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A simple and efficient synthesis of 2-alkylazulenes

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Abstract—The annulation method based on 2*H*-cyclohepta[*b*]furan-2-ones was applied for the synthesis of 2-alkylazulenes; 2-R-azulene (R = Et, *i*-Pr, *n*-Pr, *i*-Bu). Tropolone *p*-toluenesulfonate was used as a starting compound. By the two step synthesis, 1-carboxylic-3-cyanoazulene derivatives were obtained. Treatment of 1-carboxylic-3-cyanoazulene derivatives with aq H_2SO_4 resulted in decarboxylation and elimination of cyano group to give 2-alkylazulenes in good yields.

1. Introduction

Much attention has been focused on *ansa*-metallocene of group IV transition metals producing isotactic polypropylene, when activated with methylaluminoxane (MAO) and other cocatalysts. Many *ansa*-metallocene have been developed for improvement of polymerization performance and ligand system of the metallocene was found to be important for the polymerization behavior.[1] In the bis-indenyl metallocene system, the substituents at the 2-positions in the indenyl ring are important for polymerization behavior.[2] Recently, we have reported *ansa*-zirconocene bearing the azulenyl rings, Me_2Si(2-Me-4-Ph-4*H*-Azu)$_2ZrCl_2$ to produce isotactic polypropylene.[3] In the course of the design for the novel ligand in the bis-azulenyl metallocene system, we have developed a simple and efficient synthetic method of 2-substituted azulenes.

Several approaches to the synthesis of the azulene derivatives were reported earlier, however the yield was not good and selective synthesis was difficult.[4] For the synthesis of 2-methylazulene (**4a**), some strategies were reported including ring expansion by diazo acetic acid ester,[5] annulation method based on 2*H*-cyclohepta[*b*]furan-2-ones,[6] and annulation and dehydrogenation.[7] Furthermore, several methods for substitution of alkyl group at the 2-position of the azulenyl derivatives were reported previously.[8] On the other hand, few methods for the selective synthesis of 2-alkylazulenes were reported so far. For example, the synthesis of 2-ethylazulene was reported by annulation based on the enamine method. However, it was obtained as a mixture with 1,2-dimethylazulene and separation was necessary.[9] In this contribution, we report a simple and selective synthesis of 2-alkylazulenes (**4b–e**) from tropolone as a starting material.

2. Result and discussion

We applied the annulation method based on 2*H*-cyclohepta[*b*]furan-2-ones for the synthesis of 2-alkyl azulenes.[6a,10] It was previously reported that 2-methylazulene (**4a**) was prepared from 2-chlorotropone in moderate yield.[6a,11] Then this method was applied for the synthesis of 2-ethylazulene (**4b**) and we used tropolone *p*-toluenesulfonate (**1**) as a starting material, as shown in Scheme 1. Tropolone *p*-toluenesulfonate (**1**) was prepared from tropolone and *p*-toluenesulfonyl chloride in quantitative yield by the reported method.[12]

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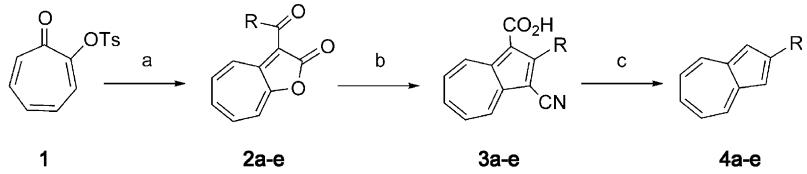

Scheme 1. Synthetic route for 2-alkylazulenes (**4a**–**e**). (a) $RCOCH_2CO_2Et$, NaOEt, EtOH; (b) $CNCH_2CO_2Et$, EtONa or DBU, EtOH; (c) aq. H_2SO_4.

The reaction of **1** and excess of ethyl propionylacetate in the presence of sodium ethoxide gave 3-propionyl-2*H*-cyclohepta[*b*]furan-2-one (**2b**) in good yield. In the reaction with 1 equiv of ethyl propionylacetate, unreacted **1** was recovered.

Treatment of **2b** with excess of ethyl cyanoacetate ester in the presence of sodium ethoxide resulted in formation of azulene ring to give 1-carboxylic-3-cyano-2-ethylazulene (**3b**) after acidic hydrolysis. Ethyl 3-propionyl-2-aminoazulene-1-carboxylate was obtained as one of the byproduct and could be removed by extraction with dichloromethane. It was reported previously that ethyl 3-acetyl-2-aminoazulene-1-carboxylate was obtained in the preparation of **3a**.[6a]

Next, we examined the decarboxylation and elimination of cyano group of **3b** in some conditions. In the synthesis of 2-methylazulene, it was reported that decarboxylation of **3a** with 85% H_3PO_4 proceeded smoothly to give **5a** in high yield,[6a] and treatment of **3a** with 85% H_3PO_4 under longer reaction time gave **4a** in a moderate yield.[6b] Furthermore, the reaction of **3a** with 75% H_2SO_4 resulted in moderate yield of **4a** and formation of **5a** and **6a** was observed.[6a] Similarly, in the course of the reaction with H_3PO_4 or H_2SO_4, decarboxylation of **3b** proceeded smoothly and gas evolution was observed at the early stage of the reaction. In the analysis of the reaction mixture by mass spectra, 1-cyanoazulene (**5b**) was observed as a main product. Further reaction resulted in the formation of 1-carbamoylazulene (**6b**) and subsequent elimination of carbamoyl group of **6b** to give 2-ethylazulene (**4b**). The yield of **4b** and reaction conditions are summarized in Table 1. In the reaction with H_3PO_4, the yield of **4b** was low and **5b** was recovered (entries 1 and 2), however in the reaction with 75% H_2SO_4, the yield of **4b** was improved (entry 4).[13] In the shorter reaction time, both **5b** and **6b** were observed (entry 6) (Chart 1).

Table 1. Reaction condition and yield of **4b**, **5b**, and **6b**[a]

Condition	Reaction time (h)	**4b** (%)	**5b** (%)	**6b** (%)
65% H_3PO_4	4	0	100	0
85% H_3PO_4	4	12	88	0
50% H_2SO_4	4	4	96	0
75% H_2SO_4	4	84[b]	0	0
75% H_2SO_4	2	100	0	0
75% H_2SO_4	0.25	29	58	13

Reaction temperature: 110 °C.
[a] Yield by GC analysis.
[b] Unidentified product was observed.

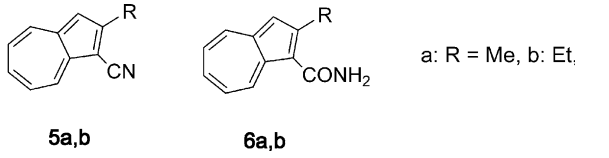

Chart 1.

Table 2. Yield of **2** and **3**

R	Base (equiv)	**2** (%)	Base (equiv)	**3** (%)
Et	NaOEt (1.2)	61	NaOEt (4)	93
i-Pr	NaOEt (2.4)	70	DBU (3)	56
n-Pr	NaOEt (2.4)	68	DBU (3)	Quant.
i-Bu	NaOEt (1.2)	77	DBU (3)	53

Table 3. Yield of alkylazulenes (**4**)

Compound	Method	**4** (%)[a]
4b (R = Et)	a	67
4c (R = *i*-Pr)	b	42
4d (R = *n*-Pr)	c	80
4e (R = *i*-Bu)	a	56

(a) 75% H_2SO_4, 90 and 120 °C, (b) 65% H_2SO_4, 90 and 110 °C, (c) 65% H_2SO_4, 100 and 120 °C.
[a] Isolated yield after purification by silica gel column chromatography.

Then, this strategy was extended for the synthesis of the other 2-alkylazulenes. 2*H*-Cyclohepta[*b*]furan-2-one derivatives (**2c**–**e**) were obtained in the reaction with corresponding β-keto ester in good yields.[14] It was reported that **2a** was obtained from 2-chlorotropone.[6a,b,15] However these 2*H*-cyclohepta[*b*]furan-2-one derivatives (**2b**–**e**) bearing acyl group derived from tropolone *p*-toluenesulfonate were novel compounds. Subsequent reaction of **2c**–**e** with ethyl cyanoacetate ester in the presence of base gave 1-carboxylic-3-cyanoazulene derivatives (**3c**–**e**) as summarized in Table 2. The decarboxylation and elimination of cyano group of **3c**–**e** was conducted in the same reaction conditions, in which the best yield of **4b** was obtained as shown in Table 3. 2-Alkylazulenes bearing primary alkyl chain (**4b** and **4d**) were obtained in higher yields, on the other hand the yields of those bearing secondary alkyl chain (**4c** and **4e**) were relatively lower due to the stability of the resulting azulenes under acidic condition at high temperature. Longer reaction time resulted in the decrease of the yield of **4**.

3. General procedures for the synthesis of 2-alkylazulene

3.1. Synthesis of 3-propionyl 2*H*-cyclohepta[*b*]furan-2-one (2b)

Tropolone *p*-toluenesulfonate (8.07 g, 29.2 mmol) and ethyl propionylacetate (6.2 mL, 43.8 mmol) were suspended in ethanol (30 mL). To the mixture was added a solution of sodium ethoxide, prepared from ethanol (60 mL) and sodium (806 mg, 35.1 mmol) at 0 °C. The mixture was stirred at room temperature overnight and at 50 °C for 45 min. To the resultant mixture was added cold water and the resulting precipitate was separated by filtration, washed with cold water, dried at 50 °C under reduced pressure to give **2b** (3.62 g, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (t, $J = 7$ Hz, 3H, CH_3), 3.07 (q, $J = 7$ Hz, 2H, CH_2), 7.30–7.45 (m, 1H), 7.50–7.60 (m, 2H), 7.65–7.70 (m, 1H), 9.23 (d, $J = 12$ Hz, 1H).

3.2. Synthesis of 1-cyano-2-ethylazulene-3-carboxylic acid (3b)

To a suspension of **2b** (3.62 g, 17.9 mmol) and 2 equiv of cyanoacetic acid ethyl ester (3.8 mL, 35.8 mol) in ethanol (50 mL) was added a solution of sodium ethoxide, prepared from ethanol (80 mL) and sodium (1.65 g, 71.7 mmol) at 0 °C. The mixture was stirred at room temperature overnight, the resultant mixture was concentrated. To the mixture was added cold water (200 mL) and extracted with dichloromethane. After the organic phase was separated, to the aqueous solution was added aqueous hydrochloric acid (1 mol/L). The resulting precipitate was separated by filtration, washed with cold water, dried at 50 °C under reduced pressure to give **3b** (3.73 g, 93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (t, $J = 7$ Hz, 3H, CH_3), 3.47 (q, $J = 7$ Hz, 2H, CH_2), 7.78–7.88 (m, 2H), 8.01 (t, $J = 10$ Hz, 1H), 8.71 (d, $J = 10$ Hz, 1H), 9.78 (d, $J = 10$ Hz, 1H).

3.3. Synthesis of 2-ethylazulene (4b)

To a 75% aqueous solution of sulfuric acid (30 mL) was added **3b** (3.7 g, 16.4 mmol) gradually and the mixture was heated at 90 °C for 2 h and at 120 °C for further 2 h. The obtained mixture was cooled, poured into an aqueous solution of sodium hydroxide (35 g), and extracted with hexane–ethyl acetate. The extract was washed with water, concentrated, and purified by silica gel column chromatography (eluent: hexane) to give **4b** as a violet crystal (1.71 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (t, $J = 7$ Hz, 3H, CH_3), 3.05 (q, $J = 7$ Hz, 2H, CH_2), 7.16 (t, $J = 10$ Hz, 2H), 7.25 (s, 2H), 7.51 (t, $J = 10$ Hz, 1H), 8.23 (d, $J = 10$ Hz, 2H).

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