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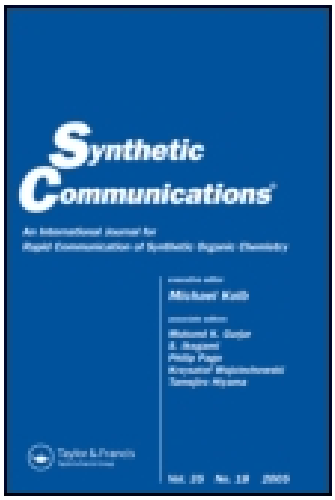

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Arylation of Diethyl 2-Chloroazulene- 1,3-dicarboxylate with Grignard Reagent

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Arylation of Diethyl 2-Chloroazulene-1,3-dicarboxylate with Grignard Reagent

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ABSTRACT

Reaction of diethyl 2-chloroazulene-1,3-dicarboxylate (**2**) with phenyl magnesium bromide, followed by oxidation with *o*-chloranil, gave diethyl 2-chloro-4-phenylazulene-1,3-dicarboxylate (**3**), diethyl 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**) and diethyl 6-phenylazulene-1,3-dicarboxylate (**5**).

Key Words: Azulenoids; Arylation; Nucleophilic substitution; Oxidation.

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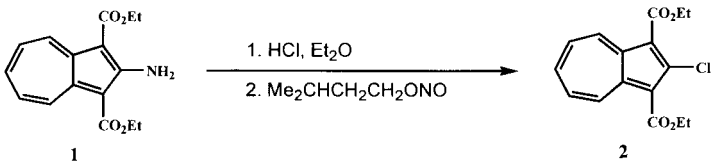
Although azulenoids were found to be a class of nonbenzenoid hydrocarbons in essential oils more than a century ago, they are still the subject of many investigations in the field of organic chemistry. These compounds find application in the preparation of dyes, in liquid crystals and in the medical treatment of inflammation and hypertension.[1,2] Recently, azuloquinones have been found to have antibacterial, antifungal and antitumor activities and to play an important role in the photosynthesis and in the respiratory electron transport chain as well as in solid state electroconductivity.[3–5] Nucleophilic substitution to introduce alkyl and aryl substituents in azulenes preferentially occurs at the 4- or 8-positions. If these positions are already occupied, and/or sterically hindered nucleophiles are used, substitution occurs at the 6-position.[1,2] The reaction of 2-alkoxy- or 2-halo-1,3-disubstituted azulenes with alkoxides, amine, sulfides and Grignard reagents leads to the replacement of the alkoxy or halogen substituents with the nucleophiles.[6–8] Recently, Dr. Takase et al. reported that 2-chloro-1,3-disubstituted azulenes with Grignard reagents or organic lithium allowed alkyl or phenyl substitution at the 4- and 6-positions.[9] In our continuous study on the synthetic application of azulenoids,[10–13] we reported herein a novel arylation of diethyl 2-chloroazulene-1,3-dicarboxylate with the Grignard reagent phenyl magnesium bromide.

Diethyl 2-aminoazulene-1,3-dicarboxylate (**1**) was prepared according to the literature,[12,13] identified by using spectroscopy and then chlorinated at the 2-position via treatment with hydrogen chloride and isoamyl nitrite to give diethyl 2-chloroazulene-1,3-dicarboxylate (**2**)[14] (Sch. 1). 2-Chloroazulene (**2**) was treated with phenyl magnesium bromide and then oxidized with *o*-chloranil to give diethyl 2-chloro-4-phenylazulene-1,3-dicarboxylate (**3**), diethyl 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**) and diethyl 6-phenylazulene-1,3-dicarboxylate (**5**), as shown in Sch. 2. The position of phenyl group in diethyl 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**) was determined by using spin decoupling and nuclear Overhauser effect difference spectrometry (NOE effect see Table 1). This finding showed that arylation of



1 2

Scheme 1.

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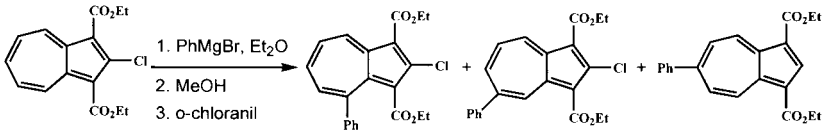

2 **3** **4** **5**

Scheme 2.

Table 1. The NOE effect of 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**).

Chemical shift of irradiation	$CO_2C\underline{H}_2$-CH_3	CO_2CH_2-$C\underline{H}_3$	5-Ph[c]	6-H	7-H	8-H
δ 7.7 (7-H)				6.97%		6.85%
δ 8.2 (6-H)			2.26%		5.47%	
δ 9.4 (8-H)	0.29%[a]	0.13%[a]			7.46%	
δ 9.8 (4-H)	0.37%[b]	0.17%[b]	5.24%			

[a]1-$CO_2CH_2CH_3$.
[b]3-$CO_2CH_2CH_3$.
[c]2′,6′-H_2 of 5-phenyl group.

Table 2. The yields of arylation of diethyl 2-chloroazulene-1,3-dicarboxylate (**2**).

Entries	Molar ratios of substrate to PhMgBr	Solvents used	Conversion (%)	Yields (%)[a]		
				3	**4**	**5**
1	1:1	Et_2O	74.9	6.4	3.3	13.8
2	1:2.5	Et_2O	97.3	23.6	7.5	32.7
3	1:3	Et_2O	100.0	5.4	4.7	31.9
4	1:1	THF	24.5	9.3	8.5	15.5
5	1:2.5	THF	92.7	10.7	2.8	13.9
6	1:3	THF	70.2	5.1	11.9	27.7

[a]Yield based on consumed diethyl 2-chloroazulene-1,3-dicarboxylate (**2**).

2-chloroazulene (**2**) with Grignard reagent occurred at the 4- or 8- and 5-positions as well as at the 6-position accompanied with elimination of the 2-Cl substituent. The yield depended significantly on the molar ratio of substrate to Grignard reagent and the solvent used (Table 2).

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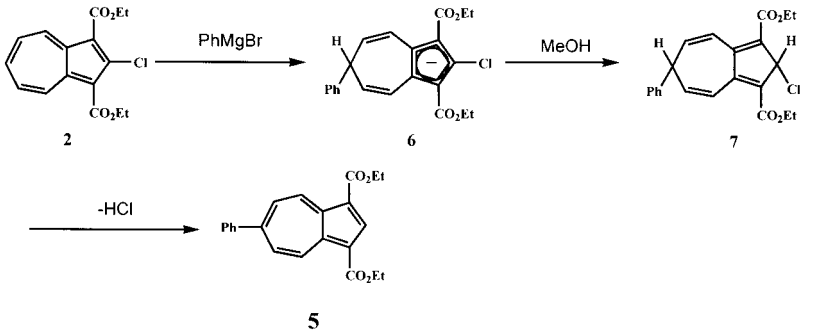

2 6 7 5

Scheme 3.

The formation of diethyl 6-phenylazulene-1,3-dicarboxylate (**5**) from diethyl 2-chloroazulene-1,3-dicarboxylate (**2**) was proposed to follow the addition–elimination mechanism[15,16] (Sch. 3). The reaction of diethyl 2-chloroazulene-1,3-dicarboxylate (**2**) with phenyl magnesium bromide is proposed to lead to a cyclopentadienyl anion (**6**), which then is protonated by methanol to produce a 2,6-dihydroazulene intermediate (**7**). Dehydrochlorination of the 2,6-dihydroazulene intermediate (**7**) afforded diethyl 6-phenylazulene-1,3-dicarboxylate (**5**).

EXPERIMENTAL

The melting points were measured without correction on a Yanagimoto Micromelting Point Apparatus. ^{1}H and ^{13}C nuclear magnetic resonance spectra were measured on a Varian VXR-300 spectrometer or a Varian INOVA-500 spectrometer. Mass spectra were determined on a VG Quattro GC/MS/MS DS spectrometer. High resolution mass spectral were determined on a VG 70-250S GC/MS spectrometer.

Diethyl 2-Chloroazulene-1,3-dicarboxylate (2)

Dry hydrogen chloride passed through a solution of diethyl 2-aminoazulene-1,3-dicarboxylate (**1**) (1.0 g, 3.48 mmol) dissolved in 50 mL of anhydrous benzene on an ice-bath for 2 h. Isoamyl nitrite (0.48 g, 4.10 mmol) was added to the reaction solution and then the mixture was stirred at room temperature overnight. The reaction solution was washed with water, dried over anhydrous sodium sulfate and evaporated.

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The residue was recrystallized from ethanol to afford 0.982 g (91.1%) of diethyl 2-chloroazulene-1,3-dicarboxylate (**2**), m.p. 78–80°C (Lit.[14]: 77–79°C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (t, $J = 7.2$, 6H), 4.50 (q, $J = 7.2$, 4H), 7.41 (t, $J = 10.2$, 2H), 7.93 (t, $J = 10.2$, 1H), 9.53 (d, $J = 10.2$, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): 14.42, 60.71, 77.42, 115.41, 130.88, 138.00, 140.19, 141.69, 164.36; MS (EI, m/Z, %): 69 (100), 233 (27.7), 261 (16.0), 306 (M+, 15.4), 308 (M + 2, 4.9); HRMS: 306.0654 (M^+), calcd. 306.0659; Anal.: Found: C: 62.49%, H: 4.94%; calcd. for $C_{16}H_{15}ClO_4$: C: 62.65%, H: 4.93%.

Typical Arylation of Diethyl 2-Chloroazulene-1,3-dicarboxylate (2)

Under a nitrogen atmosphere, an ether solution of phenyl magnesium bromide (0.815 mL of 2.5 M solution, 0.815 mmol) was added to a cold (ice-salt bath) solution of diethyl 2-chloroazulene-1,3-dicarboxylate (**2**) (0.100 g, 0.326 mmol) in a dry diethyl ether (10 mL) and the mixture was stirred for 30 min with an ice-salt bath cooling and then 30 min at room temperature. The reaction mixture was cooled (ice-salt bath), to which was added methanol (2 mL) and then stirred for 30 min. The reaction mixture was poured into 2 M HCl (1.4 mL) and then extracted with diethyl ether. The extract was washed with a saturated sodium bicarbonate solution and a brine solution, dried over anhydrous sodium sulfate and then evaporated. *o*-Chloranil (0.16 g, 0.652 mmol) was added to the residue dissolved in dry benzene (7 mL) and then stirred for 2 days at room temperature. The reaction solution was passed through a column of alumina to remove the *o*-chloranil residue and then evaporated to dry. The residue was chromatographed on silica gel and eluted with *n*-hexane–benzene (v/v = 1/20) to give a mixture of diethyl 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**) and diethyl 6-phenylazulene-1,3-dicarboxylate (**5**) and a crystal of diethyl 2-chloro-4-phenylazulene-1,3-dicarboxylate (**3**) (23.0 mg, 23.6%), m.p. 108–110°C (Lit.[9]: 108–109°C). The above mixture was separated on a TLC plate (silica gel) with a developing solvent of *n*-hexane–benzene (v/v = 1/1) to give diethyl 6-phenylazulene-1,3-dicarboxylate (**5**) (31.9 mg, 32.7%), m.p. 150–152°C and diethyl 2-chloro-5-phenylazulene-1,3-dicarboxylate (**4**) (7.3 mg, 7.5%), m.p. 108–110°C. **3**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.12 (t, $J = 7.0$, 3H), 1.47 (t, $J = 7.0$. 3H), 3.57 (q, $J = 7.0$, 2H), 4.49 (q, $J = 7.0$, 2H), 7.44–7.49 (m, 5H), 7.55–7.62 (m. 2H), 7.80–7.84 (m, 1H), 9.67 (dd, $J = 1.0$, $J = 10.0$ 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 13.82, 14.36, 60.58, 61.06, 114.04, 121.78, 128.16, 128.59, 128.62, 129.09, 133.87, 135.55, 138.13, 138.29,

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140.75, 141.27, 142.24, 151.56, 164.30, 165.06; MS (EI, *m*/*z*, %): 238 (46.8), 309 (70.6), 337 (43.7), 382 (M+, 100.0), 384 (M + 2, 39.3); HRMS: 382.0974 (M^+), calcd. 382.0972; Anal.: Found: C: 69.01%, H: 5.03%; calcd. for $C_{22}H_{19}ClO_4$: C: 69.02%, H: 5.00%; **4**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.45–1.50 (m, 6H), 4.46–4.53 (m, 4H), 7.44–7.47 (m, 1H), 7.51–7.54 (m, 2H), 7.70–7.71 (M, 2H), 7.79 (dd, $J = 1.0$, $J = 10.0$, 1H), 7.79 (t, $J = 10.0$, 1H), 8.15 (dd, $J = 1.0$, $J = 10.0$, 1H), 9.48 (dd, $J = 1.0$, $J = 10.0$, 1H), 9.89 (d, $J = 2.5$, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): 13.37, 14.42, 60.68, 114.95, 115.79, 128.25, 128.57, 129.12, 130.50, 136.88, 138.69, 140.13, 140.93, 141.61, 143.41, 144.16, 144.74, 164.32, 164.39; MS (EI, *m*/*z* %): 309 (64.3), 337 (37.5), 382 (M+, 100.0), 384 (M + 2, 36.2); HRMS: 382.0970 (M^+), calcd. 382.0972; **5**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.47 (t, $J = 7.0$, 6H), 4.45 (q, $J = 7.0$, 4H), 7.50–7.56 (m, 3H), 7.69–7.70 (m, 2H), 7.97 (d, $J = 11.0$, 2H), 8.83 (s, 1H), 9.82 (d, $J = 11.0$, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.58, 60.07, 116.42, 128.79, 128.95, 128.09, 130.90, 138.50, 142.75, 143.22, 143.57, 154.60, 165.10; MS (EI, *m*/*z*, %): 275 (76.8), 303 (55.6), 348 (M+, 100.0), 349 (M + 1, 23.1); HRMS: 348.1360 (M^+), calcd. 348.1362; Anal.: Found: C: 75.89%, H: 5.76%; calcd. for $C_{22}H_{20}O_4$: C: 75.84%, H: 5.79%.

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