Pergamon

Tetrahedron 55 (1999) 14611–14622

TETRAHEDRON

A Systematic Study of Reaction of Heterocyclic Enamines with Electrophilic Alkynes: A Simple and Efficient Synthetic Route to 2-Pyridinone-fused Heterocycles

Mei-Xiang Wang* [a], Wei-Shi Miao[a], Ying Cheng[b] and Zhi-Tang Huang* [a]

a: Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, China

b: Department of Chemistry, Beijing Normal University, Beijing 100875, China

Received 23 July 1999; revised 28 September 1999; accepted 14 October 1999

Abstract: The reaction of heterocyclic enamines with ethyl propiolate and diethyl acetylenedicarboxylate has been systematically studied. In contrast to their heterocyclic ketene aminal analogues, heterocyclic enamines reacted with electrophilic alkynes *via* the Michael addition pathway rather than the aza-ene reaction mechanism. In the presence of a strong base such as sodium ethoxide and sodium hydride, the resulting Michael addition products underwent cyclocondensation reaction readily to produce 2-pyridinone-fused heterocycles in good to excellent yield.

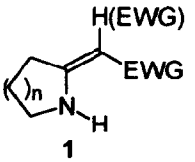
INTRODUCTION

Heterocyclic secondary enamines **1**, also known as *exo*-cyclic enaminones, enamino esters and enamino nitriles when electron-withdrawing group (EWG) being, respectively, acyl, ester and nitrile, have been shown to be the useful intermediates for the synthesis of natural products. In 1960s, Eschenmoser and his coworkers[1] pioneered the chemistry of heterocyclic enamines during their synthetic study of corrin. They achieved the reaction of enamino nitrile with iminoether as one of the key steps in the construction of the corrin ring system. Since later 1970s, heterocyclic enamines have been applied by Kishi,[2] Danishefsky,[3] Rapoport[4] and others in the synthesis of saxitoxin, camptothecin, mitomycins and alkaloids.[5-8] Very recently, synthesis of carbacephems, a new class of β-lactam antibiotics, has been reported by reducing the double bond of heterocyclic enamines followed by intramolecular cyclization.[9]

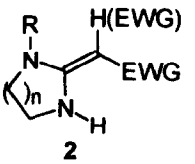
One of the interesting features of heterocyclic enamines **1** is their ambident nucleophilicity; nucleophilic reaction can take place at the site of enaminic carbon and/or of secondary amino nitrogen. This has been exemplified by the acylation reaction, which gave rise to *C*- and/or *N*-acylated products depending on the

* Corresponding authors. e-mail: wangmx@public2.east.net.cn; huangzt@public.bta.net.cn

0040-4020/99/$ - see front matter
PII: S0040-4020(99)00937-0



1



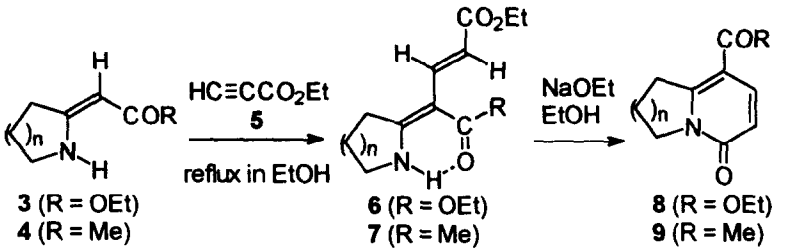
2

EWG = CN, COR', CO_2R', NO_2 etc., n = 1, 2, 3

heterocyclic structure of enamines.[10] When treated with biselectrophiles, enamines **1** acted as bisnucleophiles to give fused heterocyclic compounds. Although such annelation reactions have been successfully employed in several cases of alkaloid synthesis,[3-8] it is surprisingly to note that knowledge of the reaction of heterocyclic enamines with biselectrophilic reagents is limited and little is known regarding their reaction mechanisms.[11] This is especially true when compared with the study of its aza-analogue, heterocyclic ketene aminals **2**.[12] Notably, heterocyclic ketene aminals **2** have been shown recently to be a unique aza-ene component and they underwent aza-ene addition reaction with a number of α,β–unsaturated compounds.[13-16] Interest in the chemistries of heterocyclic enamines[17] and ketene aminals,[12] particularly the difference between them and the correlation between structure and reactivity, led us to undertake the current study. By examining systematically the reactions of heterocyclic enamines **1** with electron-deficient alkynes such as ethyl propiolate and diethyl acetylenedicarboxylate, we have found surprisingly that heterocyclic enamines **1** behave totally differently from heterocyclic ketene aminals **2** although they share structural and spectral similarities. Herein we wish to report our results. [18]

RESULTS AND DISCUSSION

Ester-substituted heterocyclic enamines **3a-c** reacted smoothly with ethyl propiolate **5** in refluxing ethanol to give **6a-c** as the sole product in good to excellent yield. In the presence of a catalytic amount of sodium ethoxide, cyclization proceeded rapidly and efficiently to furnish fused heterocycles **8a-c** in almost quantitative yield (Scheme 1). Compounds **8** were also conveniently synthesized through a one-pot operation by adding sodium ethoxide to the mixture after starting enamines **3** were converted to **6**. When acetyl-substituted heterocyclic enamines **4** were refluxed with **5** in ethanol, the reaction was less effective and the outcome was strongly dependent upon the ring size of reactants **4**. Thus, under identical conditions both six- and seven-membered heterocyclic enamines **4b** and **4c** gave the corresponding adducts **7b** (42%) and **7c** (35%), whereas the five-membered analogue **4a** produced a mixture of adduct **7a** (31%) and cyclized compound **9a** (42%). Prolonged reaction time caused conversion of **7a** and **7b** into **9a** and **9b**, respectively, but did not achieve the cyclization of seven-membered adduct **7c**. Only in the presence of sodium ethoxide did transformation of **7c** into **9c** take place effectively.



Scheme 1

The structures of all products **6-9** were established on the basis of spectroscopic evidence and elemental analyses. For the adducts **6** and **7**, observation of an NH absorption band in the infra-red spectrum and of an NH signal around 9-12 ppm in the ^{1}H-NMR spectrum excluded the possible *N*-addition structure. Such a large downfield shift of the NH signal is due to the effects of extensive conjugation and of the formation of an intramolecular hydrogen bond. The configuration of the other alkene bond was proved by the observation of a set of AB signals showing a coupling constant of 15 Hz in the ^{1}H-NMR spectra. The 2-pyridinone structure of compounds **8** and **9** was confirmed by NMR spectra which displayed an AB system of coupling constant around 9.5 Hz in ^{1}H-NMR and amide carbonyl signal around 162 ppm in ^{13}C-NMR spectra. The lactam structure was also supported by the infra-red spectrum in which an amide carbonyl vibration band was evident around 1625-1660 cm^{-1}.

The reaction of heterocyclic ketene aminals **2** with ethyl propiolate **5** has been demonstrated to proceed *via* an aza-ene addition mechanism.[13] Would heterocyclic enamines **3** and **4**, being the analogues of **2**, act similarly as an aza-ene component in organic synthesis? In order to obtain a better understanding of the reaction of heterocyclic enamines **1**, *N*-methylated heterocyclic enamines **10** were synthesized[19] and subjected to the reaction. The outcome of the reactions between **10** and **5** and between **3** and **5** are listed in Table 1.

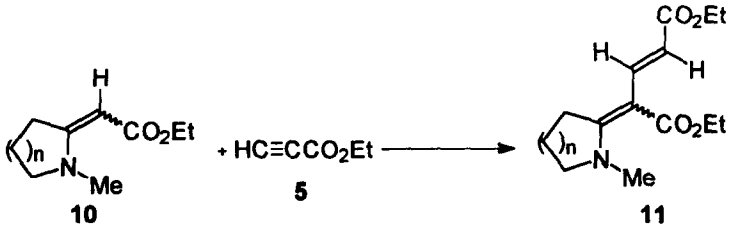
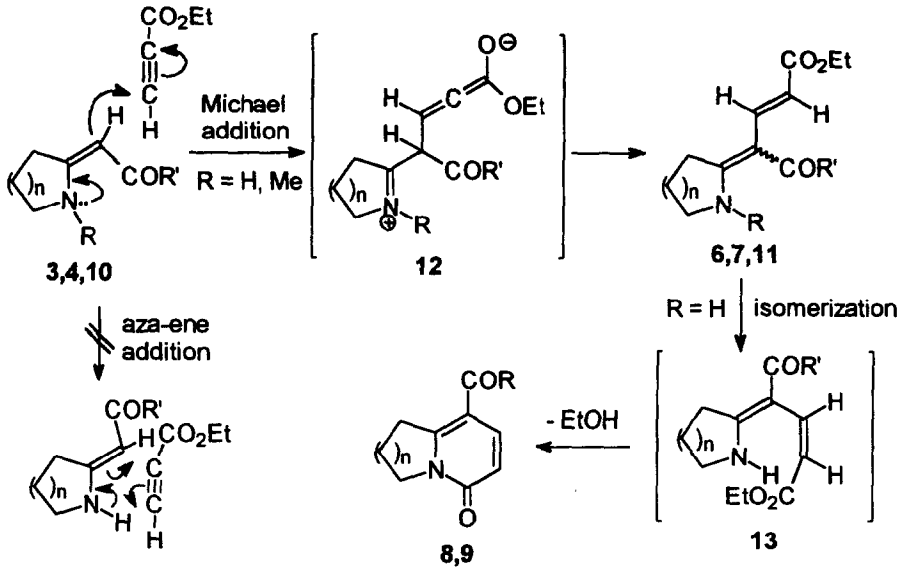


Table 1. Reaction of **3** and **10** with **5**

Entry	Reactant	Conditions	Recovered (%)	[a]Products (%)	
1	**3a**	Ethanol, reflux 16 h	**3a** (0)	**6a** (74)	**8a** (0)
2	**3a**	Dry benzene, reflux 144 h[b]	**3a** (28)	**6a** (33)	**8a** (8)
3	**3a**	Dry toluene, reflux 144 h	**3a** (10)	**6a** (0)	**8a** (45)
4	**10a**	Ethanol, reflux 16 h	**10a** (0)	**11a** (64)	
5	**10a**	Dry benzene, reflux 144 h[b]	**10a** (76)	**11a** (12)	
6	**10a**	Dry toluene, reflux 144 h	**10a** (60)	**11a** (19)	
7	**3c**	Ethanol, reflux 30 h	**3c** (0)	**6c** (87)	**8c** (0)
8	**3c**	Dry benzene, reflux 144 h[b]	**3c** (49)	**6c** (22)	**8c** (0)
9	**10c**	Ethanol, reflux 30 h	**10c** (0)	**11c** (49)	
10	**10c**	Dry benzene, reflux 144 h[b]	**10c** (51)	**11c** (9)	

a: isolated yield; b: under argon.

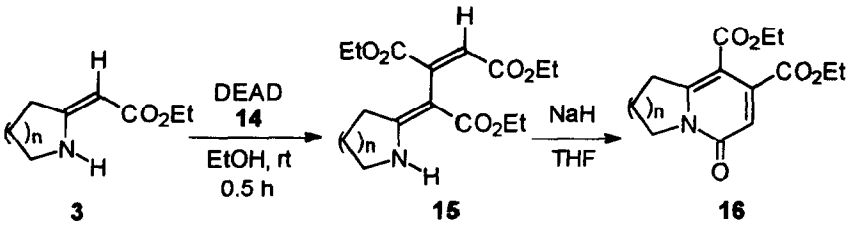
As illustrated in Table 1 (entries 1, 4, 7 and 9), both secondary enamine **3** and tertiary enamine **10** underwent similar addition reaction to ethyl propiolate **5** in protic solvents such as ethanol to form the corresponding *cis*-adducts. It should be noted that the configuration of enamine double bond of product **11** cannot be determined from the spectroscopic data, though it gave only one set of ^{1}H-NMR signals indicative of a single isomer. The results are in sharp contrast to the cases of heterocyclic ketene aminals **2**, of which only those bearing at least a secondary amino group underwent addition reaction.[13] Although reaction took place very sluggishly in an apolar solvent including dry benzene and toluene, the same product **11** was also isolated, albeit in low yield (entries 5, 6 and 10). Reaction rate of secondary enamine **3** in apolar solvents also decreased dramatically; reaction did not go to completion within 6 days (entries 2, 3 and 8). At elevated refluxing temperature, cyclization of the adduct occurred spontaneously to give **8** as the major product (entry 3). These results showed clearly that the reaction between heterocyclic enamines and ethyl propiolate did not proceed *via* an aza-ene addition pathway like that which accounts for the reaction of heterocyclic ketene aminals **2**.[13] An alternative reaction mechanism involving a Michael addition would probably operate in this case (Scheme 2).



Scheme 2

All experimental facts can best be interpreted by the mechanism depicted in Scheme 2. The Michael addition of heterocyclic enamines **3**, **4** and **10** to ethyl propiolate **5** formed adducts **6**, **7** and **11** by way of zwitterionic intermediate **12**. Isomerization of the double bonds of adducts **6** or **7** in a protic solvent or at elevated temperature resulted in the intermediate **13** which underwent cyclocondensation reaction to furnish the fused heterocycles **8** or **9**. Since the reaction proceeds *via* the zwitterionic structure **12**, a polar solvent such as ethanol can facilitate the reaction. In an apolar solvent such as benzene or toluene, that could not stabilize the dipolar structure of **12**, the rate of reaction decreased significantly. In apolar solvents, however, secondary enamines **3** and **4** exhibited higher reactivity than tertiary enamines **10** because the zwitterionic intermediate **12** (R = H) can lose a proton or rearrange to form a neutral species. Such sensitivity of reaction to the polarity of reaction media also ruled out a possible mechanism comprising [2+2] cycloaddition followed by rearrangement, which works commonly for the reaction of typical tertiary enamines and electrophilic alkynes.[20] In other words, if reaction proceeded through a [2+2] cycloaddition pathway, the outcome would be similar or identical irrespective of the structure of the reactants and conditions used. The difference between ester- and acetyl-substituted heterocyclic enamines **3** and **4** in both enaminic addition and cyclocondensation reactions reflected the different conjugation effect of the secondary enamine segment. Having an ester group attached, compound **3** yields a better conjugated system with the lone-pair electrons of nitrogen being more extensively delocalized into the double bond, as shown by the observation of a more shielded vinyl H-resonance of **3** than that of **4** in ^{1}H-NMR spectra.[17] Therefore the enaminic reactivity of **3** appears higher than that of **4**, and the reactivity of secondary amino moiety of **3** is lower than that of **4**.

We then examined the reaction of heterocyclic enamines **3** with diethyl acetylenedicarboxylate (DEAD) **14**. Being a more electron-deficient alkyne species, **14** reacted with enamines **3** very rapidly and efficiently. It took only 0.5 h for the reaction at ambient temperature in ethanol to go to completion, affording the Michael adduct **15**. Cyclocondensation of the five-membered adduct **15a** was similarly effected as that for **6** by using sodium ethoxide as a catalyst. To achieve cyclization of six- and seven-membered analogues **15b** and **15c**, however, an equimolar amount of sodium hydride in tetrahydrofuran was necessary (Scheme 3).



3 **15** **16**

Scheme 3

CONCLUSION

By examining the reactions of heterocyclic enamines with ethyl propiolate and diethyl acetylenedicarboxylate, we concluded that the reaction proceeded most probably *via* the Michael addition mechanism rather than by the aza-ene mechanism, although heterocyclic enamines have been reported to show similar structural and spectral properties to those of heterocyclic ketene aminals. The reaction has provided a very simple and efficient synthesis of 2-pyridinone-fused heterocyclic compounds.

EXPERIMENTAL

Melting points are uncorrected. IR spectra were obtained on a Perkin-Elmer 782 instrument as KBr discs. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution with $SiMe_4$ as internal standard on Varian Unity 200 and Bruker DMX-300 spectrometers. Chemical shifts are reported in ppm and coupling constants are in Hz. Mass spectra were measured on an AEI MS-50 spectrometer. Elemental analyses were carried out at the Analytical Laboratory of the Institute. All solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. Tetrahydrofuran, diethyl ether, benzene and toluene were dried by refluxing with sodium. The heterocyclic enamines **3**, [17] **4**[17] and **10**[19] were prepared according to literature methods.

General procedure for the synthesis of 6a-c

A solution of heterocyclic enamines **3** (1 mmol) and ethyl propiolate **5** (1.1 mmol) in ethanol (15 ml) was refluxed for 16-18 h. After removal of solvent under vacuum, the residue was recrystallized to give products **6a-c**.

Diethyl E-4-[(Z)-pyrrolidin-2-ylidene]-2-pentenedioate 6a

Colorless crystals; yield, 74%; mp 129-131 °C (ethanol) (Found: C, 61.49; H, 7.73; N, 5.49. $C_{13}H_{19}NO_4$ requires C, 61.64; H, 7.56; N, 5.53%); ν_{max} (KBr)/cm^{-1} 3280 (NH), 1685, 1673, 1638, 1595 and 1557; λ_{max}(MeOH)/nm 296 sh. (lgε 4.14) and 330 (4.42); δ_H 9.42 (1H, s, NH), 7.55 (1H, d, *J* 15.4), 6.12 (1H, d, *J* 15.4), 4.26 (2H, q, *J* 7.4), 4.18 (2H, q, *J* 7.4), 3.68 (2H, t, *J* 7.2), 3.01 (2H, t, *J* 7.8), 2.10 (2H, quin, *J* 7.2), 1.37 (3H, t, *J* 7.0) and 1.29 (3H, t, *J* 7.4); δ_C 171.5, 169.9, 169.6, 141.4, 108.5, 90.9, 59.7, 59.5, 48.1, 32.4, 21.3 and 14.6 (2C); *m/z* (EI) 253 (M$^+$, 54%), 208 (100), 180 (57), 162 (40), 152 (28), 134 (37) and 106 (44).

Diethyl E-4-[(Z)-piperidin-2-ylidene]-2-pentenedioate 6b

Colorless crystals; yield, 95%; mp 60.5-61 °C (ethanol) (Found: C, 62.74; H, 8.01; N, 5.23. $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24%); λ_{max}(MeOH)/nm 307 sh. (lgε 4.32) and 342 (4.51); ν_{max} (KBr)/cm^{-1} 3220 (NH), 1677, 1619, 1599 and 1568; δ_H 11.03 (1H, s), 7.73 (1H, d, *J* 15.4), 6.07 (1H, d, *J* 15.4), 4.24 (2H, q, *J* 7.2), 4.18 (2H, q, *J* 7.0), 3.38-3.48 (2H, m), 2.75-2.84 (2H, m), 1.77-1.83 (4H, m), 1.37 (3H, t, *J* 7.0) and 1.29(3H, t, *J* 7.0); δ_C 170.5, 169.7, 166.6, 139.4, 108.3, 91.4, 59.4, 59.3, 41.8, 26.7, 21.2, 19.3 and 14.4(2C); *m/z* (EI) 267 (M$^+$, 82%), 222 (80), 194 (100), 180 (34), 176 (34), 166 (37), 148 (60) and 120 (58).

Diethyl E-4-[(Z)-1,3,4,5,6,7-hexahydroazepin-2-ylidene]-2-pentenedioate 6c

Colorless crystals; yield, 87%; mp 60-62 °C (ethanol) (Found: C, 64.02; H, 8.24; N, 4.88. $C_{15}H_{23}NO_4$ requires C, 64.03; H, 8.24; N, 4.98%); ν_{max}(KBr)/cm^{-1} 3230 (NH), 1674, 1625, 1598 and 1570; λ_{max}(MeOH)/nm 307 sh. (lgε 4.19) and 340 (4.44); δ_H 10.79 (1H, s), 7.80 (1H, d, *J* 15.4), 6.06 (1H, d, *J* 15.4), 4.24 (2H, q, *J* 7.0), 4.19 (2H, q, *J* 7.0), 3.43-3.50 (2H, m), 2.78-2.83 (2H, m), 1.59-1.82 (6H, m), 1.37 (3H, t, *J* 7.0) and 1.30 (3H, t, *J* 7.0); δ_C 172.8, 170.6, 169.7, 140.9, 110.1, 92.2, 59.7, 59.6, 44.3, 29.9, 28.7, 28.6, 24.5 and 14.5 (2C); *m/z* (EI) 281 (M$^+$, 24%), 236 (25), 208 (49), 194 (30), 162 (34) and 29 (100).

General procedure for the synthesis of 8a-c

To a solution of the Michael adduct **6** (1 mmol) in ethanol (15 ml) was added a catalytic amount of sodium ethoxide (5 mg) and the reaction mixture was refluxed for 2 h. Removal of solvent under vacuum gave a residue that was fractionated by chromatography on a silica gel column using petroleum ether/ethyl acetate as an eluent to give crystalline compound **8a-c**. Heterocycles **8a-c** were also synthesized from a one-pot reaction of enamines **3a-c** with ethyl propiolate **5** simply by adding sodium ethoxide as a catalyst to the

reaction mixture after reactant **3** was consumed, as monitored by thin layer chromatography.

Ethyl 5-oxo-1,2,3,5-tetrahydroindolizine-8-carboxylate ***8a***

Colorless crystals; yield, 63%; mp 101-102.5 °C (ethanol) (lit. [11] 100-103 °C) (Found: C, 63.74; H, 6.54; N, 6.74. $C_{11}H_{13}NO_3$ requires C, 63.75, H, 6.32; N, 6.76%); λ_{max}(MeOH)/nm 273 (lgε 4.20) and 300 sh. (3.77); ν_{max}(KBr)/cm^{-1} 1686 and 1643; δ_H 7.92 (1H, d, *J* 9.5), 6.48 (1H, d, *J* 9.5), 4.29 (2H, q, *J* 7.1), 4.17 (2H, t, *J* 7.4), 3.54 (2H, t, *J* 7.9), 2.22 (2H, quin, *J* 7.6) and 1.34 (3H, t, *J* 7.1); δ_C 164.6, 162.2, 157.3, 140.6, 116.4, 106.6, 60.8, 49.4, 33.8, 20.5 and 14.3; *m/z* (EI) 207 (M$^+$, 93%), 178 (39), 162 (100) and 106 (35).

Ethyl 4-oxo-6,7,8,9-tetrahydro-4H-quinolizine-1-carboxylate ***8b***

Colorless crystals; yield, 90%; mp 52-53 °C (ethanol) (Found: C, 65.12; H, 6.81; N, 6.26. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%); λ_{max}(MeOH)/nm 277 (lgε 4.14) and 311 (3.70); ν_{max}(KBr)/cm^{-1} 1701 and 1650; δ_H 7.92 (1H, d, *J* 9.8), 6.46 (1H, d, *J* 9.8), 4.29 (2H, q, *J* 7.2), 4.06 (2H, t, *J* 6.2), 3.38 (2H, t, *J* 6.4), 1.77-2.01 (4H, m) and 1.36 (3H, t, *J* 6.8); δ_C 165.2, 162.8, 155.5, 139.6, 115.2, 107.7, 60.5, 42.3, 26.7, 21.3, 18.1 and 14.2; *m/z* (EI) 221 (M$^+$, 100%), 192 (32) and 176 (28).

Ethyl 4-oxo-4,6,7,8,9,10-hexahydropyrido[1,2-a]azepine-1-carboxylate ***8c***

Colorless crystals; yield, 98%; mp 51-51.5 °C (ethanol) (Found: C, 66.37; H, 7.30; N, 5.90. $C_{13}H_{17}NO_3$ requires C, 66.36; H, 7.29; N, 5.95%); ν_{max}(KBr)/cm^{-1} 1704 and 1660; λ_{max}(MeOH)/nm 272 (lgε 4.04) and 312 (3.66); δ_H 7.79 (1H, d, *J* 9.6), 6.46 (1H, d, *J* 9.6), 4.46-4.53 (2H, m), 4.29 (2H, q, *J* 7.0), 3.42-3.49 (2H, m), 1.70-1.88 (6H, m) and 1.36 (3H, t, *J* 7.2); δ_C 165.8, 162.6, 158.8, 139.7, 116.4, 108.7, 60.8, 43.2, 29.1, 28.9, 27.0, 25.4 and 14.2; *m/z* (EI) 235 (M$^+$, 100%), 206 (93), 190 (46), 178 (25), 134 (24) and 109 (25).

Reaction of acetyl-substituted heterocyclic enamines ***4a*** *with ethyl propiolate* ***5***

A mixture of enamines **4** (8 mmol) and ethyl propiolate **5** (8 mmol) in ethanol (30 ml) was refluxed for one day. After removal of solvent under vacuum, the residue was chromatographed on a silica gel column to give ethyl *E*-4-[(*Z*)-pyrrolidin-2-ylidene]-5-oxo-2-hexenoate **7a** and 8-acetyl-2,3-dihydro-1H-indolizin-5-one **9a**. **7a**: colorless crystals; yield, 31%; mp 119.5-121.5 °C (methanol) (Found: C, 64.39; H, 7.45; N, 6.14. $C_{12}H_{17}NO_3$ requires C, 64.55; H, 7.68; N, 6.27%); λ_{max}(MeOH)/nm 319 (lgε 4.34) and 332 (4.33); ν_{max}(KBr)/cm^{-1} 3199 (NH), 1689, 1571 and 1544; δ_H 11.40 (1H, s, NH), 7.76 (1H, d, *J* 15.8), 5.59 (1H, d, *J* 15.8), 4.20 (2H, q, *J* 7.2), 3.70 (2H, t, *J* 7.0), 2.99 (2H, t, *J* 7.6), 2.35 (3H, s), 2.09 (2H, quin, *J* 7.4) and 1.31 (3H, t, *J* 7.4); δ_C 196.5, 171.4, 168.6, 143.4, 109.0, 101.9, 59.8, 48.0, 33.5, 29.1, 20.8 and 14.4; *m/z* (EI) 223 (M$^+$, 18%), 178 (24), 162 (11) and 150 (100). **9a**: colorless crystals; yield, 42%; mp 123-124 °C (Found: C, 67.82; H, 6.45; N, 7.90. $C_{10}H_{11}NO_2$ requires C, 67.78; H, 6.26; N, 7.90%); ν_{max}(KBr)/cm^{-1} 1670, 1638 and 1627; λ_{max}(MeOH)/nm 286 (lgε 4.19); δ_H 7.78 (1H, d, *J* 9.5), 6.41 (1H, d, *J* 9.5), 4.13 (2H, t, *J* 7.6), 3.53 (2H, t, *J* 7.9), 2.42 (3H, s) and 2.19 (2H, quin, *J* 7.7); δ_C 194.5, 161.4, 157.3, 139.9, 116.0, 113.4, 48.7, 34.1, 27.7 and 20.2; *m/z* (EI) 177 (M$^+$, 44%), 162 (100) and 134 (12).

*Reaction of acetyl-substituted heterocyclic enamines **4b** with ethyl propiolate **5***

A mixture of enamines **4b** (4 mmol) and ethyl propiolate **5** (4 mmol) in ethanol (40 ml) was refluxed for 18 h. After removal of solvent under vacuum, the residue was chromatographed on a silica gel column using a mixture of petroleum ether and ethyl acetate (4:1) as an eluent to give ethyl *E*-4-[(*Z*)-piperidin-2-ylidene]-5-oxo-2-hexenoate **7b** as yellow crystals. Yield, 42%; mp 46-47 °C (hexane-ethyl acetate) (Found: C, 65.89; H, 7.38; N, 6.09. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%); ν_{max}(KBr)/cm^{-1} 3144 (NH), 1690 and 1579; λ_{max}(MeOH)/nm 324 (lgε 4.22) and 336 (4.22); δ_H 13.01 (1H, s, NH), 7.74 (1H, d, *J* 15.8), 5.55 (1H, d, *J* 15.8), 4.19 (2H, q, *J* 7.2), 3.32-3.43 (2H, m), 2.61-2.67 (2H, m), 2.30 (3H, s), 1.60-1.82 (4H, m) and 1.31 (3H, t, *J* 7.2); δ_C 195.5, 168.1, 167.1, 142.2, 110.9, 102.9, 59.4, 41.3, 29.1, 27.4, 20.7, 18.9 and 14.2; *m/z* (EI) 237 (M$^+$, 19%), 192 (15) and 164 (100). Prolonged refluxing time (more than 24 h) gave 1-acetyl-6,7,8,9-tetrahydroquinolizin-4-one **9b** as colorless crystals. Yield, 43%; mp 89.5-90 °C (Found: C, 68.95; H, 6.93; N, 7.18. $C_{11}H_{13}NO_2$ requires C, 69.09; H, 6.85; N, 7.33%); ν_{max}(KBr)/cm^{-1} 1672, 1639 and 1626; λ_{max}(MeOH)/nm 288 (lgε 4.14) and 312 sh. (3.87); δ_H 7.58 (1H, d, *J* 9.5), 6.22 (1H, d, *J* 9.5), 3.84 (2H, t, *J* 5.7), 3.11 (2H, t, *J* 6.5), 2.28 (3H, s), 1.74 (2H, quin, *J* 6.1) and 1.60 (2H, quin, *J* 6.3); δ_C 196.0, 162.0, 155.2, 139.1, 116.6, 115.2, 42.2, 29.1, 26.9, 20.9 and 17.8; *m/z* (EI) 191 (M$^+$, 53%), 176 (100), 148 (23) and 120 (14).

Synthesis of ethyl E-4-[(Z)-1,3,4,5,6,7-hexahydroazepin-2-ylidene]-5-oxo-2-hexenoate **7c** and *1-acetyl-7,8,9,10-tetrahydropyrido[1,2-a]azepin-4(6H)-one* **9c**

A mixture of enamine **4c** (3 mmol) and ethyl propiolate **5** (3 mmol) was refluxed in ethanol for one day to give after purification by chromatography ethyl *E*-4-[(*Z*)-1,3,4,5,6,7-hexahydroazepin-2-ylidene]-5-oxo-2-hexenoate **7c** as colorless crystals. Yield, 35%; mp 58-59 °C (methanol) (Found: C, 67.09; H, 8.80; N, 5.53. $C_{14}H_{21}NO_3$ requires C, 66.90; H, 8.42; N, 5.57%); ν_{max}(KBr)/cm^{-1} 3130 (NH), 1692 and 1561; λ_{max}(MeOH)/nm 322 (lgε 4.31) and 342 (4.29); δ_H 12.57 (1H, s, NH), 7.77 (1H, d, *J* 15.6), 5.53 (1H, d, *J* 15.6), 4.21 (2H, q, *J* 7.2), 3.42-3.51 (2H, m), 2.70-2.77 (2H, m), 2.29 (3H, s), 1.61-1.82 (4H, m) and 1.31 (3H, t, *J* 7.4); δ_C 195.7, 172.1, 167.9, 143.9, 113.9, 103.4, 59.8, 44.1, 30.1, 29.7, 29.3, 28.3, 24.4 and 14.3; *m/z* (EI) 251 (M$^+$, 19%) 208 (14), 206 (14) and 178 (100).

Treatment of **7c** (2 mmol) with sodium ethoxide (10 mg) in refluxing ethanol (20 ml) for 4 h yielded 1-acetyl-7,8,9,10-tetrahydropyrido[1,2-a]azepin-4(6H)-one **9c**. Purification by chromatography on a silica gel column gave pure **9c** as colorless crystals. Yield, 90%; mp 91-92 °C (hexane-ethyl acetate) (Found: C, 69.98; H, 7.27; N, 6.64. $C_{12}H_{15}NO_2$ requires C, 70.22; H, 7.37; N, 6.82%); ν_{max}(KBr)/cm^{-1} 1675, 1640 and 1625; λ_{max}(MeOH)/nm 286 (lgε 4.07) and 314 (3.78); δ_H 7.61 (1H, d, *J* 9.6), 6.47 (1H, d, *J* 9.6), 4.43-4.49 (2H, m), 3.27-3.34 (2H, m), 2.46 (3H, s) and 1.72-1.83 (6H, m); δ_C 197.2, 161.8, 157.2, 138.5, 117.0, 115.7, 43.0, 29.2, 28.9, 28.5, 26.5 and 25.0; *m/z* (EI) 205 (M$^+$, 100%), 190 (94), 176 (32) and 162 (61).

General procedure for the study of reaction between secondary or tertiary enamines ***3a,c*** *or* ***10a,c*** *with ethyl propiolate* ***5***

A mixture of **3a,c** or **10a,c** (0.5 mmol) and **5** (0.6 mmol) in 10 ml of solvent (ethanol, dry benzene and toluene) was refluxed for a period of time. After removal of solvent *in vacuo*, both starting material and product were separated by chromatography on a silica gel column using a mixture of petroleum ether/ethyl acetate as an eluent. The results are shown in Table 1.

Diethyl E-4-(1-methyl-pyrrolidin-2-ylidene)-2-pentenedioate ***11a***

Yellow oil; yield, 64% (Found: C, 62.87; H, 7.87; N, 4.93. $C_{14}H_{21}NO_4$ requires C, 62.90; H, 7.92; N, 5.24%); ν_{max}(film)/cm^{-1} 1685, 1594, 1563 and 1555; δ_H 7.57 (1H, d, *J* 15.3), 5.77 (1H, d, *J* 15.3), 4.22 (2H, q, *J* 7.1), 4.13 (2H, q, *J* 7.1), 3.58 (2H, t, *J* 7.1), 3.04 (2H, t, *J* 7.7), 2.95 (3H, s), 1.95-2.05 (2H, m), 1.30 (3H, t, *J* 7.1) and 1.24 (3H, t, *J* 7.1); δ_C 169.2, 168.4, 167.6, 142.4, 107.8, 92.6, 59.6, 59.3, 57.7, 39.2, 35.1, 20.5, 14.5 and 14.4; *m/z* (EI) 267 (M^+,100%), 222 (78), 194 (88), 180 (85), and 108 (99).

Diethyl E-4-(1-methyl-1,3,4,5,6,7-hexahydroazepin-2-ylidene)-2-pentenedioate ***11c***

Yellow oil; yield, 49% (Found: C, 64.90; H, 8.65; N, 4.52. $C_{16}H_{25}NO_4$ requires C, 65.06; H, 8.53; N, 4.74%); ν_{max}(film)/cm^{-1} 1690, 1688 and 1535; δ_H 7.66 (1H, d, *J* 15.6), 5.47 (1H, d, *J* 15.4), 4.20 (2H, q, *J* 7.2), 4.18 (2H, q, *J* 7.2), 3.43-3.47 (2H, m), 3.06 (3H, s), 2.83-2.93 (2H, m), 1.62-1.85 (6H, m), 1.31 (3H, t, *J* 7.2) and 1.28 (3H, t, *J* 7.2); δ_C 175.1, 169.3, 167.9, 142.9, 107.6, 96.7, 59.6, 59.4, 53.9, 45.9, 34.2, 28.8, 25.4 (2C) and 14.5 (2C); *m/z* (EI) 295 (M^+, 61%), 250 (45), 222 (54), 208 (100).

General procedure for the synthesis of ***15a-c***

A solution of **3a-c** (1 mmol) and diethyl acetylenedicarboxylate **14** (1 mmol) in ethanol (15 ml) was stirred at room temperature for 30 min. **15a-c** were obtained after evaporation of solvent and purification by chromatography on a silica gel column using a mixture of petroleum ether/ethyl acetate as an eluent.

Diethyl E-3-ethoxycarbonyl-4-[(Z)-pyrrolidin-2-ylidene]-2-pentenedioate ***15a***

Yellow oil which slowly solidified on standing; yield, 65%; mp 39.5-41.5 °C (Found: C, 59.10; H, 7.16; N, 4.46. $C_{16}H_{23}NO_6$ requires C, 59.06; H, 7.12; N, 4.31%); ν_{max} (KBr)/cm^{-1} 3330 (NH), 1715, 1662 and 1586; δ_H 8.70 (1H, s, br, NH), 6.66 (1H, s), 4.23 (2H, q, *J* 7.0), 4.16 (2H, q, *J* 6.8), 4.08 (2H, q, *J* 7.2), 3.53-3.68 (2H, m), 2.30-2.70 (2H, m), 1.92-2.06 (2H, m), 1.29 (3H, t, *J* 7.0), 1.26 (3H, t, *J* 6.8) and 1.17 (3H, t, *J* 7.2); δ_C 168.3, 168.2, 166.7, 165.8, 142.7, 125.8, 85.6, 61.3, 60.3, 58.9, 47.4, 31.6, 21.9, 14.3 and 14.1 (2C); *m/z* (EI) 325 (M^+, 14%), 296 (10), 280 (18), 252 (100), 224 (24), 206 (35) and 178 (29).

Diethyl E-3-ethoxycarbonyl-4-[(Z)-piperidin-2-ylidene]-2-pentenedioate ***15b***

Yellow oil; yield 73% (Found: C, 60.34; H, 7.40; N, 4.16. $C_{17}H_{25}NO_6$ requires C, 60.16; H, 7.43; N, 4.13%); ν_{max}(film)/cm^{-1} 3250 (NH), 1715, 1647 and 1594; δ_H 9.80 (1H, s, br, NH), 6.74 (1H, s), 4.23 (2H, q, *J*

7.2), 4.19 (2H, q, *J* 7.0), 4.04 (2H, q, *J* 7.0), 3.28-3.44 (2H, m), 2.16-2.40 (2H, m), 1.57-1.84 (4H, m), 1.30 (3H, t, *J* 7.6), 1.26 (3H, t, *J* 7.4) and 1.15 (3H, t, *J* 7.0); δ_C 168.2 (2C), 165.4, 162.3, 142.2, 127.2, 87.1, 61.2, 60.2, 58.6, 41.1, 26.5, 22.0, 19.3, 14.3 and 14.0 (2C); *m/z* (EI) 339 (M^+, 22%), 310 (17), 294 (18), 266 (100), 220 (37) and 192 (34).

Diethyl E-3-ethoxycarbonyl-4-[(Z)-1,3,4,5,6,7-hexahydroazepin-2-ylidene]-2-pentenedioate ***15c***

Yellow oil; yield, 75% (Found: C, 61.14; H, 7.62; N, 3.97. $C_{18}H_{27}O_6$ requires C, 61.17; H, 7.70; N, 3.96%); ν_{max}(film)/cm^{-1} 3270 (NH), 1715, 1648 and 1592; δ_H 9.85 (1H, s, br, NH), 6.73 (1H, s), 4.20 (2H, q, *J* 7.0), 4.12 (2H, q, *J* 7.0), 4.03 (2H, q, *J* 7.0), 3.31-3.40 (2H, m), 2.15-2.48 (2H, m), 1.40-1.80 (6H, m), 1.26 (3H, t, *J* 7.0), 1.22 (3H, t, *J* 7.0) and 1.12 (3H, t, *J* 7.0); δ_C 168.5, 168.4, 167.8, 165.5, 143.1, 127.2, 87.5, 61.4, 60.3, 58.8, 44.4, 30.6, 30.3, 29.5, 25.1, 14.3 and 14.1 (2C); *m/z* (EI) 353 (M^+, 21%), 324 (14), 308 (14), 280 (100), 234 (31) and 206 (28).

General procedure for the synthesis of ***16a-c***

A suspension of sodium hydride (1 mmol) and **15** (1 mmol) in dry tetrahydrofuran (15 ml) was stirred at room temperature. After the starting material **15** was disappeared as indicated by thin layer chromatography, the mixture was filtered and the filtrate was concentrated *in vacuo* to give a dark brown oil. Purification by chromatography on a silica gel column using chloroform as an eluent afforded pure **16**.

Diethyl 5-oxo-1,2,3,5-tetrahydroindolizine-7,8-dicarboxylate ***16a***

Colorless crystals; yield, 63% m.p. 73-74 °C (ethyl ether) (Found: C, 60.09; H, 6.01; N, 4.96. $C_{14}H_{17}NO_5$ requires C, 60.20; H, 6.14; N, 5.02%); ν_{max}(KBr)/cm^{-1} 1723, 1698, 1660 and 1651; δ_H 6.52 (1H, s), 4.45 (2H, q, *J* 7.0), 4.32 (2H, q, *J* 7.0), 4.22 (2H, t, *J* 7.8), 3.54 (2H, t, *J* 7.9), 2.28 (2H, quin, *J* 7.9), 1.40 (3H, t, *J* 7.0) and 1.37 (3H, t, *J* 7.0); δ_C 165.9, 163.2, 159.8, 156,8, 144.6, 115.3, 103.0, 61.0, 60.3, 48.7, 33.1, 19.6, 13.3 and 13.2; *m/z* (EI) 279 (M^+, 36%), 233 (41) and 205 (100).

Diethyl 4-oxo-6,7,8,9-tetrahydro-4H-quinolizine-1,2-dicarboxylate ***16b***

Colorless oil, yield, 40% (Found: C, 61.52; H, 6.46; N, 4.29. $C_{15}H_{19}NO_5$ requires C, 61.42; H, 6.53; N, 4.78%); ν_{max}(film)/cm^{-1} 1730 and 1665; δ_H 6.84 (1H, s), 4.32 (2H, q, *J* 7.4), 4.29 (2H, q, *J* 7.2), 4.04 (2H, t, *J* 6.1), 3.01 (2H, t, *J* 6.5), 1.80-2.00 (4H, m), 1.36 (3H, t, *J* 7.0) and 1.32 (3H, t, *J* 7.2); δ_C 166.1, 165.4, 162.1, 150.1, 141.0, 117.1, 109.6, 62.0, 61.6, 42.5, 26.3, 21.3, 18.0, 14.0 and 13.9; *m/z* (EI) 293 (M^+, 21%), 247 (74) and 219 (100).

Diethyl 4-oxo-4,6,7,8,9,10-hexahydropyrido[1,2-a]azepine-1,2-dicarboxylate ***16c***

Colorless oil; yield, 43% (Found: C, 62.78; H, 7.10; N, 4.78. $C_{16}H_{21}NO_5$ requires C, 62.52; H, 6.89; N, 4.56%); ν_{max}(film)/cm^{-1} 1735, 1730 and 1666; δ_H 6.87 (1H, s), 4.01-4.42 (6H, m), 2.92-3.01 (2H, m), 1 58-1.98 (6H, m), 1.36 (3H, t, *J* 7.0) and 1.33 (3H, t, *J* 7.0); δ_C 166.8, 165.0, 161.8, 153.2, 140.1, 118.7, 110.3, 62.0, 61.6, 43.7, 30.6, 28.9, 27.1, 25.8, 13.9 and 13.8; *m/z* (EI) 307 (M^+, 100%), 278 (73), 261 (88) and 234 (97).

ACKNOWLEDGEMENT

We thank the National Natural Science Foundation of China for financial support.

REFERENCES

1. Bertele, E.; Boos, H.; Dunitz, J. D.; Elsinger, F.; Eschenmoser, A.; Felner, I.; Gribi, H. P.; Gschwend, H.; Meyer, E. F.; Pesaro, M.; Scheffold, R. *Angew. Chem., Intt. Ed. Engl.*, **1964**, 3, 490.
2. Taguchi, H.; Yazawa, H.; Arnett, J. F.; Kishi, Y. *Tetrahedron Lett.*, **1977**, 627.
3. Danishefsky, A.; Etheredge, S. J. *J. Org. Chem.*, **1974**, 39, 3430.; Shen, W.; Coburn, C. A.; G.; Bornmann, W. G.; Danishefsky, S. *J. Org. Chem.*, **1993**, 58, 611.; Snyder, L.; Shen, W.; Bornmann, W. Danishefsky, S. *J. Org. Chem.*, **1994**, 59, 7033.
4. Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.*, **1983**, 105, 2859 and references cited therein.
5. Yamada, Y.; Hatano, K.; Matsui, M. *Agr. Biol. Chem.*, **1970**, 34, 1536.
6. Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.*, **1978**, 43, 4662.
7. Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. T. *J. Chem. Soc., Perkin Trans. 1*, **1987**, 2377.
8. Paulvannan, K.; Stille, J. R.; *J. Org. Chem.*, **1994**, 59, 1613.
9. Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.*, **1998**, 63, 8170.
10. Brunerie, P.; Celerier, J.-P.; Petit, H.; Lhommet, G. *J. Heterocyclic. Chem.*, **1986**, 23, 1183.
11. Nagasaka, T.; Inoue, H.; Hamaguchi, F. *Heterocycles*, **1983**, 20, 1099.
12. Huang, Z.-T.; Wang, M.-X. *Heterocycles*, **1994**, 37, 1233.
13. Huang, Z.-T.; Wang, M.-X. *J. Chem. Soc., Perkin Trans. 1*, **1993**, 1085.
14. Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *J. Chem. Res. (S)*, **1998**, 486.
15. Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *Tetrahedron Lett.*, **1998**, 39, 9237.
16. Zhang, J.-H.; Wang, M.-X.; Huang, Z.-T. *J. Chem. Soc., Perkin Trans. 1*, **1999**, 321.
17. Cheng, Y.; Zhao, M.; Wang, M.-X.; Wang, L.-B.; Huang, Z.-T. *Synth. Commun.*, **1995**, 25, 1339.
18. Part of this work has appeared as a preliminary communication; Cheng, Y.; Wang, M.-X.; Huang, Z.-T. *Heterocyclic Commun.*, **1995**, 1, 191.
19. Roth, M.; Dubs, P.; Gotschi, E.; Eschenmoser, A. *Helv. Chim. Acta*, **1971**, 54, 710.
20. Cook, A. G, in *Enamines: Synthesis, Structure, and Reactions*, ed. Cook, A. G., Marcel Dekker, New York, 1988, p. 347.