oxidation of **13** with chloranil gave 4-(3,3-dimethyl-2-oxobutyl)-2-chloroazulene (**8a**) as violet needles: mp 64–65 °C (hexane); IR (KBr) 1697 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.26 (9 H, s, $C(CH_3)_3$), 4.22 (2 H, s, $COCH_2$), 6.9–7.5 (5 H, m, H1,3,5,6,7), 8.14 (1 H, d, J = 10, H8). Anal. Calcd for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57; Cl, 13.60. Found: C, 73.70; H, 6.80; Cl, 13.50.

The other fractions containing dihydroazulenes were oxidized with chloranil and chromatographed on silica gel (10% ethyl acetate in hexane eluent) to give **8a** and 6-(3,3-dimethyl-2-oxobutyl)-2-chloroazulene (**9a**) (125 mg, 74%, **8a**:**9a** = ca. 1:1 on the basis of ^{1}H NMR spectral data). Further purification using HPLC (SI60-5, 7.5 × 300 mm column, 5% acetone in hexane eluent) afforded the authentic samples. **9a** as violet needles: mp 165–167 °C (hexane); IR (KBr) 1697 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.20 (9 H, s, $C(CH_3)_3$), 3.87 (2 H, s, $COCH_2$), 6.99 (2 H, d, J = 11, H5,7), 7.12 (2 H, s, H1,3), 8.04 (2 H, d, J =: 11, H4,8). Anal. Calcd for $C_{16}H_{17}ClO$: C, 73.70; H, 6.57; Cl, 13.60. Found: C, 73.73; H, 6.87; Cl, 13.65.

Reaction of 6 with 3-Methyl-3-phenyl-2-butanone Enolate. A mixture of **6** (50 mg, 0.31 mmol), 3-methyl-3-phenyl-2-butanone (150 mg, 0.93 mmol), and KO^{t}Bu (105 mg, 0.93 mmol) in dry THF (5 mL) was stirred for 8 h at room temperature. After the usual workup, the crude product was oxidized with chloranil and chromatographed on silica gel (benzene eluent) to give 1-(2-chloro-6-azulyl)-3-methyl-3-phenyl-2-butanone (**9d**) (41 mg, 41%) as blue prisms: mp 91–92 °C (hexane); IR (KBr) 1707 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.51 (6 H, s, CH_3), 3.54 (2 H, s, $COCH_2$), 6.72 (2 H, d, J = 10, H5,7), 7.07 (2 H, s, H1,3), 7.28 (5 H, s, C_6H_5), 7.92 (2 H, d, J = 10, H4,8). Anal. Calcd for $C_{21}H_{19}ClO$: C, 78.13; H, 5.93; Cl, 10.98. Found: C, 78.05; H, 6.12; Cl, 10.95.

Reaction of Azulene (7) with Pinacolone Enolate. A mixture of **7** (75 mg, 0.59 mmol), pinacolone (0.22 mL, 1.76 mmol), and KO^{t}Bu (200 mg, 1.78 mmol) in dry THF (4 mL) was stirred for 2 h at 0 °C. After the usual workup, the crude product was oxidized with chloranil and chromatographed on silica gel (Waco gel 300, 40% hexane in benzene eluent) to give 1-(6-azulyl)-3,3-dimethyl-2-butanone (**11a**) (30.1 mg, 23%) as blue needles: mp 101–103 °C; IR (KBr) 1692 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.19 (9 H, s, $C(CH_3)_3$), 3.89 (2 H, s, $COCH_2$), 6.92 (2 H, d, J = 10, H5,7), 7.24 (2 H, d, J = 4, H1,3), 7.74 (1 H, t, J = 4, H2), 8.16 (2 H, d, J = 10, H4,8). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.70; H, 8.24.

Further elution afforded 1-(4-azulyl)-3,3-dimethyl-2-butanone (**10a**) (10.3 mg, 8%) as blue prisms: mp 115–119 °C (hexane); IR (KBr) 1705 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.24 (9 H, s, $C(CH_3)_3$), 4.31 (2 H, s, $COCH_2$), 6.85–7.60 (5 H, m, H1,3,5,6,7), 7.73 (1 H, t, J = 4, H2), 8.26 (1 H, d, J = 10, H8). Anal. Calcd for $C_{16}H_{18}O$: C, 84.91; H, 8.02. Found: C, 84.67; H, 8.26.

Registry No. **1**, 36044-40-3; **2a**, 120418-45-3; **2b**, 120418-47-5; **3a**, 120418-46-4; **3b**, 120418-48-6; **3c**, 120418-49-7; **4**, 54522-71-3; **5a**, 120418-50-0; **6**, 36044-31-2; **7**, 275-51-4; **8a**, 120418-51-1; **9a**, 120418-52-2; **9d**, 120418-53-3; **10a**, 120418-54-4; **11a**, 120418-55-5; **12**, 120418-43-1; **13**, 120418-44-2; ^{t}BuCOMe, 75-97-8; Me_2CO, 67-64-1; $MeCOCH_2CO_2Me$, 105-45-3; $PhCMe_2COMe$, 770-85-4; Et_2CO, 96-22-0; $^i Pr_2CO$, 565-80-0.

Alkylthio Aromatic Amines

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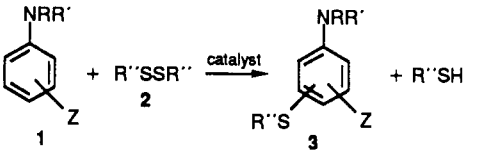
We recently reported that the aluminum phenoxide-catalyzed reaction of phenols with alkyl disulfides provides a superior synthesis of *o*-(alkylthio)phenols.[2] Our interests in ortho-alkylated phenols and ortho-alkylated aromatic amines prompted us to investigate whether alkylthio aromatic amines could be similarly prepared. Except for the preparation of sulfenamides,[3] the synthetic utility of the reaction of aromatic amines with alkyl disulfides has remained unexplored. We report that moderate to good yields of alkylthio aromatic amines can be achieved by reacting aromatic amines with aliphatic disulfides in the presence of Lewis acid catalysts, particularly aluminum chloride and copper iodide (Table I). Alkylthiation is accomplished either by heating a stirred mixture of catalyst, disulfide, and aromatic amine to a predetermined temperature (method A) or by slow addition of the disulfide to a heated mixture of aromatic amine and catalyst (method B). The latter procedure generally results in shorter reaction times while the former is somewhat more convenient. As with the alkylthiation of phenols, appropriate aromatic amines give ortho/para mixtures which are conveniently separated by fractional distillation, the ortho isomer being more volatile.



Z = H, alkyl, NH_2, Cl, OCH_3; R', R = H, CH, CH_3; R'' = CH_3, C_2H_5

A number of catalysts were evaluated for their efficacy in promoting the reaction of aniline with dimethyl disulfide (Table II). Certain metal halides and mild protonic acids catalyzed the formation of (methylthio)anilines. Copper iodide gave the best yield of 2-(methylthio)aniline, and aluminum chloride gave the best yield of 4-(methylthio)-aniline. By contrast, phenol reacts with dimethyl disulfide in the presence of aluminum catalysts to give predominantly 2-(methylthio)phenol (ortho/para = 2.4).[2] Scoping experiments showed that indole, aromatic diamines, and aromatic monoamines containing alkyl, methoxy, or chlorine substituents underwent alkylthiation successfully. Sluggish reaction was achieved with *o*-nitroaniline while *p*-bromoaniline gave several side products. Reaction of

(1) A portion of this work is described in U.S. Patent 4,594,453.
(2) Ranken, P. F.; McKinnie, B. G. *Synthesis* **1984**, 117.
(3) Bentley, M. D.; Douglass, I. B.; Lacadie, J. A.; Weaver, D. C.; Davis, F. A.; Eitelman, S. J. *J. Chem. Soc., Chem. Commun.* **1971**, 1625.

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