Pergamon

Tetrahedron Letters, Vol. 38, No. 37, pp. 6501-6504, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01514-1

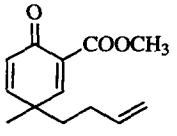
An Efficient Procedure for the Synthesis of Thiophene-containing Polycyclic Compounds via Polyene Cyclization Promoted by the Cross Conjugated β-Keto Ester System

Hsing-Jang Liu* and Duong Duc-Phi Tran

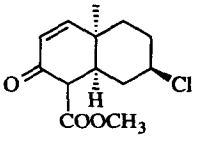
Department of Chemistry, University of Alberta
Edmonton, Alberta, Canada, T6G 2G2

Abstract: The cross conjugated β-keto ester system was found to be an excellent promoter for polyene cyclization involving a thiophene ring to facilitate the synthesis of polycyclic thiophene-containing compounds. © 1997 Elsevier Science Ltd.

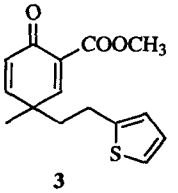
Polycyclic thiophene derivatives often show desirable medicinal properties and many have been the subject of extensive investigation for potential use as pharmacodynamic agents and as therapeutical agents for treatment of central nervous system disorder, metabolic disease, infection disease, etc.[1] The continuous demand of new compounds of this family for therapeutical evaluation has encouraged the development of new synthetic methods to facilitate the construction of polycyclic thiophene derivatives, especially those of structural complexity which could not be readily prepared by the existing methods. We have previously observed the cross conjugated β-keto ester system as an excellent promoter for polyene cyclization. For example, brief treatment (15 min) of enone ester **1** with aluminum chloride at -78°C in ether gave the bicyclic chloride **2** in good yield.[2] In principle, this cyclization process can be extended to expedite the preparation of hetero-polycyclic compounds by replacing the side chain double bond in **1** with a heterocyclic ring system such as furan, thiophene or pyridine. Accordingly, an efficient method for the synthesis of highly functionalized polycyclic thiophene-containing compounds has been developed. The preliminary results are described herein.



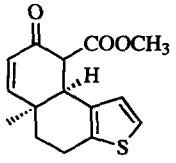
1



2



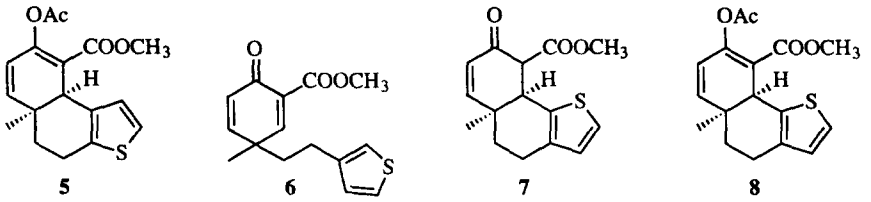
3



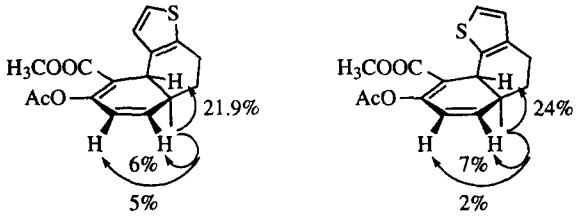
4

When dienone ester **3** was treated with stannic chloride (1.5 eq) in dichloromethane at -78°C for 15 min, the tricyclic compound **4** was formed as a single product in quantitative yield.[3] The structure of this compound was verified by its conversion (acetic anhydride in pyridine, room temperature, overnight) to the corresponding enol acetate **5**, the stereochemistry of which was assigned based on the NOE experimental results (see **5a**). The cyclization of the isomeric dienone ester **6** was found to be even more facile. The

cyclization occurred readily in chloroform solution (apparently traces of hydrochloric acid were present) at room temperature for a short period (~ 4 h) to give a quantitative yield of the tricyclic thiophene derivative **7**. The structure of this compound was also confirmed by the formation of the corresponding enol acetate **8**, of which the stereochemistry was deduced again by NOE experiment (see **8a**).



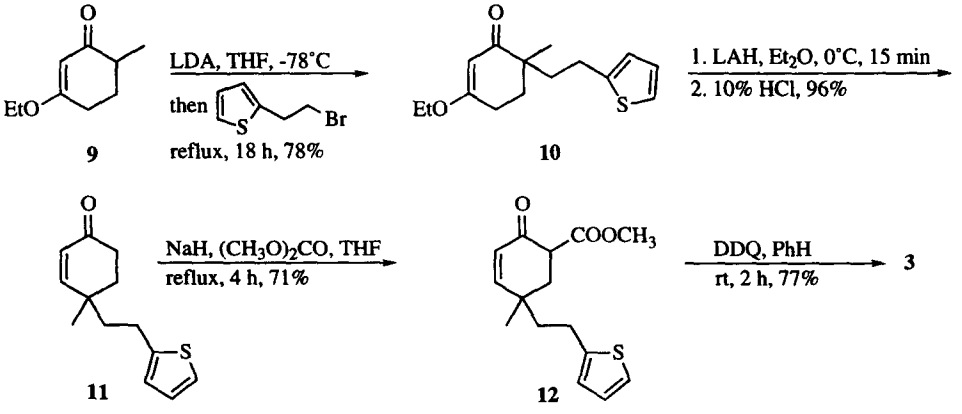
5 **6** **7** **8**



5a **8a**

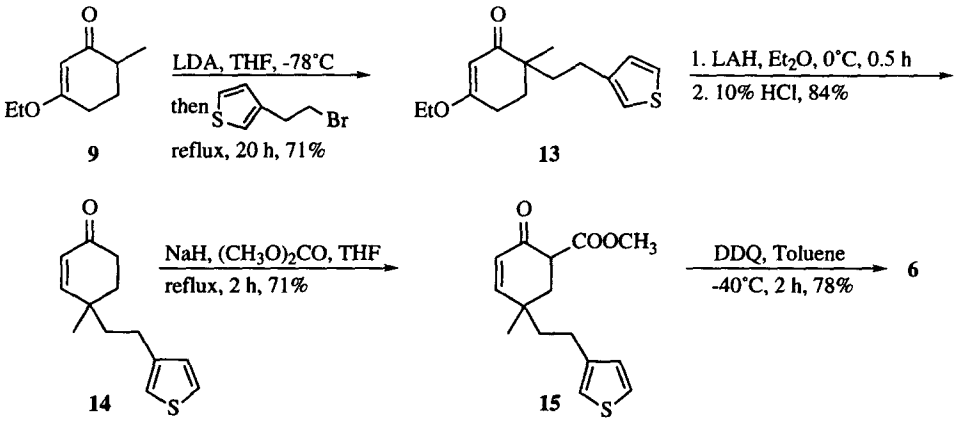
Dienone esters **3** and **6** were readily prepared from 3-ethoxy-6-methyl-2-cyclohexenone (**9**) as follows. Kinetic deprotonation of **9** in tetrahydrofuran at -78°C using lithium diisopropylamide as a base followed by treatment with 2-(2-bromoethyl)thiophene (2 eq) in refluxing tetrahydrofuran for 18 h gave rise to thiophene derivative **10** in 78% yield (Scheme 1). This compound was readily reduced (0°C, 15 min) by lithium aluminum hydride in ether, and the resulting alcohol rearranged to give the desired enone **11** (96% yield) upon brief exposure to 10% hydrochloric acid. Enone **11** was subjected to carbomethoxylation with dimethyl carbonate and sodium hydride in refluxing tetrahydrofuran for 4 h. Subsequent oxidation of the resulting keto ester **12** thus obtained in 71% yield with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in benzene[4] at room temperature for 2 h afforded a 77% yield of dienone **3** required for the cyclization. A

Scheme 1



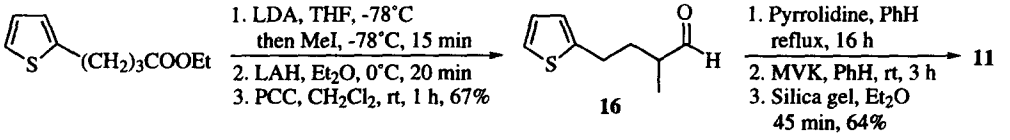
similar synthetic sequence involving 3-(2-bromoethyl)thiophene as the alkylating agent was found to be equally effective for the preparation of the isomeric dienone **6** via intermediates **13-15** (Scheme 2).

Scheme 2



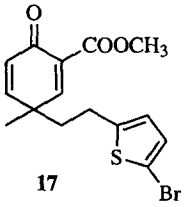
An alternative synthetic approach is demonstrated with the formation of enone **11** in Scheme 3. In this approach, ethyl 4-(2-thienyl)butanoate was methylated with lithium diisopropylamide and methyl iodide (tetrahydrofuran, -78°C, 15 min), and the product was converted to aldehyde **16** (67% overall yield) via reduction with lithium aluminum hydride (ether, 0°C, 20 min) and oxidation with pyridinium chlorochromate (dichloromethane, room temperature, 1 h).[5] Formation of the corresponding pyrrolidine enamine (pyrrolidine, refluxing benzene, 16 h) followed by condensation with methyl vinyl ketone (benzene, room temperature, 3 h)[6] gave the desired enone **11** in 64% yield after brief treatment (room temperature, 45 min) of the crude condensation product with silica gel in ether.

Scheme 3

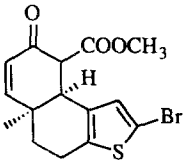


Bromo dienone **17**, readily prepared in 67% yield from keto ester **12** by bromination (*N*-bromosuccinimide, carbon tetrachloride, room temperature, 2 h) and dehydrobromination (1,8-diazabicyclo-[5.4.0]undec-7-ene, benzene, room temperature, 4 h),[7] was also subjected to the Lewis acid catalyzed cyclization. Treatment of **17** with stannic chloride at room temperature for 3 h gave a quantitative yield of the cyclization product **18** whose structure was further confirmed by the formation of the corresponding enol acetate **19**.[8] Similarly, treatment of bromo dienone **20**, readily obtained in 66% yield from keto ester **15** by the bromination and dehydrobromination sequence, with aluminum chloride in ether at 0°C for 2 h resulted in the formation of the cyclization product **21** in 80% yield. Confirmation of its structure was also achieved by acetylation giving rise to enol acetate **22**.[8] These experiments serve to further demonstrate the effectiveness of the cross conjugated β-keto ester system in promoting the ionic cyclization. Even with a poor nucleophilic thiophene due to the presence of the electron-withdrawing bromine atom, the cyclization in

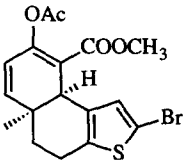
each case still proceeded with a high degree of efficiency. It is also noteworthy that by placing a bromine atom at C-2 of the thiophene ring in compound **20**, the cyclization involving the otherwise less reactive C-4 center became viable.



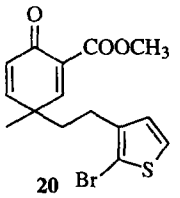
17



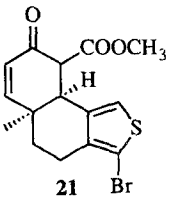
18



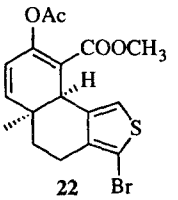
19



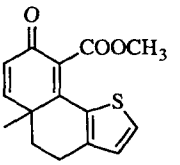
20



21



22



23

As illustrated above, the polyene cyclization induced by the cross conjugated β-keto ester system presents itself as an excellent synthetic method for the formation of highly functionalized polycyclic thiophene-containing compounds.[9] The cyclization is rapid under mild conditions, highly regio- and stereoselective, and the products which contain a high degree of functionalization are formed in uniformly high yield. This approach can be extended to the preparation of a variety of polycyclic thiophene derivatives for therapeutical evaluation by suitable selection of the reactants involved in Schemes 1-3 and by modification of the existing functionalities in the products. For example, oxidation of tricyclic thiohene **7** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and a catalytic amount of acetic acid in tetrahydrofuran for 4 days at room temperature gave the corresponding dienone thiophene **23** in 98% yield.[11]

REFERENCES AND NOTES

1. Weissberger, A.; Taylor, E. C. *Thiophene and its derivatives*; Gronowitz, S., Ed.; John Wiley & Sons, Inc.: Toronto, 1985, part IV, pp. 397-478.
2. Liu, H. J.; Sun, D.; Shia, K. S. *Tetrahetron Lett.* **1996**, *37*, 8073-8076.
3. 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 the new compounds.
4. Walker, P.; Hiebert, J. D. *Chem. Rev.* **1967**, *67*, 153-195.
5. Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis*, **1982**, 245-258.
6. Chan, Y.; Epstein, W. W. *Org. Synth.* **1973**, *53*, 49-52.
7. Liu, H. J.; Ulibarri, G.; Nelson, L. A. K. *Can. J. Chem.* **1994**, *72*, 2416-2427.
8. The results from the NOE experiment were found to be similar to those of the corresponding unbrominated compound.
9. See reference 10 and references cited therein for a previous preparation of polycyclic thiophene derivatives via polyene cyclization. In this preparation, the cyclization was promoted by an allylic alcohol moiety. The yields of products were modest (~50%).
10. Macco, A. A.; de Brouwer, R. J.; Buck, H. M. *J. Org. Chem.* **1977**, *42*, 3196-3199.

11. We are grateful to the Natural Sciences and Engineering Research Council of Canada and the University of Alberta for financial support.

(*Received in USA* 5 *June* 1997; *revised* 11 *July* 1997; *accepted* 14 *July* 1997)