95　10　27

行政院國家科學委員會補助專題研究計畫 ∨ 成 果 報 告
□期中進度報告

雙環[2.2.2]辛烯及倍半雙環[2.2.2]辛烯稠合喹琳及喹琳二酮

Quinoline and Quinolin-5,8-dione Fused Derivatives of Bicyclo[2.2.2]octene and
sesquibicyclo[2.2.2]octene

計畫類別：X個別型計畫　　□整合型計畫

計畫編號：NSC　94 – 2113 – M – 029 –004

執行期間：94 年 08 月 01 日至 95 年 07 月 31 日

　　計畫主持人：林振東

　　計畫參與人員：趙尚達

成果報告類型(依經費核定清單規定繳交)：X精簡報告　□完整報告

本成果報告包括以下應繳交之附件：
□赴國外出差或研習心得報告一份
□赴大陸地區出差或研習心得報告一份
□出席國際學術會議心得報告及發表之論文各一份
□國際合作研究計畫國外研究報告書一份

處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、
　　　　　列管計畫及下列情形者外，得立即公開查詢
　　　　　　□涉及專利或其他智慧財產權，□一年□二年後可公開查詢

執行單位：東海大學 化學系

中 華 民 國 　 94 年 　 10 　 月 　 26 　 　 日

關鍵詞：喹啉，双環〔2.2.2〕辛烯，弗利蘭德反應。

　　喹啉稠合双環〔2.2.2〕辛烯化合物，可使用双環〔2.2.2〕辛-5-烯-2-酮與 2-胺苯甲醛，在鹼性酒精溶液中進行弗利蘭德(Friedlander)反應而獲得。接著進行照光反應，無論使用二苯酮作為催化劑與否皆會因照光時間延長而造成產物分解。類似地，若使用3,6-二甲氧-2-胺苯甲醛，則所得的縮合產物，直接以硝酸銨鈰進行氧化反應可順利得到喹啉-5,8-二酮親雙烯化合物，此化合物可作為親雙烯物，與 1,3-環己二烯進行立體選擇行的[4+2]環化反應而形成多環煙。

　　接著將隔間的双環〔2.2.2〕辛烯，提昇至倍半双環〔2.2.2〕辛烯探討。主要的四環酮合成步驟可以採用苯乙烯硫醯作為乙炔及乙烯的相當物和双環〔2.2.2〕辛烯稠合的 1,3-環己二烯部分進行〔4+2〕環化反應。同樣地再利用弗利蘭德反應即可達成喹啉稠合倍半双環〔2.2.2〕辛烯衍生物。

Keywords: Quinoline, Bicyclo[2.2.2]octene, Friedländer Reaction

Bicyclo[2.2.2]octene bearing a quinoline fused at etheno bridge can be prepared from Friedländer reaction of bicyclo[2.2.2]oct-5-en-2-one with 2-aminobenzaldehyde. Photoreaction of the resulting quinoline with sensitizer and without sensitizer is described. Similarly, bicyclo[2.2.2]octene bearing a quinolin-5,8-dione is prepared by treatment of the bicyclic ketone with 3,6-dimethoxy-2-aminobenzaldehyde followed by conventional oxidation step. The π-facial stereoselectivity on the activated carbon-carbon double bond of *p*-benzoquinone moiety is shown from the [4+2] cycloaddition with 1,3-cyclohexadiene followed by Alder's rule to give the *anti-endo* and *syn-endo* cycloadducts

Extended work to the synthesis of quinoline fused sesquibicyclo[2.2.2]octenes is prepared from tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-9,13-dien-4-one with 2-aminobenzaldehyde in good yield.　The key step for preparation of the required tetracyckic ketone in Friedländer reaction is the Diels-Alder cyclization of phenyl vinylsulphone, an ethylene equivalent, with the bicyclo[2.2.2]octene-fused cyclohexdiene ring.

Introduction

　　The preparation of bicyclo[2.2.2]octatriene (barellene) was first reported by Zimmerman[1], since then the mechanistic studies of photochemical reaction has become an interesting subject to organic chemists.[2] When barellene was irradiated in the presence of a triplet sensitizer, semibullvalene was produced in a high yield with the di-π-methane rearrangement. On the other hand, direct irradiation of barellene followed a different path to yield 1,3,5,7-cyclooctatetraene. The detailed studies of the potential energy surfaces involved the singlet and triplet states were recently reported by Fructos to support the Zimmerman mechanism for the photosensitized

reaction of barellene.[3]

SCHEME 1
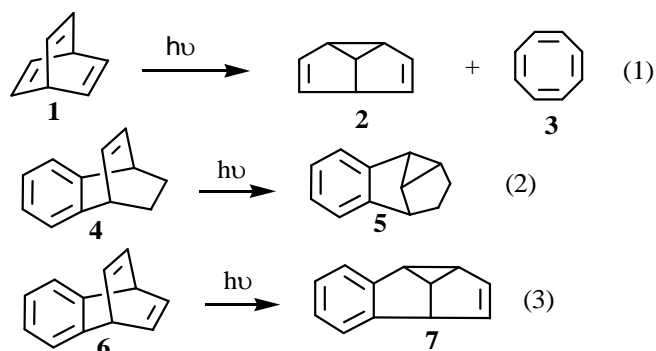
Tetracyclic tetraene **10** was first prepared by Prinzbach, from the ring enlargement of diketone **8** with diazoacetic ester / BF$_3$. The proximity of the two face-to-face double bonds allowed exclusive [2+2] cycloaddition and quantitative formation of hexacyclic diene **10** in photoreaction.[4]
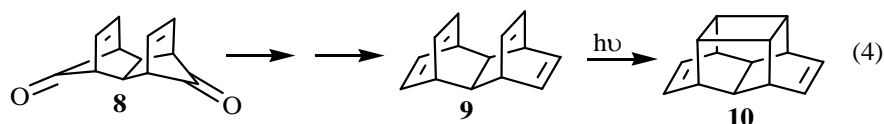

    Despite polycyclic hydrocarbons containing a series of all *syn*- condensed bicyclo[2.2.2]heptenes are widely studied in the field of transannular orbital interaction[5] and employed as building blocks in the synthesis of macromolecules[6], not many reports about oligocondensed bicyclo[2.2.2]octene have been published.[7,8]

    It is noteworthy that irradiation of **11** gives formation of semibullvalene **12** as the only product and this is the only example of aza-di-π-methane rearrangement that involves a quinoxaline chromophore**.** In contrast with **11**, quinoxaline **13** gave intramoleculr [2+2] cycloaddition as the only product. After the process of excitation and intersystem crossing, the diradical **14** was formed first and then followed by transannular bonding with the second etheno bridge immediately to form diradical **15**. Susequently, the resulting **15** decayed to the ground state of cage product **16**.[9]

    Nitrogen in quinoline fused bicyclo[2.2.2]octene based derivatives should be useful to enhance the complexation and perform stronger facial selectivity and the longer wavelength absorption is expected to broaden the scope of hyperconjugation between all *syn*-etheno bridges. These concepts bring us to the preparation of quinoline and quinolindinoe fused bicyclo[2.2.2]octene based derivatives. In this report we describe the use of Friedlander quinoline synthesis for the preparation of quinoline-fused bicycle[2.2.2]octene and tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradecadiene rings, and it has been shown that parallel face-to-face double bonds of the later readily undergoes intramolecular [2+2] cyclization.

(5)

11   **12**

SCHEME 2

13   **14**


15   **16**
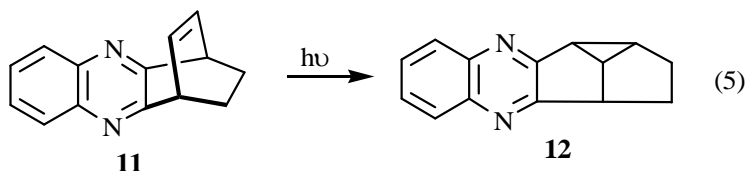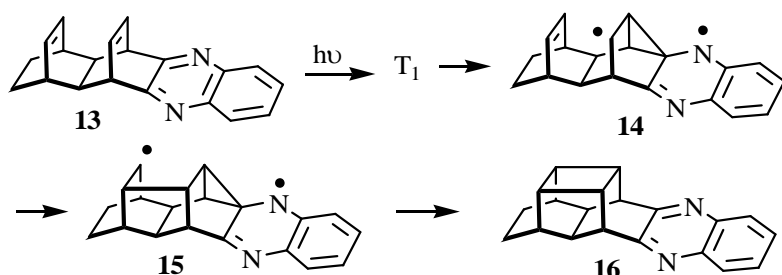
Results and Discussion

I. Synthesis of quinoline fused derivatives of bicyclo[2.2.2]octenes.

We have previously employed 2-chloroacrylyl chloride as a ketene equivalent in the Diels-Alder reaction with the fused 1,3-cyclohexadiene ring to construct the corresponding bicycle[2.2.2]octanone moiety.[10] However, 2-chloroacrylyl chloride is highly moisture sensitive and has to be used immediately after preparation. General preparation of this compound is started from the commercially available methyl acrylate through tedious chlorination, acidic hydrolysis, acyl chlorination and elimination steps.[11] A more direct, although less efficient, synthesis of bicycle[2.2.2]octenone **20** described by Kozikowski and Schmiesing[c] is summarized in Scheme 3. The ketone **20** was readily accessed from 1,3-cyclohexdiene by Diels-Alder reaction with acrylonitrile followed by chlorination and treatment of potassium hydroxide in dimethylsulfoxide solution.[12] Under optium conditions the isolated yield of the ketone **20** was 52 %.

SCHEME 3

17   **18**   **19**   **20**
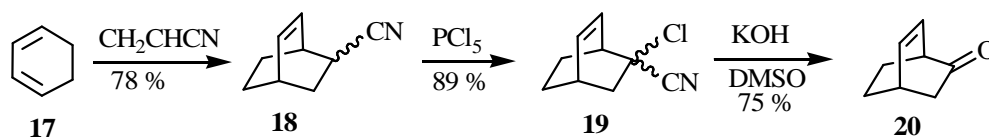
Reduction of 2-nitrobenzaldehyde **21** followed by condensation with **20** in the presence of $SnCl_2$ and $ZnCl_2$ did not produce desired **25** successfully. Reduction of **21** with ferrous sulfate afforded aminoaldehyde **22** in 58 % yield. Due to the self-condensation on standing, we normally prepare aminoaldehydes before use.[13] The Friedländer synthesis of quinoline fused bicycle[2.2.2]octene **25** was then obtained from base-promoted condensation of 2-aminobenzaldehyde with ketone **20** in 78 % yield. The reaction mechanism is illustrated in Scheme 4. The irradiation of a solution of quinoline **25** in hexane or containing 2 molar

equivalent of benzophenone through a Pyrex filter with a 500-W medium-pressure Hg lamp under a nitrogen atmosphere for 12 h at 0 °C did not give the di-π-methane rearrangement products **26** or **27**. In ¹H-NMR spectroscopy, we found that absorptions at δ 6.57~6.61 for the protons on the carbon-carbon double bond disappeared and very complicated signals shown between δ 1.15 and δ 2.50 were generated. We believe that decomposition of the preliminary products may proceed under prolonged irradiation.
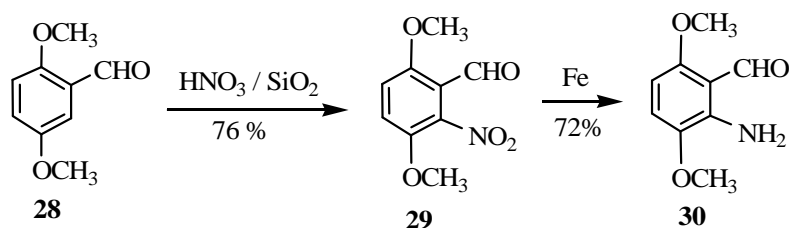
SCHEME 4
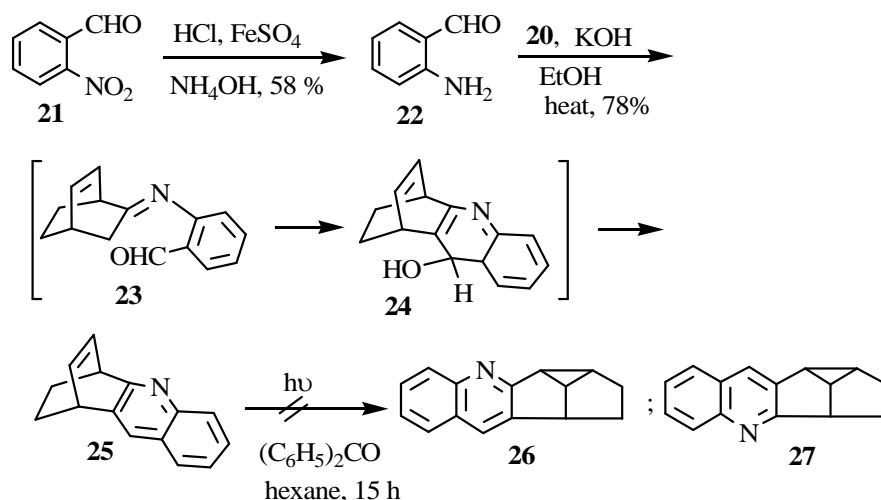
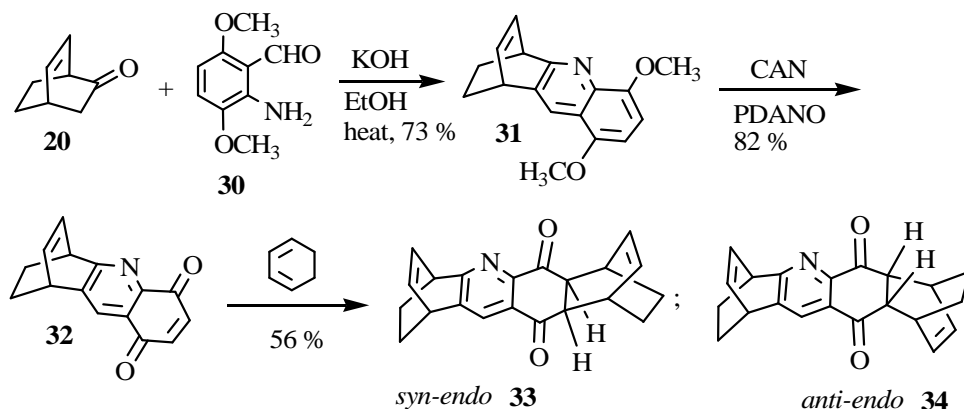## II. Synthesis of quinolin-5,8-dione fused derivatives of bicyclo[2.2.2]octenes.

Nitration of 2,5-dimethoxybenzaldehyde **28** with a 10:1 molar excess of silica gel coated with nitric acid under ultrasonic agitation gave 3,6-dimethoxy-2-nitrobenzaldehyde **29** in 74% yields accompanied by 19 % yield of 3,6-dimethoxy-4-nitrobenzaldehyde. Reduction of isolated aldehyde **29** with iron powder produced aminoaldehyde **30** in good yield.[14] The aminoaldehyde **30** then underwent Friedländer condensation with ketone **20** to provide quinoline **31**. The dimethoxybenzo ring of **31** can be oxidized to the corresponding quinoline **32** using ceric ammonium nitrate (CAN) and catalytic amount of pyridine-2,6-dicarboxylic acid N-oxide (PDANO).[15] The ¹H-NMR spectrum of **32** showed a singlet for the proton on the embedding pyridine (δ 8.06), two doublet signals for the CH=CH protons of quinoid ring (δ 7.07 and δ 6.77), a multiplet signals for the CH=CH bridge protons (δ 6.56), two multiplet signals for the bridgehead protons (δ 4.45, δ 4.20)and two 2-proton multiplets for the CH_2-CH_2 bridge (δ 1.15~1.74). The Diels-Alder reaction of **32** with 1,3-cyclohexadiene gave a mixture of cycloadducts **33** and **34**.
The ¹H-NMR spectrum of this mixture showed two singlet peaks at δ 8.14 and 8.06 for protons of the pyridine rings.

SCHEME 5

**SCHEME 6**

syn-endo **33**   ;   anti-endo **34**

III. Synthesis of quinoline fused derivatives of sesquibicyclo[2.2.2]octenes.

In order to extend our work to the quinoline fused sesquibicyclo[2.2.2]octenes we first prepare tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-9,13-dien-4-one **39** from tetracyclic ketone **35** as illustrated in Scheme 7. The synthesis of tetracyclic ketone **35** was carried out based on the previously reported procedure starting from 1,8,9,10-tetrachloro-11,11-dimethoxytricyclo[6.2.1.027]undeca-3,5,9-triene **40** in four steps.[10] Thermal decomposition of carbon monoxide from ketone **35** followed by Diels-Alder cycloaddition with phenyl vinylsulphone, a synthetic equivalent of ethylene, to afford a mixture of isomeric cycloadducts **36**, **37**. Reductive elimination of benzenesulfonyl group by sodium amalgam gave tetracyclic alcohol **38** in 80 % yield. Conventional pyridium chlorochromate (PCC) oxidation of **30** then cleanly provided the desired tetracyclo[6.2.2.2^{3,6}.0^{2,7}]tetradeca-9,13-dien-4-one **39** in 27% overall yield from ketone **35.** The structure of **35** was established by Infrared absorptions and NMR spectroscopy.

With tetracyclic dienone **35** on hand, we examined the Friedländer in tha same manner as syntheses of **25** and **31**. Treatment of aminoaldehyde **22** in ethanol solution with **35** afforded the quinoline **40** in 62 % after purification on silica gel. The structural assignment for quinoline **40** was based on the ^{1}H- NMR (300 MHz) analysis showing signals at δ 8.11 (d, 1 H, J = 8.1 Hz), 7.75 (m, 2 H), 7.65 (m, 1 H), 7.49 (m, 1 H), 6.07~6.16 (m, 2 H), 5.86~5.95 (m, 2 H), 4.2 (m, 1 H), 3.90 (m, 1 H), 2.59~2.65 (m, 2 H), 2.11~2.24 (m, 2 H), 1.44 (m, 2 H), 1.16 (m, 2 H); and ^{13}C-NMR δ 166.4, 145.4, 137.0, 132.4, 132.2, 132.1, 131.7, 128.6, 128.2, 127.3, 127.0, 126.6, 125.6, 48.85, 45.07, 43.47, 41.92, 34.77, 34.66, 27.03, 26.70.

SCHEME 7
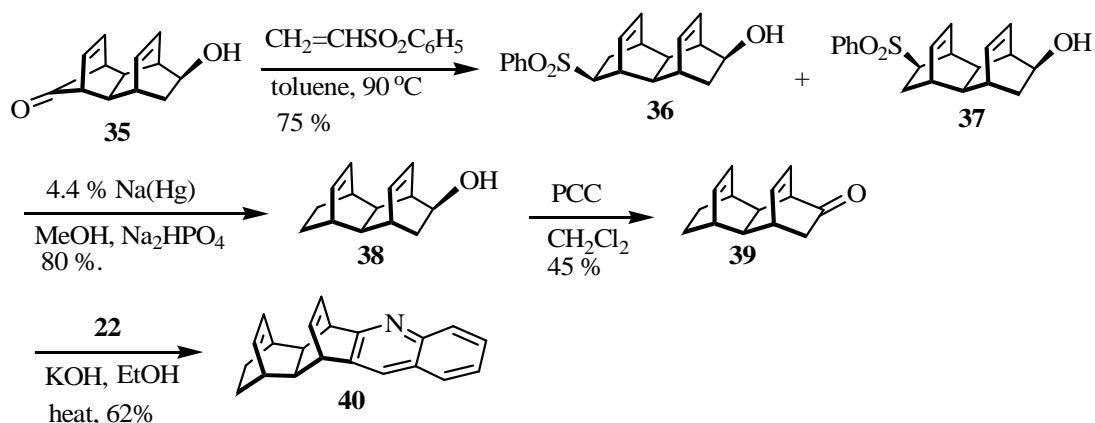
In conclusion, our studies have demonstrated that Friedländer quinoline synthesis can be applied to bicyclo[2.2.2]octenone and sesquibicyclo[2.2.2]octadienone resulting in the formation of a variety of flank fused-quinoline polycarbocycle system. Further studies on the mechanism of photoreaction and synthetic potential of these methods are in progress.

References:

1. Zimmerman, H. E.; Grunewald, G. L. *J. Am. Chem. Soc.* **1966**, *88*, 183.
2. (a) Zimmerman, H. E.; Givens, R. S.; Pagni, R. M. *J. Am. Chem. Soc.* **1968**, *90*, 6096. (b) Zimmerman, H. E.; Bender, C. O. *J. Am. Chem. Soc.* **1970**, *92*, 4366. (c) Hemetsberger, H.; Nispel, F. *Tetrahedron*, **1990**, *46*, 3823. (d) Zimmerman, H. E.; Kutateladze, A. G.; Maekawa, Y.; Mangette, E. *J. Am. Chem. Soc.* **1994**, *116,* 9795. (e) Liao, C. C.; Peddinti, R.   K.; Editor(s): Horspool, W.; Lenci, F. "CRC Handbook of Organic Photochemistry and Photobiology" (2nd Ed.), CRC Press LLC. **2004**, *32*/1-*32*/17.
3. Frutos, L. M.; Sancho, U.; Castaňo, O. *Org. Lett*. **2004**, *6*, 1229.
4. Melder, J. P.; Wahl, F.; Fritz, H.; Prinzbach, H. *Chimia* **1987**, *41*, 426.
5. (a) Paddon-Row, M. N. *Acc. Chem. Res.* **1994**, *27*, 18. (b) Lokan, N. R.; Paddon-Row, M. N.; Koeberg, M.; Verhoeven, J. W. *J. Am. Chem. Soc*. **2000**, *122*, 5057. (c) Bell, T. D. M.; Jolliffe, K. A.; Ghiggino, K. P.; Oliver, A. M.; Shepard, M. J.; Langford, S. L.Paddon-Row, M. N. *J. Am. Chem. Soc.*   **2000**, *122*, 10661.   (d) Koeberg, M.; de Groot, M.; Verhoeven, J. W.; Lokan, N. R.; Shephard, M. J.; Paddon-Row, M. N. *J. Phys. Chem. A* **2001**, *105*, 3417.
6. (a) Lokan, N. R.; Craig, D. C.; Paddon-Row, M. N. *Synlett*, **1999**, *4*, 397. (b) Klarner, F. G.; Polkowska, J.; Panitzky, J.; Seelbach, U. P.; Burkert, U.; Kamieth, M.; Baumann, M.; Wigger, A. E.; Boese, R.; Blaser, D. *Eur. J. Org. Chem,* **2004**, 1405
7. Melder, J. P.; Wahl, F.; Fritz, H.; Prinzbach, H. *Chimia* **1987**, *41*, 426.
8. (a) Grimme, W.; Wortmann, J.; Frowein, D.; Lex, J.; Chen, G.; Gleiter, R. *J. Chem. Soc. Perkin Trans. 2,* **1998**, 1893. (b) Grimme, W.; Gossel, J.; Lex, J. *Angew. Chem. Int. Ed.* **1998**, *37*, 473

9. Behr, J.; Braun, R.; Martin, H. D.; Rubin, M. B.; Steigel, A. *Chem. Ber*, **1991**, *124*, 815.

10. Lin, C. T.; Hwang, B. P.; Chou, T. C. *J. Chin. Chem. Soc.* **1993**, *40*, 159.

11. (a) Kozikowski, A.P.; Schmiesing, R. J. *J. Org. Chem.,* **1983**, *48*, 1000. (b)　Freeman, P. K.; Balls, D. M.; Brown, D. J. *J. Org. Chem.*, **1968**, *33*, 2211.

12. Kozikowski, A.P.; Schmiesing, R. J. *J. Org. Chem.*, **1983**, *48*, 1000.

13. Smith, L. I.; Opie, J. W., *Org. Syn.*, **1955**, Vol. III, 58.

14. Thummel, R. P.; Chirayil, S.; Hery, C.; Lim, J. L.; Wang, T. L. *J. Org. Chem.* **1993**, *58*, 1666.

15. (a) Hua, D. H.; Tamura, M.; Huang, X.; Stephany, H. A.; Helfrich, B. A.; Perchellet, E. M.; Sperfslage, B. J.; Perchellet,J.-P.; Jiang, S.; Kyle, D. E.; Chiang, P. K. *J. Org. Chem.* **2002**, *67*, 2907. (b) Zhu, X.-Z.; Chen, C.-Feng *J. Org. Chem.* **2005**, *70*, 917.

計畫成果自評：

　　本報告內容與原計畫方向相符，達成預期目標合成 Friedlander 縮合產物 25, 31, 40 等三種，並進行照光反應探討重排反應。研究得知 Friedlander 縮合反應很容易運用在双環〔2.2.2〕辛烯及倍半双環〔2.2.2〕辛烯酮，對學術或應用具有價值、整理分析資料後適合在學術期刊發表。