

Intramolecular Friedel-Crafts Alkylation Promoted by the Cross Conjugated β -Keto Ester System. An Efficient Approach to Highly Functionalized Hydrophenanthrenes and Hydrochrysenes.

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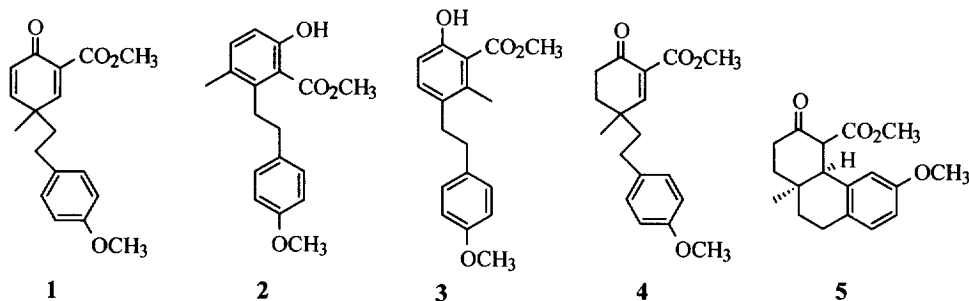
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Abstract: The cross conjugated β -keto ester system was shown to be an excellent promoter for the intramolecular Friedel-Crafts alkylation to facilitate the rapid construction of highly functionalized phenanthrene and chrysenes derivatives. © 1999 Elsevier Science Ltd. All rights reserved.

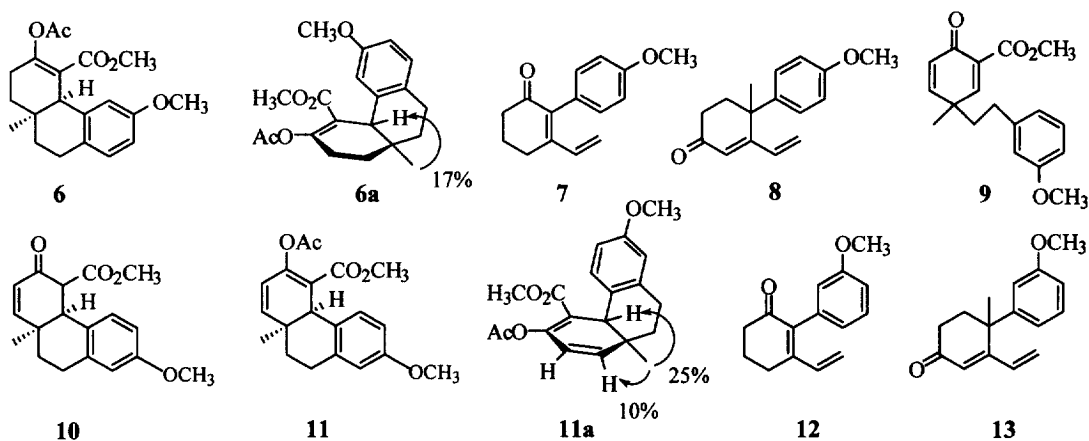
Keywords: Friedel-Crafts alkylation; Cross conjugated β -keto ester system; Hydrophenanthrene and hydrochrysenes systems

Polyene cyclization is a powerful synthetic tool which has been applied widely for the preparation of polycyclic systems.¹ The success of the process, in general, depends largely upon the suitable choice of the initiator.¹ Recently, we have observed the cross conjugated β -keto ester system as an excellent promoter which effects efficient construction of polycyclic carbocyclic and heterocyclic systems.² The efficiency of this newly developed method has been demonstrated in the total synthesis of the acetylenic sesquiterpene dehydrochamaecynol.³ We wish now to present the use of this promoter to facilitate the rapid formation of the highly functionalized hydrophenanthrene and hydrochrysenes systems, each of which forms the nucleus of a large number of naturally occurring compounds.⁴

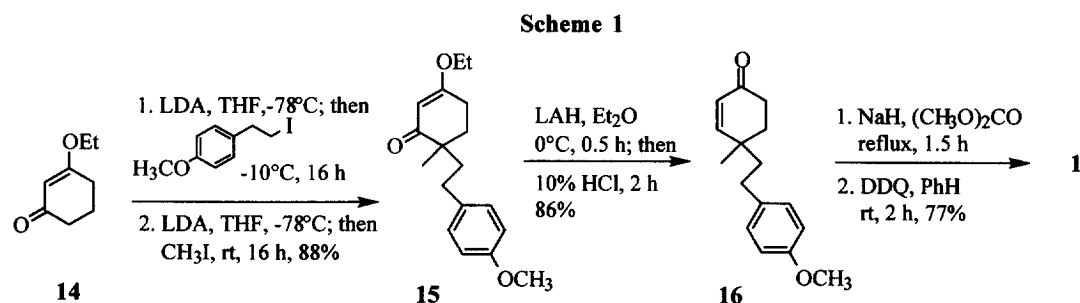


Our initial investigation was carried out on the dienone ester **1**. However, treatment of this compound with stannic chloride in dichloromethane at room temperature for 16 h gave only the rearrangement products **2** and **3** in 19:1 ratio in a combined yield of 56%.⁵ The dienone-phenol rearrangement process was suppressed and the desired cyclization realized, when the dihydro derivative **4** was subjected to treatment with stannic chloride.

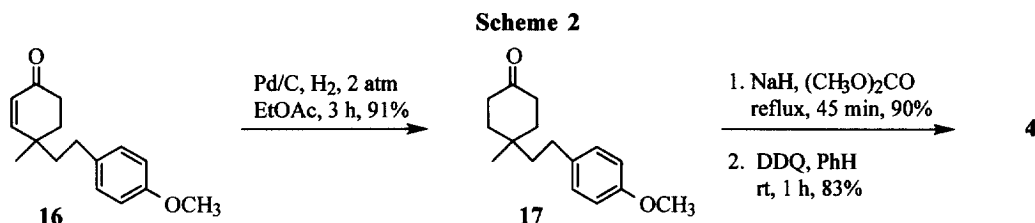
After 24 h at room temperature, the desired hydrophenanthrene **5** was produced in 84% yield.⁶ The structure of this compound was established by its conversion, using acetic anhydride and pyridine, to the corresponding enol acetate **6**, of which the stereochemistry was deduced by the NOE experiment (see **6a**). Majetich and co-workers have studied, with varying degrees of success, the intramolecular Friedel-Crafts alkylation involving the fully conjugated dienone system as an initiator.^{6a} Unfortunately, neither compound **7** nor **8** was found to undergo cyclization. Clearly, the cross conjugated β -keto ester system involved in the current study is a superior initiator which promotes more efficiently the intramolecular Friedel-Crafts alkylation. As expected, with compound **9** which contains a methoxy group at the *ortho/para* position relative to the potential site of cyclization and thus exerts greater electron donating effect, the cyclization was extremely facile. Upon treatment with stannic chloride, compound **9** was found to cyclize rapidly even at -78°C and the desired cyclization product **10** was obtained in quantitative yield after 30 min. Interestingly but not surprisingly on the steric ground, the cyclization occurred completely *via* the *para* position relative to the methoxy group. Compound **10** was shown to be highly enolizable ($>20\%$) and its ring junction stereochemistry was confirmed by the NOE experiment on the corresponding enol acetate **11** (see **11a**). Similar substituent effect on the rate of cyclization was also observed by Majetich *et al.* for the fully conjugated dienone system. In sharp contrast to the lack of reactivity of dienones **7** and **8**, the isomeric compounds **12** and **13** gave the expected hydrophenanthrene derivatives in *ca.* 60% yields when subjected to treatment with boron trifluoride etherate in refluxing cyclohexane.^{6a}



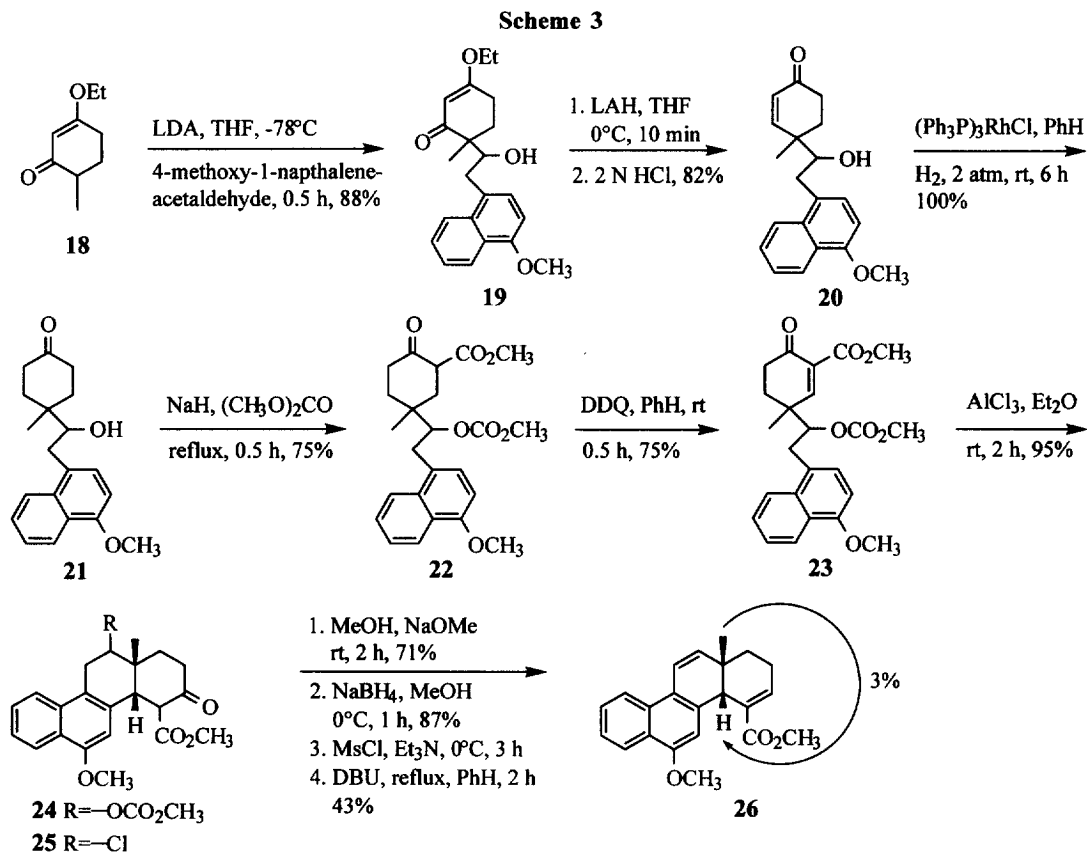
Compound **1** was prepared from enone **14** according to the synthetic sequence illustrated in Scheme 1. Alkylation of **14** with lithium diisopropylamide and 2-(4-methoxyphenyl)ethyl iodide followed by methylation



gave the dialkylation product **15** in 88% yield. Compound **15** was then converted to the enone **16** (86% yield) by lithium aluminum hydride reduction and subsequent treatment with hydrochloric acid. Carbomethoxylation of **16** with sodium hydride and dimethyl carbonate followed by oxidation with 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) gave a 77% yield of dienone ester **1**. When a similar sequence was applied using 2-(3-methoxyphenyl)ethyl iodide as the alkylating agent in the first step, a 58% yield of compound **9** was obtained. Enone ester **4** was readily accessible from enone **16** in 68% overall yield via catalytic hydrogenation (**16** to **17**), carbomethoxylation and DDQ oxidation (Scheme 2).



By introducing a suitable aromatic appendage, the above procedure can be conceivably extended to the preparation of compounds containing various numbers of aromatic rings with pre-existing functionalities. The formation of the hydrochrysene system, for example, could be easily achieved as follows.



The synthesis commenced with the aldol condensation of enone **18**⁷ and 4-methoxy-1-naphthalene-acetaldehyde⁸ to give an 88% yield of an inseparable mixture of two diastereomeric ketols **19**. Lithium aluminum hydride reduction followed immediately by acid treatment afforded the corresponding cyclohexenone derivatives **20** which were hydrogenated using Wilkinson's catalyst to give the saturated ketones **21** (82% yield from **19**). Subsequent treatment of **21** with sodium hydride and dimethyl carbonate resulted in the formation of the β -keto ester moiety with concomitant protection of the alcohol in the form of a carbonate. DDQ oxidation of the mixture of keto esters **22** thus obtained in 75% yield gave two diastereomeric enone esters **23** in a 6:1 ratio and 75% combined yield. Cyclization of **23** was readily effected by aluminum chloride⁹ in ether at room temperature for 2 h and the highly functionalized hydrochrysenes derivatives **24** were obtained in virtually quantitative yield. The ring junction stereochemistry of these diastereomeric compounds was determined by conversion (methanolysis, sodium borohydride reduction, mesylation, and elimination) to compound **26** whose structure was confirmed by spectroscopic methods especially nmr spectroscopy with the assistance of NOE experiment.

The above results indicate that the cross conjugated β -keto ester system can serve as a convenient and highly effective promoter to facilitate the intramolecular Friedel-Crafts alkylation, whereby highly functionalized polycyclic systems, which may find use as advanced intermediates towards various natural products, can be rapidly generated.¹⁰

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- The yields were calculated based on isolated compounds by flash chromatography. Satisfactory ir, nmr (¹H and ¹³C), high resolution mass spectra and elemental analysis were obtained for all new compounds.
- For recent preparation of hydrophenanthrenes, see: (a) Majetich, G.; Liu, S.; Fang, J.; Siesel, D.; Zhang, Y. *J. Org. Chem.* **1997**, *62*, 6928-6951; (b) Chiu, C. K. F.; Govindan, S. U.; Fuchs, P. L. *J. Org. Chem.* **1994**, *59*, 311-323; (c) Spino, C.; Crawford, J.; Bishop, J. *J. Org. Chem.* **1995**, *60*, 844-851; (d) Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 4322-4323.
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- This compound was prepared in 63% yield from 4-methoxy-naphthaldehyde *via* sequential treatment with Ph₃P=CHOCH₃ (THF, rt, 16 h) and 10% hydrochloric acid (THF, rt, 2 days).
- Interestingly, when the reaction was carried out with stannic chloride in dichloromethane at room temperature for 1 day, carbonates **24** and the corresponding chlorides **25** were formed quantitatively in equal amount.
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