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A novel approach to benz[*e*]indenes

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ABSTRACT

A number of benz[*e*]indene derivatives have been prepared at room temperature in good to excellent yields by treating 3-(2-formyl-cycloalkenyl)-acrylic acid esters with diphosphorus pentasulfide. An azulene derivative was also synthesized by this simple method.

Indene ring frameworks are present in a large number of biologically active compounds.[1] Reduced benz[*e*]indenes are structurally related to steroids and some derivatives enhance the actions of the inhibitory neurotransmitter γ-aminobutyric acid (GABA) at $GABA_A$ receptors.[2] Because of this pharmacological criterion, these benz[*e*]indene compounds are of interest as lead compounds for identifying new drug candidates possessing tranquillo-sedative, anticonvulsive, analgesic, antianginal, local anesthetic, and anti-inflammatory activities.[3] The benz[*e*]indene derivative **1** (Fig. 1), a cyclopenta[*a*]naphthalene derivative, shows a mild growth inhibitory activity to L1210 and CCRF-CEM leukemic cells in culture and interacts with DNAs and poly(deoxyribo-nucleotides) as reported by Kundu.[4] Benz[*e*]indene derivatives also have practical applications as organic light-emitting diode devices.[5]

While indenes are extensively prepared using expensive catalysts of palladium, platinum, ruthenium, niobium, and aluminum[6], neuroactive benz[*e*]indene compounds are generally prepared by partial degradation of steroid precursors.[7] Synthesis of cyclopenta[*a*]naphthalene derivatives is achieved by multi-step reactions.[4,8] In conjunction with our synthetic efforts on heterocycles[9] and carbocycles[10] exploiting the Pd-catalyzed intramolecular Heck reaction on substrates derived from β-bromovinyl aldehydes,[11] we herein present an efficient, P_4S_{10}-mediated one-step room temperature route to benz[*e*]indene derivatives or cyclopenta[*a*]naphthalene derivatives (Scheme 1) from 3-(2-formyl-cycloalkenyl)-acrylic acid esters with which we have already reported the synthesis of furan, dihydrofuran, and pyrrole derivatives.[12]

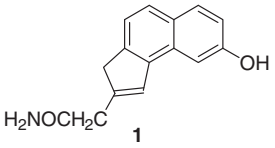
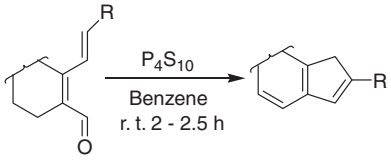
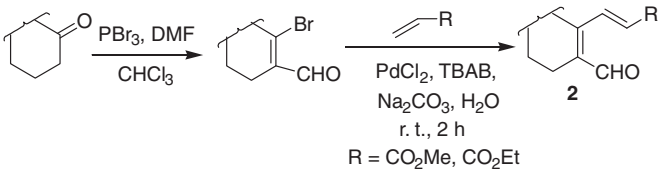


Figure 1. DNA-binding agent.



Scheme 1. Synthesis of indene derivatives.



Scheme 2. Synthesis of 3-(2-formyl-cycloalkenyl)-acrylic acid ester.

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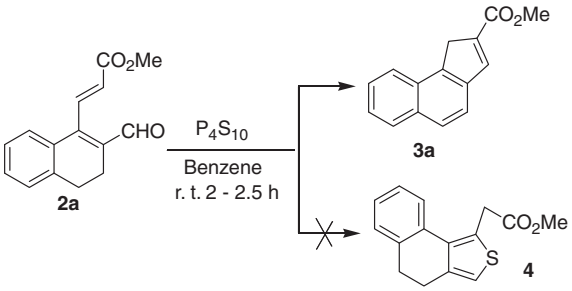


Scheme 3. Synthesis of indene derivative from substrate **2a**.

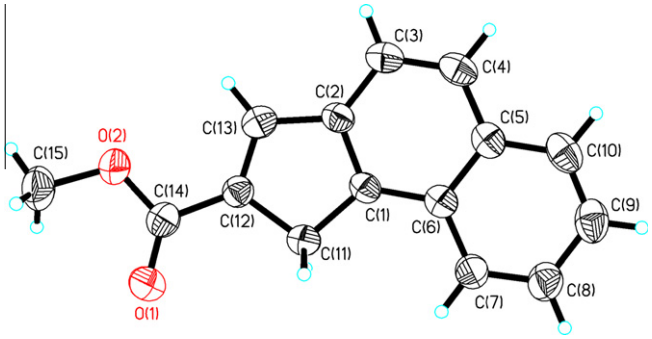
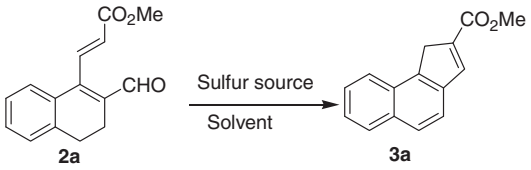


Figure 2. ORTEP view of the molecule **3a**.

Table 1
Optimization of the reaction condition by using different sulfur sources at room temperature



Entry	Sulfur source	Solvent	Yield[a] (%)
1	LR	Benzene	NR
2	LR	Dichloromethane	NR
3	Na_2S	THF	NR
4	P_4S_{10}	Dichloromethane	75
5	P_4S_{10}	Benzene	92

Reaction conditions: reaction was carried out with formyl-alkene **2a** (1.0 mmol) and sulfur source (1.5 mmol) in solvent (10 mL) at room temperature for 2 h. NR: no other reaction and complete recovery of the starting materials.

[a] Isolated yields after purification by column chromatography.

The starting materials **2** were synthesized in good yields (90–99%) by our reported procedure[12], where β-bromovinyl aldehydes were treated with acrylate esters in the presence of

Table 2
Synthesis of indenes

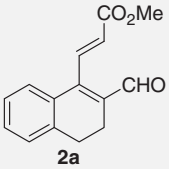
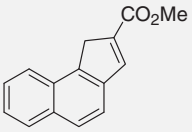
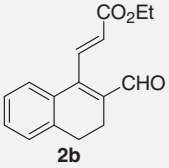
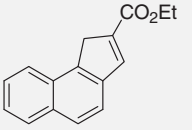
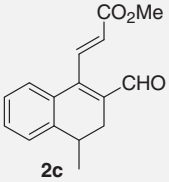
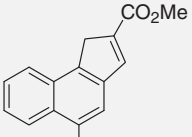
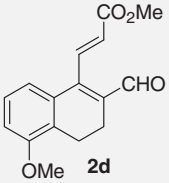
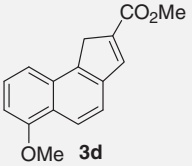
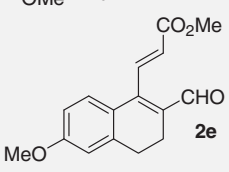
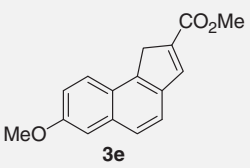
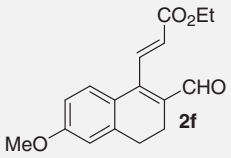
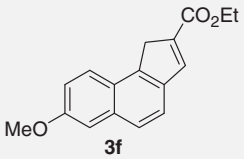
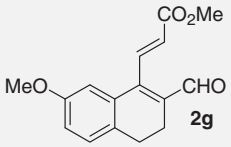
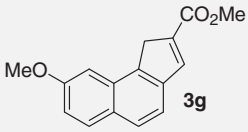
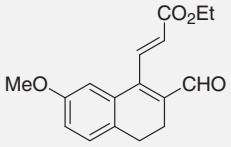
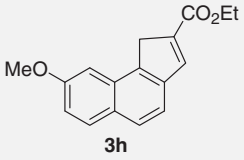
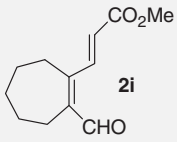
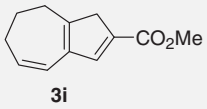
Entry	Alkene **2**	Indene **3**	Time (h)	Yield[a] (%)
1	 **2a**	 **3a**	2	92
2	 **2b**	 **3b**	2.5	90
3	 **2c**	 **3c**	2	95
4	 **2d**	 **3d**	2.5	85
5	 **2e**	 **3e**	2	90

Table 2 (*continued*)

Entry	Alkene **2**	Indene **3**	Time (h)	Yield[a] (%)
6	 **2f**	 **3f**	2	88
7	 **2g**	 **3g**	2.5	85
8	 **2h**	 **3h**	2.5	82
9	 **2i**	 **3i**	2	80

Reaction was carried out with formyl-alkene **2** (1.0 mmol) and P_4S_{10} (1.5 mmol) in benzene at room temperature for 2–2.5 h.

[a] Isolated yields after purification by column chromatography.

palladium chloride, sodium carbonate, and tetrabutylammonium bromide in water at room temperature for 2–3 h (Scheme 2) thereby, producing Pd(0) nanoparticles in situ.[13]

In an attempt to synthesize thiophene derivatives **4** (Scheme 3) from substrates **2** using P_4S_{10}, interestingly we obtained benz[*e*]-indene derivative **3a** when 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid methyl ester (**2a**) was treated with P_4S_{10} in benzene under argon at room temperature for 2 h.

Usually, the non-benzenoid double bond of an indene is in a fixed position, and tautomerization happens only through the cooperation of a base.[14] Most of the reports[8] involving the synthesis of benz[*e*]indenes correspond to a mixture of 1*H*-benz[*e*]indene and 3*H*-benz[*e*]indene. But with our method, only one isomer, that is, 1*H*-benz[*e*]indene derivative **3a** was obtained, wherein lies the beauty of our methodology. The structure of **3a** was confirmed by single-crystal X-ray diffraction. An ORTEP drawing of the compound **3a** with the atom numbering is shown in Figure 2.

Optimization of our reaction condition was done with **2a** as the model substrate by changing different sulfur sources (Table 1). When the reaction was carried out with Lawesson's reagent (LR) in benzene or CH_2Cl_2 at room temperature or Na_2S in THF at room temperature we did not get any cyclized products. We were delighted to obtain benz[*e*]indene derivative **3a** in 92% yield by treatment of substrate **2a** with 1.5 equiv P_4S_{10} in benzene under argon at room temperature for 2 h (Table 1, entry 5). P_4S_{10} in dichloromethane also gave successful results (Table 1, entry 4). The reaction was incomplete with <1.5 equiv of P_4S_{10}.

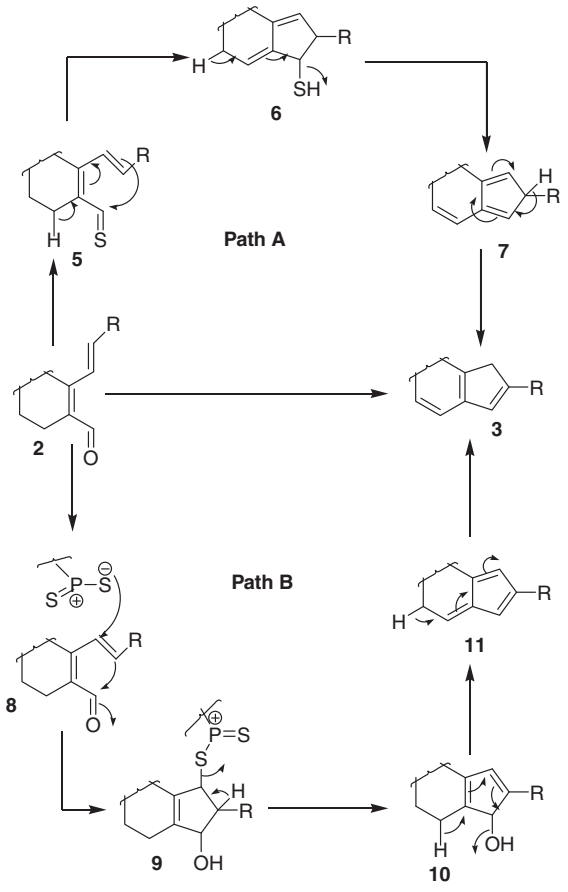
Having established the exact structure and with the standard protocol in hand, we next set out to examine the scope and limitation of this intramolecular cyclization reaction and the results are shown in Table 2. Various 3-(2-formyl-cycloalkenyl)-acrylic acid esters were subjected to treatment with P_4S_{10}.[15] In all the cases indene derivatives were obtained in good to excellent yields. This cyclization reaction was not limited to 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylic acid ester derivatives. For example, 1,6,7,8-tetrahydro-azulene derivative **3i** was also obtained from the substrate **2i** in good yield (Table 2, entry 9). Unfortunately, the reaction of P_4S_{10} with 3-(2-formyl-cyclohex-1-enyl)-acrylic acid methyl ester and 4-naphthalen-2-yl-6-oxo-hexa-2,4-dienoic acid methyl ester afforded a mixture of decomposed products. The compounds **3g** and **3h** are structurally somewhat related to the cyclopenta[*a*]naphthalene derivative **1**, which binds to DNAs.[4] We believe that further structural manipulations of these molecules might lead to useful cancer chemotherapeutic agents.

Mechanistically, it can be postulated that initially intermediate thio-aldehyde **5** is formed, which being too reactive, readily undergoes intramolecular cyclization to give intermediate **6** (Path A, Scheme 4). Entropically favored elimination of H_2S and subsequent isomerization leads to the more conjugated indene derivative **3**. In case of 3-(2-formyl-3,4-dihydro-naphthalen-1-yl)-acrylate substrates the additional driving force is aromatization of the adjacent ring.

However, an alternative possibility can also be pointed out (Path B, Scheme 4). A P_4S_{10}-mediated intramolecular Baylis–Hillman type reaction, followed by elimination of water and subsequent isomerization could also lead to our indene derivatives **3**.

We are not aware of a practicable way of deciding conclusively between the mechanisms given in Scheme 4. We prefer the former Path A on account of the absence of any literature report of P_4S_{10} promoting Baylis–Hillman reaction. Also the formation of thio-aldehyde intermediate **5** is assumed, based on the reported synthesis of thione from α,β-unsaturated ketone at room temperature[16] employing Lawesson's reagent which behaves analogously as P_4S_{10}.

In conclusion, we have illustrated a novel and expeditious P_4S_{10}-promoted synthesis of benz[*e*]indene derivatives from 3-(2-formyl-cycloalkenyl)-acrylic acid esters without employing any tedious sequence. The beauty of this method lies in the fact that it is



Scheme 4. Plausible mechanisms for the P_4S_{10}-mediated synthesis of benz[*e*]indene derivatives.

very mild, simple, and highly efficient. Further mechanistic studies and synthetic applications of the starting materials are in progress.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.031.

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15. *General procedure for the preparation of indene and azulene*:
To a solution of 3-(2-formyl-cycloalkenyl)-acrylic acid ester (1 mmol) in benzene (10 mL), P_4S_{10} (1.5 mmol) was added and the resulting solution was stirred at room temperature for 2–2.5 h under argon. Upon completion of the reaction, the mixture was diluted with ether and filtered through a sintered funnel. The filtrate was washed with brine solution, dried over Na_2SO_4 and then concentrated. The product was purified by column chromatography using ethyl acetate/petroleum ether as eluent and silica-gel (60–120 mesh) as the stationary phase.
Spectral data of representative compounds:
5-Methyl-1*H*-cyclopenta[*a*]naphthalene-2-carboxylic acid methyl ester (**3c**): yellow solid. Mp 124 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.68 (s, 3H), 3.86 (s, 3H), 3.90 (s, 2H), 7.40 (s, 1H), 7.44–7.54 (m, 2H), 7.73 (t, J = 2.0 Hz, 1H), 7.92–8.00 (m, 2H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.8, 37.5, 51.6, 122.0, 124.6, 125.2, 125.9, 126.4, 130.0, 132.2, 134.2, 136.5, 139.8, 141.0, 142.1, 165.4. IR (KBr): ν_{max} (cm^{-1}) = 2955, 1711, 1593, 1592, 1498, 1450, 1432, 1293, 1265, 1207, 1080, 975, 915, 750, 733. HRMS calcd for $C_{16}H_{15}O_2$ (MH^+) m/z = 239.1072, found m/z = 239.1089. Anal. Calcd for $C_{16}H_{14}O_2$ (238.0994): C, 80.65; H, 5.92. Found C, 80.47; H, 6.04.
1,6,7,8-Tetrahydro-azulene-2-carboxylic acid methyl ester (**3i**): yellow gummy-liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.83–1.95 (m, 2H), 2.39–2.45 (m, 2H), 2.66 (bs, 2H), 3.36 (d, J = 1.6 Hz, 2H), 3.76 (s, 3H), 5.81–5.92 (m, 1H), 6.07 (d, J = 11.2 Hz, 1H), 7.22 (s, 1H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 23.66, 31.10, 31.73, 44.85, 51.24, 123.92, 133.77, 133.93, 143.24, 143.81, 147.55, 164.91. Anal. Calcd for $C_{12}H_{14}O_2$ (190.0994): C, 75.76; H, 7.42. Found C, 75.93; H, 7.27.
16. (a) Bonini, B. F.; Comes-Franchini, M.; Fochi, M.; Mazzanti, G.; Ricci, A.; Varchi, G. *Tetrahedron Lett.* **1999**, *40*, 6473; (b) Weiss, D.; Gaudig, U.; Beckert, R. *Synthesis* **1992**, 751.