Pergamon

Tetrahedron Letters 40 (1999) 3827–3830

TETRAHEDRON LETTERS

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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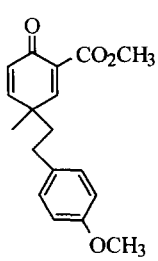
Received 8 March 1999; accepted 19 March 1999

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 chrysene derivatives.

Keywords: Friedel-Crafts alkylation; Cross conjugated β-keto ester system; Hydrophenanthrene and hydrochrysene 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 dehydrochamaecynenol.[3] We wish now to present the use of this promoter to facilitate the rapid formation of the highly functionalized hydrophenanthrene and hydrochrysene systems, each of which forms the nucleus of a large number of naturally occurring compounds.[4]



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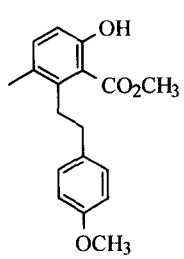

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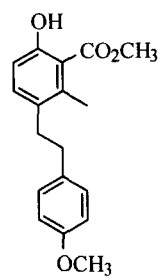

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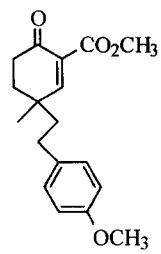

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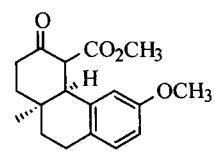

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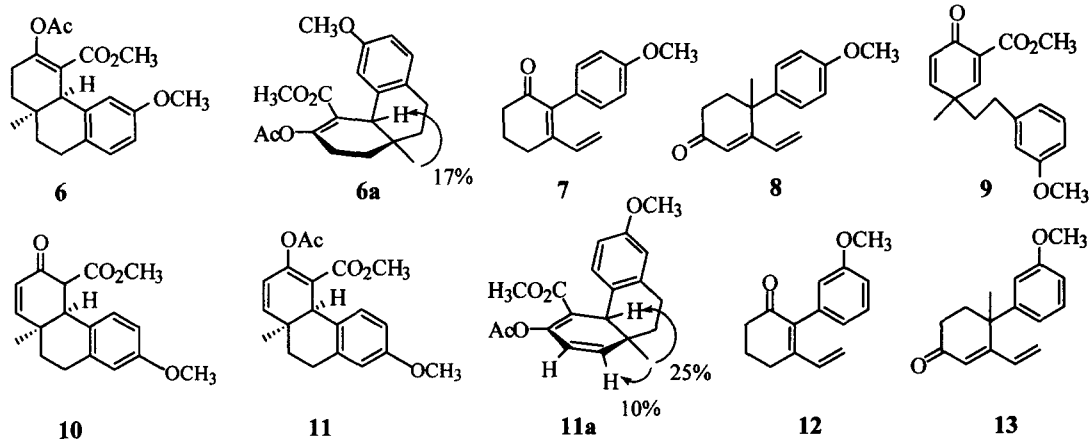
Our initial investigation was carried out on the dienone ester **1**. However, treatment of this compound with stannic chloride in dichloromethane at room temperature for 16 h gave only the rearrangement products **2** and **3** in 19:1 ratio in a combined yield of 56%.[5] The dienone-phenol rearrangement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

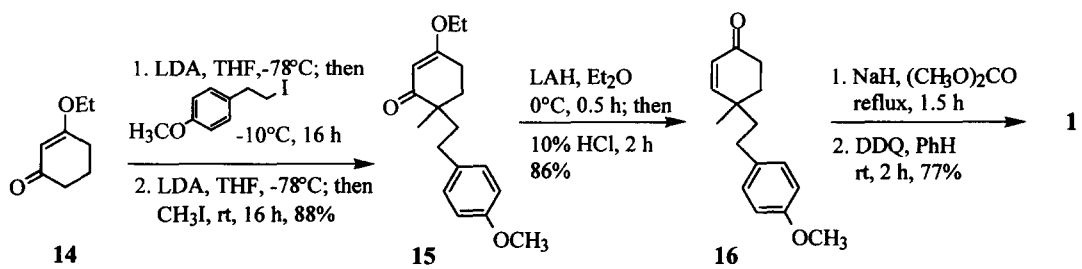
0040-4039/99/$ - see front matter
PII: S0040-4039(99)00658-9

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 triflouride etherate in refluxing cyclohexane.[6a]



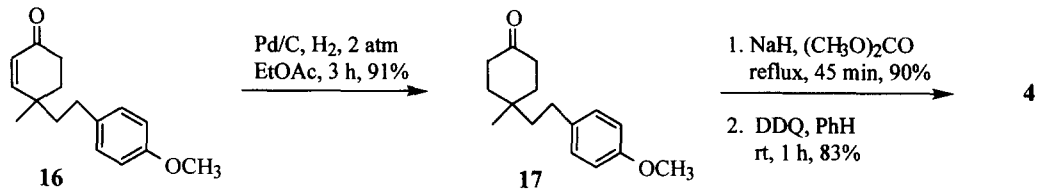
Compound **1** was prepared from enone **14** according to the synthetic sequence illustrated in Scheme 1. Alkylation of **14** with lithium diisopropylamide and 2-(4-methoxyphenyl)ethyl iodide followed by methylation

Scheme 1



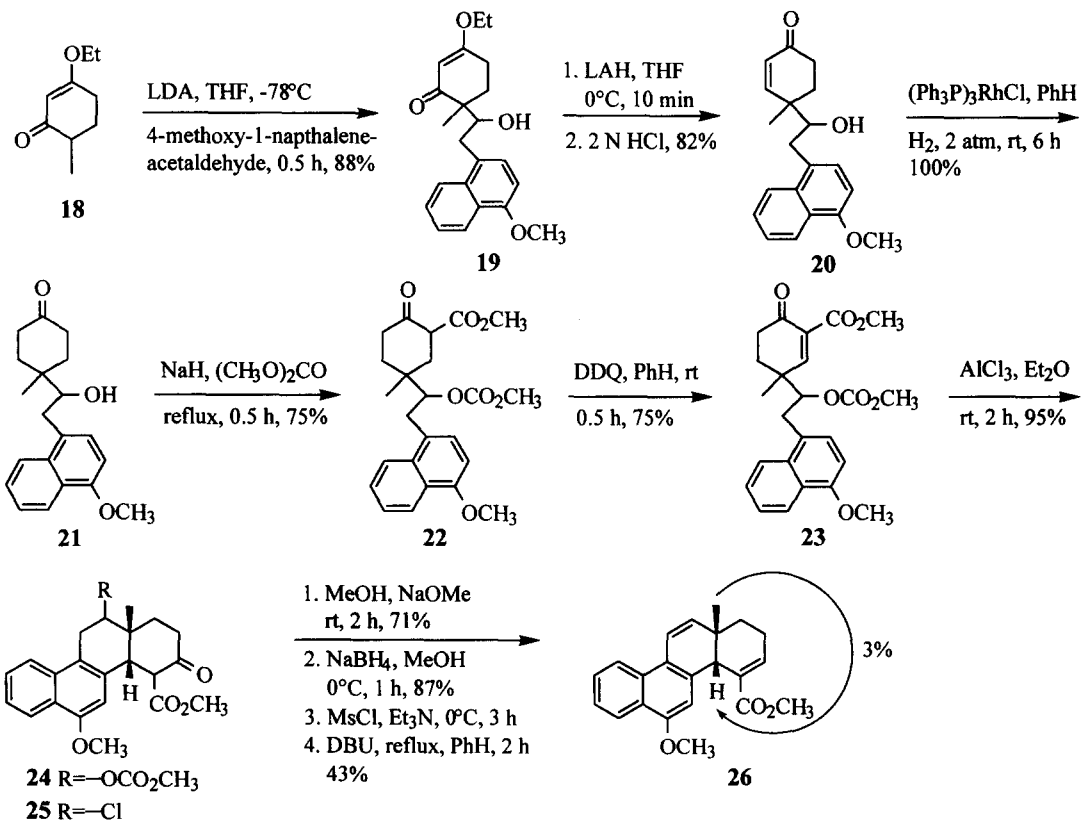
gave the dialkylation product **15** in 88% yield. Compound **15** was then converted to the enone **16** (86% yield) by lithium aluminum hydride reduction and subsequent treatment with hydrochloric acid. Carbomethoxylation of **16** with sodium hydride and dimethyl carbonate followed by oxidation with 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).

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.

Scheme 3



The synthesis commenced with the aldol condensation of enone **18**[7] and 4-methoxy-1-naphthaleneacetaldehyde[8] 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 chloride[9] in ether at room temperature for 2 h and the highly functionalized hydrochrysene 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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5. The yields were calculated based on isolated compounds by flash chromatography. Satisfactory ir, nmr (^{1}H and ^{13}C), high resolution mass spectra and elemental analysis were obtained for all new compounds.
6. 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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8. This compound was prepared in 63% yield from 4-methoxy-naphthaldehyde *via* sequential treatement with Ph_3P=$CHOCH_3$ (THF, rt, 16 h) and 10% hydrochloric acid (THF, rt, 2 days).
9. 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.
10. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the National Science Council of the Republic of China for financial support.