JOC*Article*

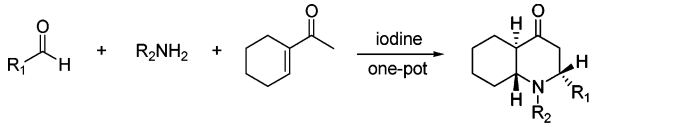
# Stereoselective Three-Component Synthesis of *trans-endo*-Decahydroquinolin-4-one Derivatives from Aldehydes, Aniline, and Acetylcyclohexene

Chunchi Lin, Hulin Fang, Zhijay Tu, Ju-Tsung Liu, and Ching-Fa Yao*

*Department of Chemistry, National Taiwan Normal University, 88, Section 4, Tingchow Road, Taipei, Taiwan 116, Republic of China*

*cheyaocf@scc.ntnu.edu.tw*

*Received May 12, 2006*




The diastereoselective synthesis of *trans-endo*-decahydroquinolin-4-one (**4**) via a three-component reaction of aldehydes (**1**), anilines (**2**), and 1-acetylcyclohexene (**3**) in the presence of iodine in a one-pot reaction at room temperature is described. The short reaction time, easy workup, excellent yield, and mild reaction conditions make this novel annulation strategy both practical and attractive.

## Introduction

The rapid assembly of molecular diverse compounds is an important goal of synthetic organic chemistry and one of the key paradigms of modern drug discovery. One approach to address this challenge involves the development of atom-economical, single-pot, multicomponent coupling reactions.[1] Multicomponent processes, which additionally benefit from technically simple protocols, the use of common laboratory equipment, time and energy savings, and environmental advantages have been of particular interest to both academic and industrial scientists.[2] An example of such a three-component reaction is the synthesis of hydroquinolinone derivatives. Due to the vast utility of hydroquinolinone derivatives, various methods for preparing these compounds have been reported.[3]

Bicyclic decahydroquinolinones have been prepared via the application of Lewis acid-catalyzed Diels−Alder reactions of trimethylsilyl enol ethers and imines (Scheme 1).[4] However, these reactions cannot be carried out in a one-pot operation with an aromatic aldehyde (**1**), aniline (**2**), and 1-acetylcyclohexene (**3**) because the imine and trimethylsilyl enol ether of 1-acetylcyclohexene (**3**) must be prepared in advance. Additionally, the amines and water that are present during the formation of the imine intermediate are incompatible with both trimethylsilyl enol ether and Lewis acids. It should be noted that the diastereoselective synthesis of decahydroquinolinone derivative is also a stereochemical challenge as four isomers can be generated as the reaction proceeds.[4] The development of an efficient one-pot, stereo- and chemoselective procedure affording decahydroquinolinone derivatives (**4**) from aromatic aldehydes (**1**), anilines (**2**), and 1-acetylcyclohexene (**3**) would constitute an import advance.

Iodine has recently emerged as a Lewis acid imparting high regio- and chemoselectivity in various transformations.[5] One of the remarkable features of iodine is its efficient activity under neat conditions or high-concentration conditions. Thus, we considered iodine to be an ideal Lewis acid for effecting one-pot syntheses of decahydroquinolinone derivative from aromatic aldehydes (**1**), anilines (**2**), and 1-acetylcyclohexene (**3**) (Scheme 2). Herein, we describe the iodine-mediated three-component coupling of an aniline, aldehyde, and 1-acetylcyclohexene under

(1) Evdokimov, N. M.; Magedov, I. V.; Kireev, A. S.; Kornienko, A. *Org. Lett.* **2006**, *8*, 899.

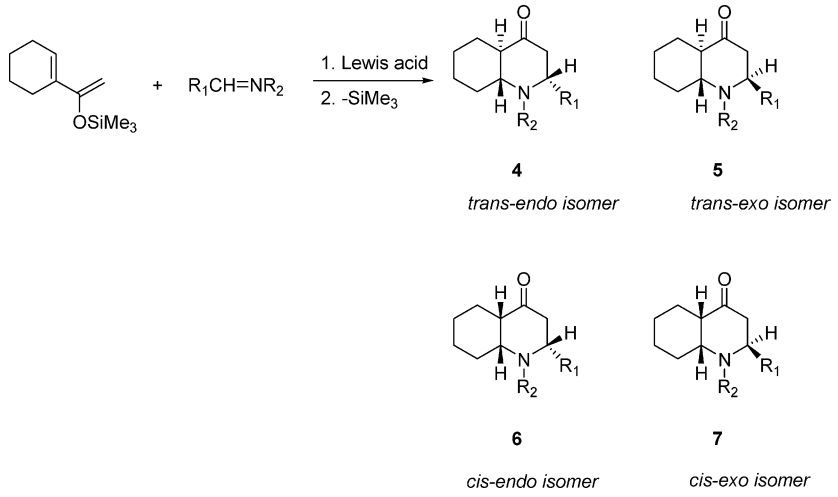
(2) (a) Ramo'n, D. J.; Miguel, Y. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602. (b) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471. (c) Ugi, I.; Heck, S. *Comb. Chem. High Throughput Screening* **2001**, *4*, 1. (d) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, 366.

(3) (a) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (b) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099. (c) Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3559. (d) Kobayashi, S.; Komiyama, S.; Ishitani, H. *Angew. Chem., Int. Ed.* **1998**, *37*, 979. (e) Bromidge, S.; Wilson, P. C.; Whiting, H. *Tetrahedron Lett.* **1998**, *39*, 8905. (f) Jorgensen, K. A.; Hazell, R. G.; Johansen, M.; Yao, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 3121. (g) Jorgensen, K. A.; Hazell, R. G.; Audrain, H.; Johansen, M.; Yao, S. *J. Am. Chem. Soc.* **1998**, *120*, 8599. (h) Kobayashi, S.; Kusakabe, K.-I.; Komiyama, S.; Ishitani, H. *J. Org. Chem.* **1999**, *64*, 4220. (i) Jorgensen, K. A.; Hazell, R. G.; Saaby, S.; Yao, S. *Chem. Eur. J.* **2000**, *6*, 2435.

(4) (a) Le Coz, L.; Veyrat-Martin, C.; Wartsky, L.; Seyden-Penne, J.; Bois, C.; Philoche-Levisalles, M. *J. Org. Chem.* **1990**, *55*, 4870. (b) NogueÂ, D.; Paugam, R.; Wartski, L. *Tetrahedron Lett.* **1992**, *33*, 1265. (c) Paugam, R.; Wartski, L. *Tetrahedron Lett.* **1991**, *32*, 491. (d) Paugam, R.; Valenciennes, E.; Coz-Bardol, L. L.; Garde, J.-C.; Wartski, L.; Lance, M.; Nierlich, M. *Tetrahedron*: *Asymmetry* **2000**, *11*, 2509.

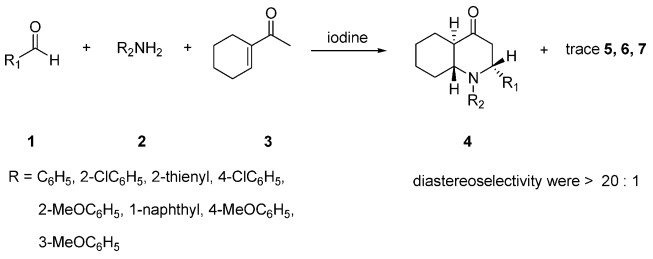
10.1021/jo060992c CCC: $33.50 
Published on Web 07/18/2006

**SCHEME 1. The Conformations of Compounds 4, 5, 6, and 7**[a]




[a] The conformation of products **4**−**7** was deduced from the values of the half bandwidth of H-9 and H-10 protons or their coupling constants.

**SCHEME 2. The Three-Component Synthesis of Hydrodecaquinolinone Derivative**




neat or high-concentration conditions to afford *trans*-*N*-phenyl-2-aryldecahydroquinolin-4-one in excellent yields and diastereoselectivities.

## Result and Discussion

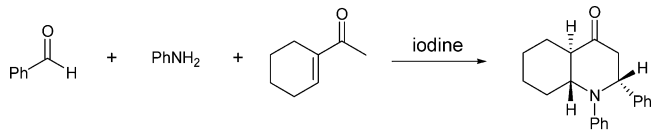
For the one-pot preparation of *trans-endo-N*-phenyl-2-phenyldecahydroquinolin-4-one (**4**), initial experiments were carried out with benzaldehyde (**1**) ($R_1 = C_6H_5$), aniline (**2**) ($R_2 = C_6H_5$), and 1-acetylcyclohexene (**3**) in the presence of iodine at room temperature. Optimization of the ratios of **1**, **2**, **3**, and iodine ultimately afforded reasonable yields of *trans-endo-N*-phenyl-2-phenyldecahydroquinolin-4-one (**4**) (Table 1, entries 1−7). In preliminary experiments with different amounts of iodine, first, reaction of **1**, **2**, and **3** in the presence 0.2 equiv of iodine for 48 h afford *trans-endo-N*-phenyl-2-phenyldecahydroquinolin-4-one (**4**) in 52%, with 40% of benzaldehyde (**1**) recovered (entry 1). Surprisingly, increasing the amount of iodine (0.5 equiv) improved the results dramatically giving 76% of **4** (entry 2). Similarly, the reaction proceeded rapidly with good yield (75%) when the amount of iodine was increased to 1.0 equiv for 4 h under similar conditions (entry 3). However, the yields decreased to 59% when the reaction was performed in the presence of an excess amount (1.5 equiv) of iodine for 18 h (entry 4). A possible explanation for the decrease in product yields (**4**) is that part of iodine could have reacted with aniline to give 4-iodoaniline.[6] On the basis of the conditions of entry 4, we also found the optimal amount of aniline (**2**) and 1-acetylcyclohexene (**3**) to be 1.2 and 2.0 equiv, respectively (entries 5−7). Solvent also has a significant impact on the reaction efficiency and yields (entries 8−13). Ethyl ether is commonly used when iodine is employed as a Lewis acid; however, in certain cases it can be replaced by ethyl acetate (EA) or other solvents. DMSO, $CH_2Cl_2$, $CH_3OH$, and $CHCl_3$ were screened as solvents but unsatisfactory yields and/or long reaction times were observed in the one-pot system (entries 8−12). However, the use of ethyl ether led to excellent yields of the three-component reaction products (entries 13 and 14). After a series of optimization experiments, ethyl ether was found to be the best solvent and the yield of **4** reached 99% (diastereoselectivity >20:1) when 1.0 equiv of benzaldehyde (**1**) was reacted with 2.0 equiv of aniline (**2**), 1.5 equiv of **3**, and 1.0 equiv of iodine in ethyl ether at room temperature for 2 h (entry 14). By the way, the stereochemistry and conformation of product **4** has been confirmed by Wartski and Seyden-Penne already.[4a] Under thermodynamic control, product **4** is highly favored and the conformations of *trans-endo-N*-phenyl-2-aryldecahydroquinolin-4-one derivatives (**4**) were determined by single-crystal X-ray diffraction studies of **4**, **8**, **9**, and **15** (see Figure 1 and Supporting Information).

In Table 2, the reaction of aryl aldehyde (**1**) (1.0 equiv), aniline (**2**) (1.5 equiv), and 1-acetylcyclohexene (**3**) (2.0 equiv) in the presence of iodine (1.0 equiv) in 0.5 mL of ethyl ether at room temperature gave *trans-endo-N*-phenyl-2-aryldecahydro-

(5) (a) Kim, K. M.; Ryu, E. K. *Tetrahedron Lett*. **1996**, *37*, 1441. (b) Firouzabadi, H.; Iranpoor, N.; Hazarkhani, H. *J. Org. Chem*. **2001**, *66*, 7527. (c) Firouzabadi, H.; Iranpoor, N.; Sobhani, S. *Tetrahedron Lett*. **2002**, *43*, 3653. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett*. **2002**, *43*, 9703. (e) Bandgar, B. P.; Shaikh, K. A. *Tetrahedron Lett*. **2003**, *44*, 1959. (f) Saeeng, R.; Sirion, U.; Sahakitpichan, P.; Isobe, M. *Tetrahedron Lett*. **2003**, *44*, 6211. (g) Yadav, J. S.; Reddy, B. V. S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett*. **2004**, *45*, 2951. (h) Phukan, P. *J. Org. Chem*. **2004**, *69*, 4005. (i) Phukan, P. *Tetrahedron Lett*. **2004**, *45*, 4785. (j) Sun, J.; Dong, Y.; Wang, X.; Wang, S.; Hu, Y. *J. Org. Chem*. **2004**, *69*, 8932. (k) Bhosale, R. S.; Bhosale, S. V.; Bhosale, S. V.; Wang, T.; Zubaidha, P. K. *Tetrahedron Lett*. **2004**, *45*, 9111. (l) Ke, B.; Qin, Y.; He, Q.; Huang, Z.; Wang, F. *Tetrahedron Lett*. **2005**, *46*, 1751. (m) Banik, B. K.; Fernandez, M.; Alvarez, C. *Tetrahedron Lett*. **2005**, *45*, 2479. (n) Chu, C.-M.; Gao, S.; Sastry, M. N. V.; Yao, C.-F. *Tetrahedron Lett*, **2005**, *46*, 4971. (o) Ko, S.; Sastry, M. N. V.; Lin, C.; Yao, C.-F. *Tetrahedron Lett*, **2005**, *46*, 5771. (p) Shivaji, V. M.; Sastry, M. N. V.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett*. **2005**, *46*, 6345. (q) Lin, C.; Hsu, J.; Sastry, M. N. V.; Fang, H.; Tu, Z.; Liu, J.-T.; Yao, C.-F. *Tetrahedron* **2005**, *61*, 11751. (r) Ko, S.; Lin, C.; Tu, Z.; Wang, Y.-F.; Wang, C.-C.; Yao, C.-F. *Tetrahedron Lett*. **2006**, *47*, 487. (s) Gao, S.; Tzeng, T.; Sastry, M. N. V.; Chu, C.-M.; Liu, J.-T.; Lin, C.; Yao, C.-F. *Tetrahedron Lett*. **2006**, *47*, 1889.

(6) Monnereau, C.; Blart, E.; Odobel, F. *Tetrahedron* **2005**, *46*, 5421.

**TABLE 1. The Determination of Optimal Conditions for the Synthesis of *trans-endo-N*-Phenyl-2-phenyldecahydroquinolin-4-one 4[a]**




**1** **2** **3** **4**

| entry | **1** (mmol)[b] | **2** (mmol)[b] | **3** (mmol)[b] | solvent[b] | $I_2$ (mmol)[b] | time (h) | **4** (%)[c,d] |
|---|---|---|---|---|---|---|---|
| 1 | 1.0 | 1.2 | 1.5 | − | 0.2 | 48 | 52[e] |
| 2 | 1.0 | 1.2 | 1.5 | − | 0.5 | 8 | 76 |
| 3 | 1.0 | 1.2 | 1.5 | − | 1.0 | 4 | 75 |
| 4 | 1.0 | 1.2 | 1.5 | − | 1.5 | 18 | 59 |
| 5 | 1.0 | 1.2 | 2.0 | − | 1.0 | 2 | 80 |
| 6 | 1.0 | 1.2 | 3.0 | − | 1.0 | 5 | 76 |
| 7 | 1.0 | 1.5 | 1.5 | − | 1.0 | 2 | 68 |
| 8 | 1.0 | 1.2 | 2.0 | 0.5 mL of DMSO | 1.0 | 48 | 31 |
| 9 | 1.0 | 1.2 | 2.0 | 0.5 mL of $CH_2Cl_2$ | 1.0 | 18 | 83 |
| 10 | 1.0 | 1.2 | 2.0 | 0.5 mL of EA | 1.0 | 18 | 93 |
| 11 | 1.0 | 1.2 | 2.0 | 0.5 mL of $CH_3OH$ | 1.0 | 48 | 88 |
| 12 | 1.0 | 1.2 | 2.0 | 0.5 mL of $CHCl_3$ | 1.0 | 18 | 99 |
| 13 | 1.0 | 1.2 | 2.0 | 0.5 mL of ether | 1.0 | 8 | 96 |
| 14 | 1.0 | 1.5 | 2.0 | 0.5 mL of ether | 1.0 | 2 | 99 |

[a] Reactions were carried out at room temperature. [b] Commercially available reagents and solvent were used without further purification or drying. [c] NMR yields. [d] Diastereoselectivities of >20:1 were observed. [e] 30% benzaldehyde was recovered.

quinolin-4-one (**4**) in good to excellent yields. Under optimal reaction conditions, a variety of aldehydes (**1**) and substituted anilines (**2**) were investigated and the results are summarized in Table 2. Most of the aldehydes (**1**) reacted readily to produce **4** in excellent yields and high diastereoselectivity (>20:1). The reactions of aldehydes (**1**) containing electron-donating groups show only a slightly slower reaction rate and lower yields than those containing electron-withdrawing groups (entries 1−6). We observed reduced chemical yields for both ortho-substituted and naphthyl benzaldehydes regardless of the electronic nature of the substitutent (entries 4, 5, and 8). This suggests that steric factors for ortho-substituted imine intermediates can significantly attenuate the reaction yield. In addition, heteroaromatic aldehyde (**1g**) can also serve as a substrate in this reaction, giving the corresponding *trans-endo-N*-phenyl-2-thienyldecahydroquinolin-4-one (**13**) in 60% and 40% of the side product *trans*-2-benzylaminocyclohexyl-2-thienyleth-1-enyl ketone (**13**α) (entry 7). The determination of the structure of (**13**α) was confirmed in an X-ray study and the structure is shown in Figure 2. Substitution effects concerning the aniline (**2**) were also briefly studied. Although the electronic nature of aniline (entries 9 and 10) and the aldehyde (entries 3 and 10) qualitatively appears to impact reaction rate, these factors have no observed impact on the diastereoselectivity of the process.

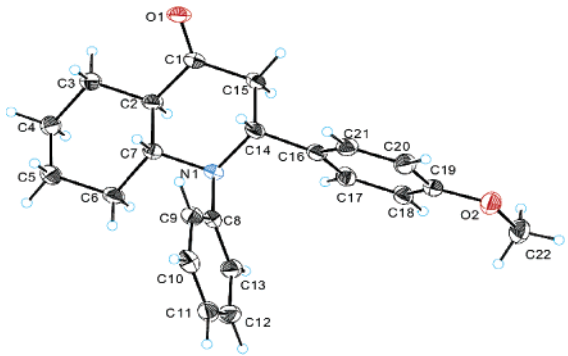
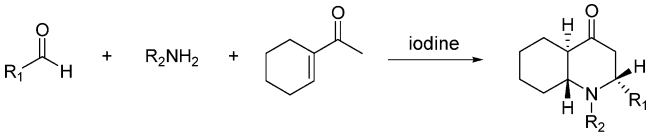



**FIGURE 1.** Single-crystal X-ray diffraction study of **9**.

**TABLE 2. The Prepared *trans-Endo-N*-phenyl-2-aryldecahydroquinolin-4-one[a]**



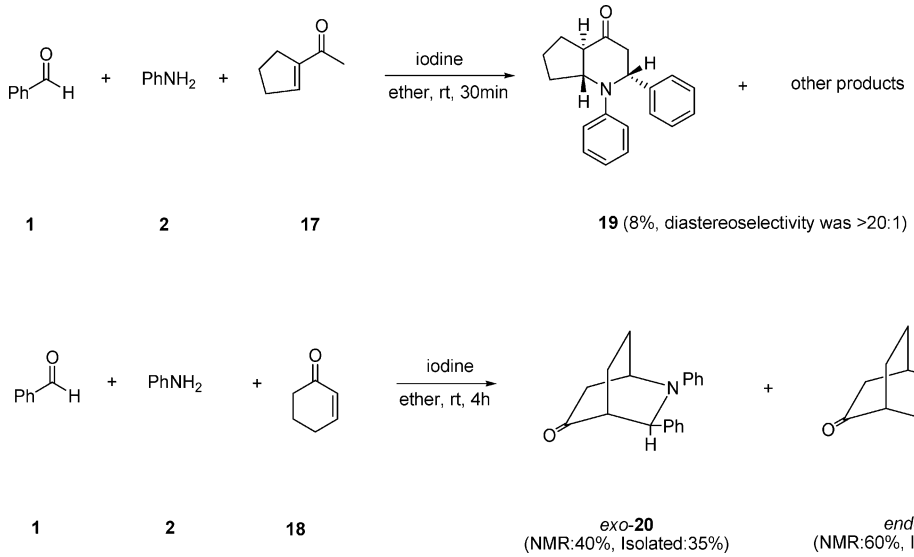

**1** **2** **3** **4**

| entry | $R_1$[b] | $R_2$[b] | time (h) | product | (NMR/isolated) yield (%) |
|---|---|---|---|---|---|
| 1 | $C_6H_5$ | $C_6H_5$ | 2.0 | **4** | 99/95 |
| **2** | 4-$ClC_6H_5$ | $C_6H_5$ | 1.5 | **8** | 96/92 |
| **3** | 4-$MeOC_6H_5$ | $C_6H_5$ | 4.0 | **9** | 85/80 |
| **4** | 2-$ClC_6H_5$ | $C_6H_5$ | 1.5 | **10** | 58/52 |
| **5** | 2-$MeOC_6H_5$ | $C_6H_5$ | 2.0 | **11** | 73/68 |
| **6** | 3-$MeoC_6H_5$ | $C_6H_5$ | 3.0 | **12** | 86/83 |
| **7** | 2-thienyl | $C_6H_5$ | 2.5 | **13** | 60[c]/55 |
| **8** | 1-naphthyl | $C_6H_5$ | 1.5 | **14** | 74/70 |
| **9** | $C_6H_5$ | 4-$ClC_6H_5$ | 1.0 | **15** | 90/87 |
| **10** | $C_6H_5$ | 4-$MeOC_6H_5$ | 5.0 | **16** | 93/88 |

[a] Reaction was carried out at room temperature. [b] Commercially available reagents were used without further purification and the solvent was used without drying. [c] 40% of **13**α was isolated and the structure was determined by the single-crystal X-ray diffraction that was shown in Figure 2.

Finally, we also examined the reactions of other enones such as acetylcyclopentene (**17**) and cyclohexenone (**18**) with **1** and **2** in the presence of 1 equiv of iodine under similar conditions. However, the desired product *trans-endo-N*-phenyl-2-phenyloctahydropyrin-4-one (**19**) from **17** was obtained only in 8% yield with high diastereoselectivity and other unidentified products were also generated in the one-pot process within 30 min at room temperature. The reaction was also amenable to cyclohexenone (**18**) to yield 3-*exo*-phenyl-2-phenyl-2-azabicyclo-[2.2.2]octan-5-one (*exo*-**20**) and 3-*endo*-phenyl-2-phenyl-2-azabicyclo[2.2.2]octan-5-one (*endo*-**20**) isomers in quantitative NMR yield and the ratio of *exo*-**20**:*endo*-**20** was 2:3 (Scheme 3). All the spectral data of **19** and **20** are consistent with the literature report.[4c,7] The generation of **19** and **20** is assumed to be similar to the generation of **4**−**16**.

**SCHEME 3. The Reaction was Amenable to Acetylcyclopentene and Cyclohexenone**




In summary, we successfully designed, synthesized, and evaluated a three-component coupling reaction of structurally diverse aldehydes (**1**) with aniline (**2**) and 1-acetylcyclohexene (**3**) resulting in the formation of some substituted *trans-endo-N*-phenyl-2-aryldecahydroquinolin-4-one (**4**). This one-pot process proceeds in ethyl ether solution at room temperature with excellent yields and diastereoselectivities (>20:1). The direct use of commercially available and inexpensive reagents, easy workup, short reaction times, and mild reaction conditions make this novel annulation strategy both attractive and practical.

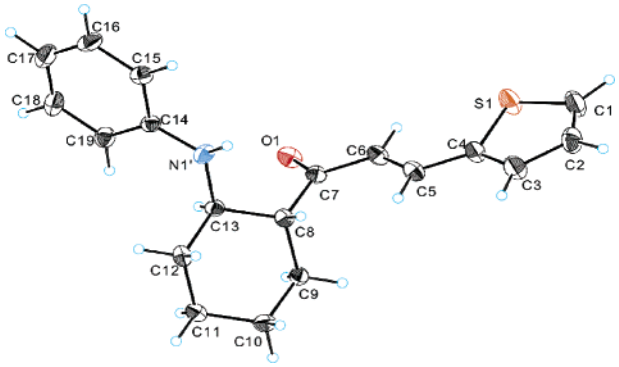



**FIGURE 2.** Single-crystal X-ray diffraction study of **13α**.

## Experimental Section

**(a) General.** All reactions were performed under 0.5 mL of ethyl ether at room temperature. Analytical thin-layer chromatography was performed with E. Merck silica gel 60F glass plates and flash column chromatography used E. Merck silica gel 60 (230−400 mesh). MS or HRMS were measured with a JEOL JMS-D300 or a JEOL JMS−HX110 spectrometer. $^1$H NMR and $^{13}$C NMR spectra were recorded with a Bruker Aavance EX 400 spectrometer. The single-crystal X-ray diffraction studies were by Nonius Kappa CCD Axis.

**(b) Materials.** Chemical such as aldehyde (**1**), aniline (**2**), 1-acetylcyclohexene (**3**), 1-acetylcyclopentene (**17**), 2-cyclohex-1-one (**18**), and iodine and solvent were purchased from Aldrich and/or Acros Chemical Co and were not purified or dried before used.

(7) Babu, G.; Perumal, P. T. *Tetrahedron* **1998**, *54*, 1627.

**(c) Synthesis of 4 and 8−16.** Typical experimental procedures for the synthesis of products **4** and **8−16** (**4**: $R^1 = C_6H_5$, $R^2 = C_6H_5$; **8**: $R^1 = 4\text{-}ClC_6H_4$, $R^2 = C_6H_5$; **9**: $R^1 = 4\text{-}MeOC_6H_4$, $R^2 = C_6H_5$; **10**: $R^1 = 2\text{-}ClC_6H_4$, $R^2 = C_6H_5$; **11**: $R^1 = 2\text{-}MeOC_6H_4$, $R^2 = C_6H_5$; **12**: $R^1 = 3\text{-}MeOC_6H_4$, $R^2 = C_6H_5$; **13**: $R^1 = 2$-thienyl, $R^2 = C_6H_5$; **14**: $R^1 = 1$-naphthyl, $R^2 = C_6H_5$; **15**: $R^1 = C_6H_5$, $R^2 = 4\text{-}ClC_6H_4$, **16**: $R^1 = C_6H_5$, $R^2 = 4\text{-}MeOC_6H_4$) are the following: A mixture of aldehyde (**1**) (1.0 mmol), aniline (**2**) (1.5 mmol), 1-acetylcyclohexene (**3**) (2.0 mmol), and iodine ($I_2$) (1.0 mmol) was added to ethyl ether (0.5 mL) in one pot at the same time and the mixture was then stirred at room temperature for several hours. After completion of the reaction (monitored by TLC), the solution was washed with an ice cold saturated $Na_2S_2O_{3(aq)}$ solution (2 × 10 mL when iodine was used) and then extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were washed sequentially with brine and ice water and dried over anhydrous $Na_2SO_4$. Evaporation of the organic solvent afforded the crude products which were purified by short flash column chromatography followed by recrystallization from hexane and ethyl acetate if necessary.

**(d) Syntheis of 19, *exo*-20, and *endo*-20.** Typical experimental procedures for the synthesis of products **19**, *exo*-**20**, and *endo*-**20** are the following: The mixture of benzaldehyde (**1**) (1.0 mmol), aniline (**2**) (1.5 mmol), 1-acetylcyclopentene (**17**) or cyclohexenone (**18**) (2.0 mmol), and iodine ($I_2$) (1.0 mmol) was added to ethyl ether (0.5 mL) in one pot at the same time and the mixture was then stirred at room temperature over a period of several hours. After completion of the reaction (monitored by TLC), the solution was washed with an ice cold saturated $Na_2S_2O_{3(aq)}$ solution (2 × 10 mL when iodine was used) and then extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic phases were washed sequentially with brine and ice water and dried over anhydrous $Na_2SO_4$. Evaporation of the organic solvent afforded the crude products which were purified by short flash column chromatography followed by recrystallization from hexane and ethyl acetate if necessary.

**Acknowledgment.** Financial support from the National Science Council of the Republic of China is gratefully acknowledged.

**Supporting Information Available:** Experimental procedures, characterization data, and representative $^1$H and $^{13}$C spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060992C