Pergamon

Tetrahedron 58 (2002) 2821–2829

TETRAHEDRON

Unexpected ring size effect of the annulation reaction of heterocyclic secondary enamines with dicarboxylic acid dichlorides

Ying Cheng,[a,*] Hai-Bo Yang,[a] Mei-Xiang Wang[b,*] and David J. Williams[c]

[a]*Department of Chemistry, Beijing Normal University, Beijing 100875, People's Republic of China*
[b]*Center for Molecular Science, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100080, People's Republic of China*
[c]*Department of Chemistry, Imperial College, London SW7 2AY, UK*

Received 8 November 2001; revised 14 January 2002; accepted 14 February 2002

Abstract—Heterocyclic enamines are versatile ambident nucleophilic reagents able to react with both aliphatic and aromatic dicarboxylic acid dichlorides in diverse manners. The reaction outcome was strongly dependent upon the heterocyclic structure of the enamines and the nature of the diacid dichlorides employed.

1. Introduction

Heterocyclic secondary enamines **1**, also known as *exo*-cyclic enaminoesters, enaminones, and enamino nitriles when the electron-withdrawing group (EWG) is ester, acyl, and cyano, respectively, are versatile intermediates for the synthesis of natural products and heterocyclic compounds. In the 1960s, Eschenmoser and his co-workers[1] pioneered the chemistry of heterocyclic enamines during their synthetic studies of corrin. They used the reaction of an enamino nitrile with iminoether as one of the key steps in the construction of the corrin ring system. Since the late 1970s, heterocyclic enamines have been investigated by Kishi,[2] Danishefsky,[3–5] Rapoport[6] and others in the synthesis of saxitoxin, camptothecin, mitomycins and alkaloids.[7–12] Recently, a synthesis of carbacephems, a new class of β-lactam antibiotics, has been reported[13] by reducing the double bond of *exo*-cyclic enaminoesters followed by intramolecular cyclization.

One of the most intriguing features of heterocyclic secondary enamines **1** is their ambident bisnucleophilicity; nucleophilic reaction can take place at the site of enaminic carbon and/or the secondary amino nitrogen. This has been exemplified[14,15] by the acylation reaction using simple carboxylic acid chlorides, which gave rise to *C*- and/or *N*-acylated products depending upon both the heterocyclic structure of enamines and the structure of carboxylic acids. Much attention has been given to the annulation reactions between heterocyclic enamines and α,β-unsaturated compounds in the past decades[16,17] and a systematic investigation of the reaction of *exo*-cyclic enamino esters with electrophilic alkynes has appeared very recently.[18] Surprisingly, however, no reaction of heterocyclic secondary enamines with dicarboxylic acid dichlorides, simple and strong biselectrophilic species, has yet been reported. We envisaged that annulation of enamines **1** through diacylation using dicarboxylic acid dichlorides should produce polyfunctionalized fused heterocyclic derivatives that would be valuable precursors to hydroxylated pyrrolizidine[19] and indolizidine[20] alkaloids such as rosmarinecine and castanospermine and their analogues. By systematically examining the reactions of heterocyclic secondary enamines with both aliphatic and aromatic dicarboxylic acid chlorides, we have been astonished by the unexpected diversity of reaction patterns which are strongly dependent upon the structures of both reactants. Herein we wish to report our results.[21]

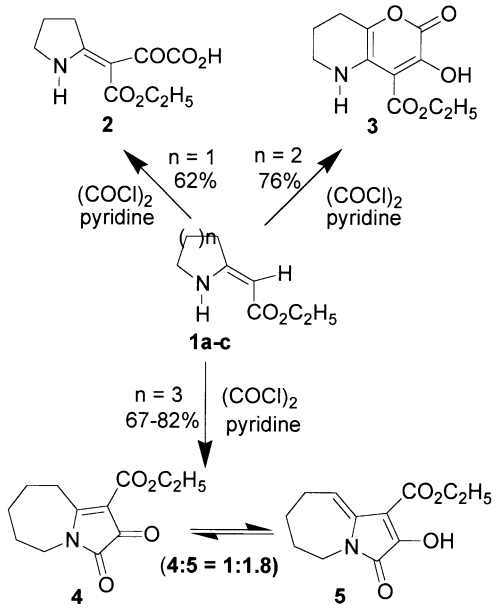
2. Results and discussion

Initially, we chose the cheap and commercially available oxalyl chloride as the biselectrophilic reagent, expecting formation of pyrrol-2,3-dione-fused heterocycles. In the presence of pyridine as an acid scavenger, enamines of different heterocyclic ring size (**1a–c**) reacted smoothly and efficiently with oxalyl chloride at −15 to −10°C in methylene chloride. Surprisingly, however, the reaction produced completely different heterocyclic ring systems, depending on the structure of the starting heterocyclic enamines. Whilst the five-membered enamine **1a** gave the *C*-acylated product **2** in 62% yield, the six-membered

Keywords: annulation; heterocyclic secondary enamines; dicarboxylic acid dichlorides.

* Corresponding authors. Tel.: +8610-6220558; e-mail: mxwang@infoc3.icas.ac.cn; Tel.: +8610-62564628; fax: +8610-62569564; e-mail: yincheng@95777.com

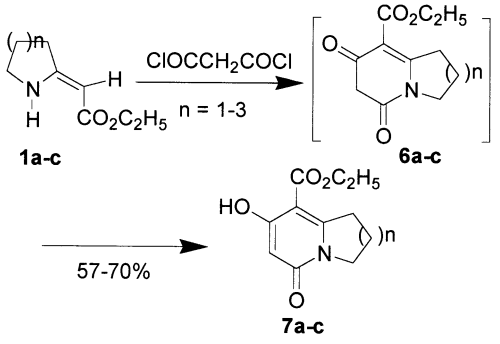
0040–4020/02/$ - see front matter
PII: S0040-4020(02)00177-1



Scheme 1. Reaction of enamines **1a–c** with oxalyl chloride.

analog **1b** afforded a totally unexpected pyranone **3** as the sole product in 76% yield. Only in the case of the seven-membered enamine **1c**, did the reaction form the expected condensed heterocyclic product **4** in 67% yield. The use of diethyl ether instead of methylene chloride as the solvent did not affect the formation of **2** and **3**, but improved the yield of **4** from 67 to 82%. As evidenced by both ^{1}H and ^{13}C NMR data, each of which showed two sets of signals, product **4** co-existed as an equilibrium mixture with the hydroxylated pyrrol-2-one-fused azepine compound **5**. The ratio of **4** to **5**, determined roughly by ^{1}H NMR, was about 1:1.8. (Scheme 1).

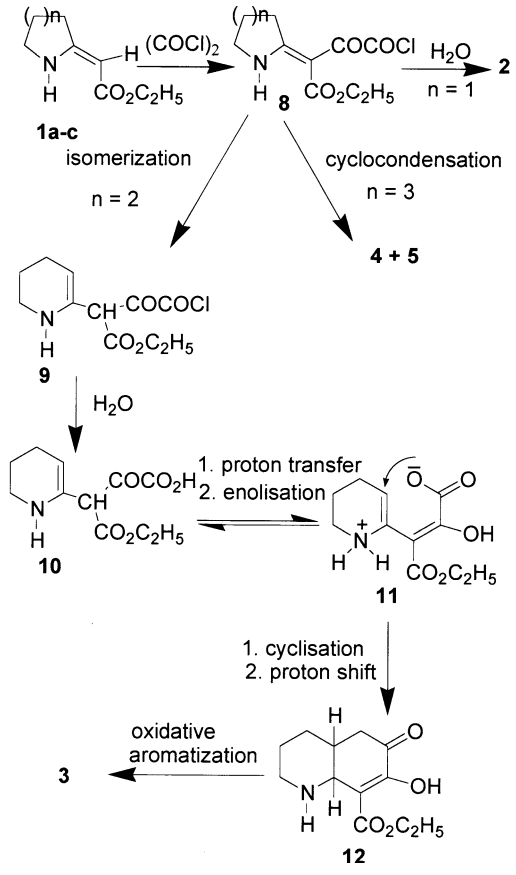
Intrigued by the diversity of reactions with oxalyl chloride, we then examined reaction of heterocyclic enamines **1a–c** with other dicarboxylic acid dichlorides. It has been reported[22] that only at an elevated temperature (155°C), does 2-pyrrolidylidene acetate **1a** undergo annulation with substituted di-2,4,6-trichlorophenyl malonates. Under similar conditions as that for oxalyl chloride, we found that malonyl chloride reacted rapidly and effectively with all enamines **1a–c** tested to afford hydroxylated 2-pyridinone-fused heterocycles **7** as the sole products in good yields (Scheme 2).



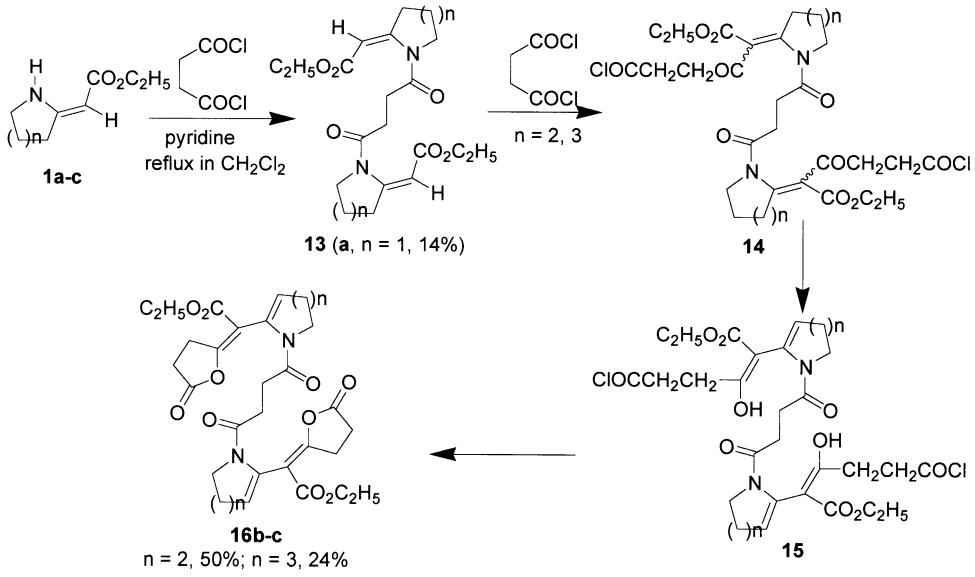
Scheme 2. Reaction of enamines **1a–c** with malonyl chloride.

It is worth noting that in all the aforementioned cases, no *N*-acylated products were obtained, regardless of both the ring size of the heterocyclic enamines and the structure of dicarboxylic acid dichlorides. This is different from the acylation reactions of enamines **1** using mono-carboxylic acid halides, which have been reported[14] to yield *C*- and/or *N*-acylated products depending on the heterocyclic structure of the enamine.

Apparently, compound **2** has resulted from the hydrolysis of the initially formed *C*-acylated intermediate **8** (n=1), while the formation of product **4** was probably effected by the cyclization of the intermediate **8** (n=3). The energy gained from both aromatization and intramolecular hydrogen bond formation between the hydroxy and carbonyl groups stabilizes the hydroxylated pyrrol-2-one structure, giving **5** as the major isomer in equilibrium. The formation of **7** most probably stemmed from a similar *C*-acylation, cyclocondensation followed by aromatization. To account for the formation of the pyranone product from the six-membered enamine **1b**, a reaction mechanism comprising proton-assisted cyclisation and oxidative aromatization is proposed. As depicted in Scheme 3, intermediate **8** (n=2) isomerizes to form the tetrahydropyridine **9**. It has been reported[14,17] that six-membered *exo*-cyclic enamine derivatives tend to shift their double bond from the *exo*- to *endo*-position. Being an amino acid, the hydrolysis intermediate **10** would tautomerize into its zwitterionic form **11** thus facilitating cyclization of the carboxylic anion to



Scheme 3. Proposed reaction pathways between enamines and oxalyl chloride.



Scheme 4. Reaction of enamines with succinyl chloride.

the enaminium double bond to form lactone **12**. Oxidative aromatization of **12**, caused by atmospheric oxygen, would then lead to the formation of the product **3** (Scheme 3).

When the bis-electrophiles were extended to succinyl chloride, the reaction became very sluggish at low temperature. Only under the conditions of refluxing in methlyene chloride, did the reaction proceed effectively. However, a very different chemistry was encountered. In all cases, *N*-acylation took place. For example, the five-membered heterocyclic enamine **1a** gave succinamide **13** in moderate yield while the six- and seven-membered heterocyclic enamines **1b** and **1c** led to the formation of the lactone-bearing succinamide derivatives **16b** and **16c** in the yield of 50 and 24%, respectively (Scheme 4). Spectroscopic data and microanalysis confirmed the structure of compound **13**. The structures of **16b** and **16c** were determined unambiguously by the X-ray crystallography. It is interesting to note that in the ^{1}H NMR spectra almost all the methylene protons of the heterocyclic rings in **16b** and **16c** gave broad peaks at room temperature and they became sharpened at 80°C.

As illustrated in Scheme 4, heterocyclic enamines **1a–c** reacted with succinyl chloride in a different fashion. Instead of the *C*-acylation and subsequent cyclisation observed for the reaction with malonyl chloride, di-*N*-acylation took place first between one succinyl chloride and two enamine molecules to give succinamide **13**. The difficulty of forming fused seven-membered ring products may account for the di-*N*-acylation reaction rather than annulation in these cases. Being more reactive than the five-membered analog **13a**, the six- and seven-membered heterocyclic intermediates **13b–c** underwent further diacylation at their

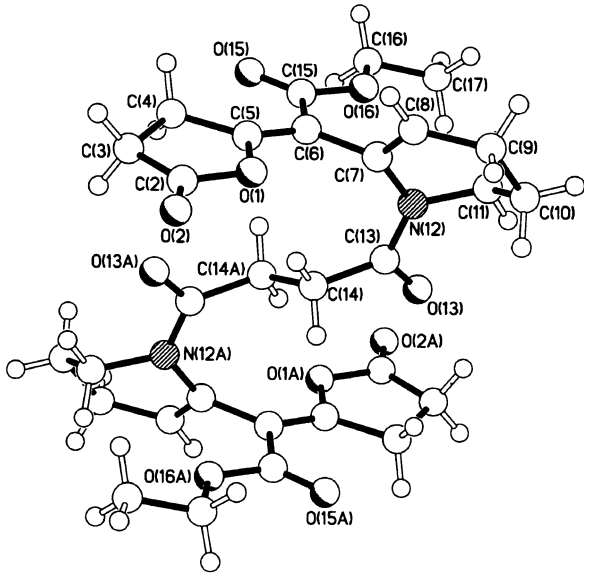


Figure 1. The molecular structure of **16b**.

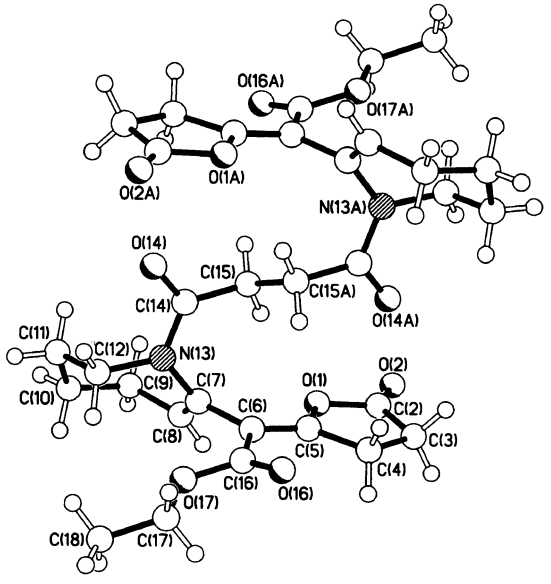
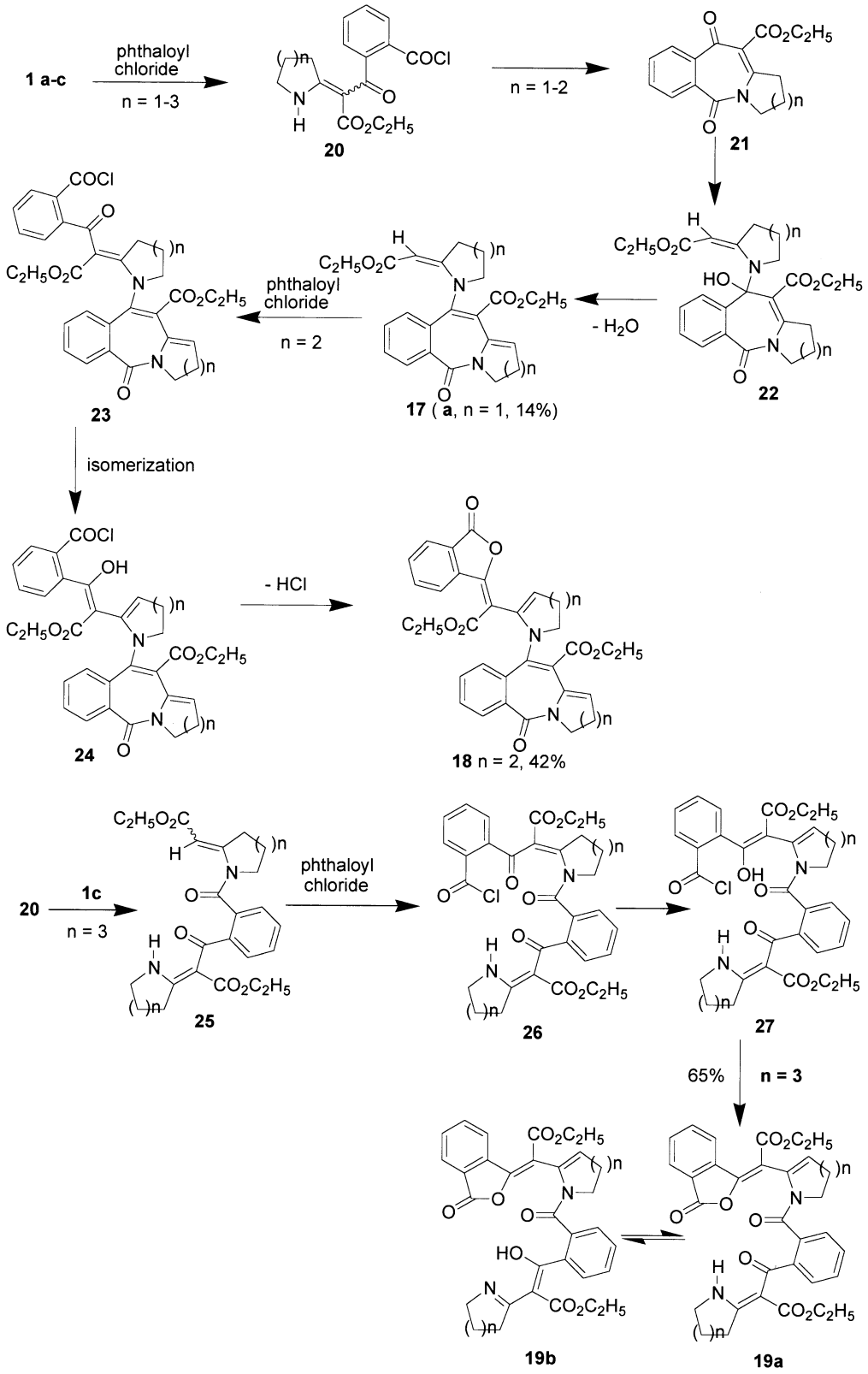


Figure 2. The molecular structure of **16c**.



Scheme 5. Reaction of enamines with phthaloyl dichloride.

enaminic carbons to form intermediate **14** which enolised and lactonised to afford the final product **16** (Scheme 4). The spectroscopic data were insufficient to elucidate the structure of **16** and therefore their structures were determined by single crystal X-ray analysis. These analyses showed both **16b** and **16c** to have inversion symmetry and established unambiguously the patterns of bonding present in these two compounds and the conformations that they adopt in the solid state. The X-ray structures of **16b** and **16c** are shown in Figs. 1 and 2, respectively.

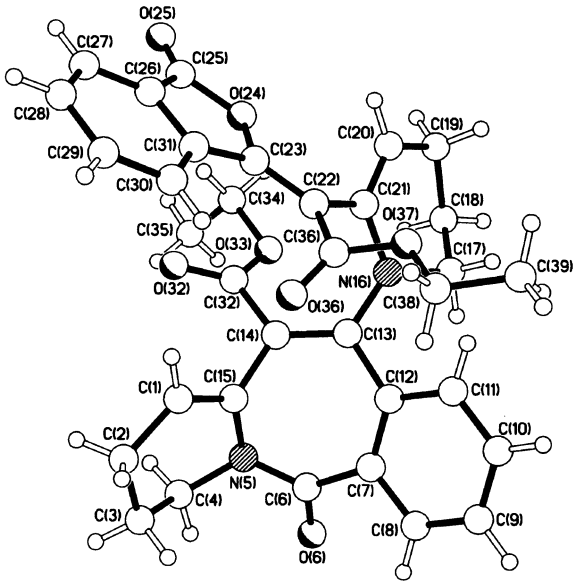


Figure 3. The molecular structure of **18**.

In order to construct a new azepine ring through the annulation, we thought a rigid dicarboxylic acid dihalide such as phthaloyl dichloride might help, as the initially formed mono-*C*-acylation or mono-*N*-acylation intermediate would bring the rest of the carboxylic acid chloride group proximal to the secondary amino N atom or the enaminic carbon atom. The idea worked, but in a more complicated manner; the reaction outcome was again determined by the heterocyclic structure of enamines **1** (Scheme 5). Whilst the lactone-containing benzo[*d*]pyridino[1,2-*a*]azepinone **18** was isolated in moderate yield from the reaction of the six-membered heterocyclic enamine **1b** with phthaloyl dichloride in refluxing methylene chloride, the five-membered heterocyclic enamine **1a** gave the enamine-substituted benzo[*d*]pyrrolo[1,2-*a*]azepinone product **17a**, albeit in low yield. In the case of the seven-membered heterocyclic enamine **1c**, most surprisingly, compound **19** was produced in good yield. The structure of **17** was evidenced by its spectroscopic data. The observation of a singlet vinyl proton peak at 4.40 ppm indicated the presence of an enamine moiety whilst a triplet vinyl proton peak at 5.52 ppm suggested a dihydropyrrole moiety. The spectroscopic data were not sufficient enough to elucidate the structures of compounds **18** and **19**, and their structures were finally established by single crystal X-ray diffraction analysis. Similar to compound **16**, ^{1}H NMR spectrum of compounds **18** and **19** showed broad peaks corresponding to the heterocyclic protons at room temperature and these peaks sharpened as the probe temperature increased. The tautomeric equilibrium between secondary enamine ketone **19a** and imine enol **19b** in solution was also observed, as the ^{1}H NMR spectrum of **19** gave two sets of signals. The tautomeric ratio of **19a** to **19b**, which varied with temperature, was not determined because of the difficulty in assigning the peaks. The X-ray structures of compounds **18** and **19a** are shown in Figs. 3 and 4, respectively.

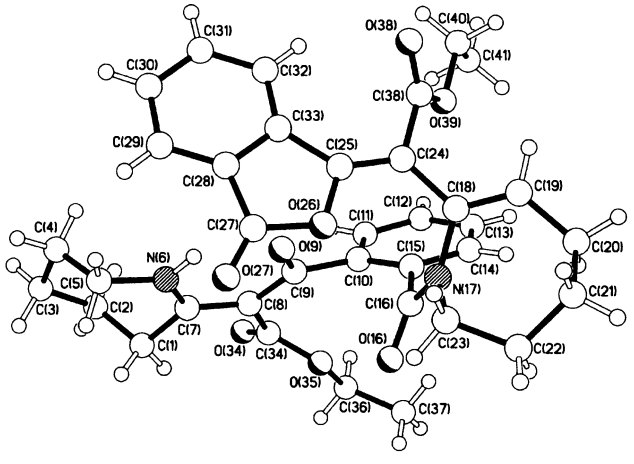


Figure 4. The molecular structure of **19a**.

The formation of different products **17**–**19** from the reaction of heterocyclic enamines **1a**–**c** and phthaloyl dichloride can be best interpreted by the reaction pathways depicted in Scheme 5. The *C*-acylation of enamines followed by intramolecular *N*-acylation led to the intermediate **21** (n=1, 2) which underwent intermolecular condensation with the secondary amino group of enamines **1a**–**b** to yield **17**. Further acylation of **17b** (n=2) by secondary phthaloyl dichloride resulted in the intermediate **23** which isomerized and lactonized to furnish product **18** (n=2). In contrast to its five- and six-membered analogs, the *C*-acylated seven-membered heterocyclic intermediate **20** acted as an acylating agent to react secondary amino group of the second enamine molecule **1c** with the formation of **25**. Further acylation at the enaminic carbon followed by isomerization and lactonization yielded product **19**.

The results obtained from this study clearly indicate that the reaction between heterocyclic enamines **1a**–**c** and both aliphatic and aromatic dicarboxylic acid dichlorides is strongly dependent upon the structures of both reactants. Being an ambident nucleophile, heterocyclic enamines **1a**–**c** appeared extremely sensitive towards the dicarboxylic acid dichlorides used. This was exemplified by the formation of different types of compounds such as **3**, **7** and **14** from one enamine species **1b** when treated with dicarboxylic acid dichloride homologs. More strikingly, heterocyclic enamines exhibited an unexpected ring size effect on the enaminic and secondary amino reactivity, the five-, six- and seven-membered heterocyclic enamine analogs producing diverse types of products when they were allowed to react with the same dicarboxylic acid dichloride. In most cases, both five- and six-membered heterocyclic enamines **1a**–**b** displayed greater enaminic reactivity than secondary amino group while for the *N*-acylated enamines, the enaminic reactivity of the six- and seven-membered compounds appeared higher than that of the five-membered analog. In addition, the six-membered compound showed the highest tendency to shift its *exo*-cyclic double bond to the *endo* position during the course of the reaction. However, it should be noted that the precise reason for the various reaction pathways for the enamines of the different heterocyclic ring structures remains unclear. This may arise from a combined effect of the ambident conjugation system comprising a secondary amino nitrogen, a double bond and an ester carbonyl within a molecule, and the tendency for double bond migration

from the *exo*- to the *endo*-position together with the ring strain generated from the formation of fused heterocycles. In other words, the ring size of heterocyclic secondary enamines **1** plays an important and subtle part in determining the reaction outcome.

3. Conclusion

In conclusion, we have demonstrated that heterocyclic enamines **1a–c** are versatile ambident nucleophilic reagents able to react with both aliphatic and aromatic dicarboxylic acid dichlorides. It has also been revealed that the reaction outcome was strongly dependent upon the heterocyclic structure of the enamines and the nature of the diacid dichlorides employed. By reacting heterocyclic enamines with dicarboxylic dichlorides we have provided simple, convenient and powerful methods for the synthesis of a wide arrange of heterocyclic compounds such as γ-, δ- and ε-lactam-fused heterocycles, γ- and δ-lactone derivatives that are not easily prepared from other means. The novel products obtained from this study could serve as the potential precursors to the indolizidine and quinolizidine alkaloids and their analogs, the research being actively studied in this laboratory.

4. Experimental

4.1. General

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra in $CDCl_3$ or DMSO-d_6 were obtained on Varian 200, Varian 300 and Avance 500 Bruker spectrometers. IR spectra were obtained on a HITACHI-260-50 spectrometer as liquid films or KBr discs. Mass spectra were measured on a KYKY-ZHT-5 mass spectrometer. Elemental analyses were performed on a GMBH Vario EL instrument.

All reagents were obtained from commercial suppliers. The reaction solvent dichloromethane was dried with phosphorus pentoxide, and the ethyl ethane was dried with sodium, respectively. Column chromatography was performed using 200–300 mesh silica gel. The enamines **1a–c** were prepared followed the literature method.[23]

4.2. General procedure for the reactions between 1a–c and oxalyl chloride

Under nitrogen atmosphere, the oxalyl chloride (10 mmol) in dichloromethane (10 mL) was added dropwise to the mixture of enamine **1a–c** (10 mmol) and dry pyridine (20 mmol) in dichloromethane(30 mL) cooled in an ice–salt bath to form a yellow solution. After the reaction proceeded in 3 h at −15 to −10°C, silica gel (5–10 g) was added to the mixture and the solvent was removed under vacuum. The product absorbed on silica gel was column chromatographed, followed by recrystallisation from ethyl acetate–petroleum ether to give pure product **2**, **3** or **4**. When the reaction of **1c** with oxalyl chloride was carried out in dichloromethane, it gave an oil product in 67% yield. However, the same reaction in ethyl ether afforded a yellow solid product in 82% yield. If the reaction was performed in toluene, the product was obtained in 80–92%. The compounds **4** and/or **5** were sensitive to heat. If the solvent was removed by heating during the work-up, dark oil was resulted.

4.2.1. 3-Ethoxy-2,4-dioxo-3-(2-pyrrolidin-2-yl)butanoic acid 2. White crystals: mp 139–140°C; ^{1}H NMR ($CDCl_3$) δ 11.40 (1H, s, OH), 9.82 (1H, s, br, NH), 4.20 (2H, q, J=6.9 Hz, OCH_2), 3.75 (2H, t, J=6.8 Hz, NCH_2), 3.31 (2H, t, J=7.6 Hz, $CH_2C{=}C$), 2.10 (2H, m, CH_2), 1.29 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 184.7, 177.1, 170.4, 166.8, 94.2, 60.4, 48.6, 35.2, 20.4, 13.8. IR (KBr) 3300, 3000, 2800, 2620, 1720, 1670, 1610 cm^{-1}; MS (EI) *m/z*: 227 (M^+, 2%), 209 (20), 182 (100), 154 (90), 136 (70), 135 (60), 110 (80), 109 (100). Anal. Calcd for $C_{10}H_{13}NO_5$: C, 52.86; H, 5.77; N, 6.16. Found: C, 52.69; H, 5.86; N, 6.19.

4.2.2. Ethyl 3-hydroxy-2-oxo-5,6,7,8-tetrahydro-2*H*-pyrano[3,2-*b*]pyridine-4-carboxylate 3. Pale yellow crystals: mp 194–195°C; ^{1}H NMR ($CDCl_3$) δ 11.85 (1H, s, OH), 9.64 (1H, s, br, NH), 4.47 (2H, q, J=7.0 Hz, OCH_2), 3.75 (2H, t, J=5.6 Hz, NCH_2), 2.54 (2H, t, J=6.2 Hz, $CH_2C{=}C$), 2.05 (2H, m, CH_2), 1.44 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 167.3, 158.4, 150.3, 148.6, 110.1, 104.1, 62.8, 38.3, 27.5, 27.1, 14.3; IR (KBr) 3550, 3400, 2960, 1650, 1460 cm^{-1}; MS (EI) *m/z* 239 (17%, M^+), 193 (100). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85. Found: C, 55.26; H, 5.49; N, 5.87.

4.2.3. Ethyl 2,3-dioxo-2,5,6,7,8,9-hexahydro-3*H*-pyrrolo-[1,2-*a*]azepine-1-carboxylate 4 and ethyl 2-hydroxy-3-oxo-5,6,7,8-tetrahydro-3*H*-pyrrolo[1,2-*a*]azepine-1-carboxylate 5. Yellow powder from the reaction of **1c** and oxalyl chloride in ethyl ether): mp 84–90°C; two sets of ^{1}H and ^{13}C NMR corresponding to **4** and **5** were observed. ^{1}H NMR ($CDCl_3$) δ 9.54 (0.64H, s, br, OH), 6.27 (0.64H, t, J=6.1 Hz, CH=C), 4.39 (1.28H, q, J=7.1 Hz, OCH_2), 4.28 (0.72H, q, J=7.1 Hz, OCH_2), 3.88–3.81 (2H, m, NCH_2), 3.39 (0.72H, br, $CH_2C{=}C$), 2.50 (1.28H, m, $CH_2C{=}C$), 1.88 (4H, m, $2CH_2$), 1.70 (0.72H, m, CH_2), 1.42–1.31 (3H, dt, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 185.5, 178.1, 165.9, 162.4, 162.0, 156.5, 133.3, 115.9, 105.6, 103.6, 101.0, 61.6, 60.5, 43.2, 41.3, 30.1, 28.5, 27.7, 27.4, 26.6, 26.4, 25.7, 14.3, 14.3; IR (KBr) 3150, 1720, 1710, 1620 cm^{-1}; MS (EI) *m/z* 237 (49%, M^+), 191 (100), 163 (61). Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.48; H, 6.38; N, 5.58.

4.3. Reaction with malonyl chloride

4.3.1. Reactions of 1a with malonyl chloride. Under nitrogen atmosphere, the malonyl chloride (3.5 mmol) in dichloromethane (15 mL) was added dropwise to the solution of enamine **1a** (3.5 mmol) in dichloromethane (15 mL) cooled in an ice–salt bath. The resulting orange mixture with some white precipitates was stirred at −15 to −10°C for about 3 h. After removal of the precipitates through filtration, the mother liquid was neutralised with 5% NaOH solution. Extraction with chloroform, followed by column chromatography and recrystallisation gave ethyl 7-hydroxy-5-oxo-1,2,3,5-tetrahydro-8-indolizinecarboxylate **7a** as white crystals, mp 133–135°C (lit.[24] mp 131°C).

4.3.2. Reactions of 1b with malonyl chloride. Under nitrogen atmosphere, the malonyl chloride (3.5 mmol) in dichloromethane (15 mL) was added dropwise to the solution of enamine **1b** (3.5 mmol) and dry triethylamine (7 mmol) in dichloromethane (15 mL) cooled in an ice–salt bath to form a orange mixture with white solid (triethylamine hydrogen chloride salt) precipitating. The mixture was stirred at −15 to −10°C for 3 h. After removal of the precipitates, the filtrate was concentrated to give after column chromatography the pure ethyl 8-hydroxy-6-oxo-1,3,4,6-tetrahydro-2*H*-9-quinolizinecarboxylate **7b** as white crystals, mp 154–155°C (lit.[25] mp 152–154°C).

4.3.3. Reactions of 1c with malonyl chloride. Under nitrogen atmosphere, the malonyl chloride (3.5 mmol) in dry toluene (10 mL) was added dropwise to the solution of enamine **1c** (3.5 mmol) in toluene (10 mL) cooled in an ice–salt bath to form a yellow solution with white solid precipitating. The mixture was stirred at −15 to −10°C for about 1 h. After the removal of toluene under vacuum, the residue was chromatographed to give ethyl 2-hydroxy-4-oxo-4,6,7,8,9,10-hexahydropyrido[1,2-*a*]azepine-1-carboxylate **7c** as white crystals. Mp 175–177°C; ^{1}H NMR ($CDCl_3$) δ 11.20 (1H, br, OH), 6.09 (1H, s, C═CH), 4.50 (2H, bs, NCH_2), 4.43 (2H, q, J=6.8 Hz, OCH_2), 3.23 (2H, bs, CH_2C═C), 1.79 (6H, bs, $3CH_2$), 1.40 (3H, t, J=6.8 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 169.1, 165.7, 163.4, 159.2, 101.6, 97.3, 62.1, 42.8, 31.4, 28.6, 27.0, 25.0, 14.0. IR (KBr) 2950, 1720, 1660, 1620, 1560 cm^{-1}; MS (EI) *m/z* 251 (M^+, 88%), 205 (100), 177 (81); Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.81; N, 5.57. Found: C, 61.90; H, 7.04; N, 5.67.

4.4. General procedure for the reaction between 1a–c and succinyl chloride

Under nitrogen atmosphere, succinyl chloride (5.7 mmol) in dry dichloromethane (20 mL) was added dropwise to the solution of enamine **1a–c** (4.7 mmol) and pyridine (11.4 mmol) in dichloromethane (15 mL) cooled in an ice-salt bath. The white solid precipitated and the colour of the solution turned red. The mixture was stirred under refluxing for about 20–22 h, and then silica gel (5–10 g) was added. After removal of the solvent under vacuum, the pure products **13**, **16b–c** absorbed on silica gel were obtained after column chromatography and further recrystallisation.

4.4.1. Bis-2-ethoxycarbonylmethylenepyrrolidyl succinamide 13. White crystals from ethyl acetate and petroleum ether: mp 205–206°C; ^{1}H NMR ($CDCl_3$) δ 6.90 (1H, s, C═CH), 4.11 (2H, q, J=7.1 Hz, OCH_2), 3.84 (2H, t, J=7.1 Hz, NCH_2), 3.19 (2H, t, J=7.6 Hz, CH_2C═C), 2.81 (2H, s, CH_2CO), 2.00 (2H, m, CH_2), 1.24 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 171.7, 168.9, 156.7, 148.6, 99.6, 59.4, 49.7, 31.3, 21.6, 14.4. IR (KBr) 1700, 1620 cm^{-1}; MS (FAB) *m/z*: 393 (M+1, 2%), 238 (100); Anal. Calcd for $C_{20}H_{28}N_2O_6$: C, 61.21; H, 7.19; N, 7.13. Found: C, 61.02; H, 7.03; N, 7.13.

4.4.2. Compound 16b. Pale yellow crystals from ethyl acetate and petroleum ether: mp 135–137°C; ^{1}H NMR (DMSO-d_6) (25°C) δ 5.14 (1H, br, C═CH), 4.05 (2H, br, OCH_2), 3.50 (2H, br, NCH_2), 3.20 (2H, br, CH_2C═C), 2.74 (2H, t, J=7.7 Hz, CH_2COO), 2.41 (2H, br, CH_2CO), 2.16 (2H, br, CH_2C═C), 1.77 (2H, br, CH_2), 1.15 (3H, t, J=7.0 Hz, CH_3); ^{1}H NMR (DMSO-d_6) (80°C) δ 5.19 (1H, t, J=3.7 Hz, C═CH), 4.07 (2H, q, J=7.1 Hz, OCH_2), 3.55 (2H, t, J=5.5 Hz, NCH_2), 3.23 (2H, t, J=8.0 Hz, CH_2C═C), 2.73 (2H, t, J=8.3 Hz, CH_2COO), 2.42 (2H, s, CH_2CO), 2.15 (2H, m, CH_2C═C), 1.78 (2H, m, CH_2), 1.16 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.4, 169.8, 166.1, 131.6, 122.7, 118.7, 109.6, 60.5, 44.7, 42.5, 29.4, 27.2, 26.3, 23.2, 14.2; IR (KBr) 1820, 1710, 1640, 1630 cm^{-1}; MS (EI) *m/z* 584 (M^+, 2%), 335 (60), 334 (100), 288 (63), 252 (55), 251 (95). Anal. Calcd for $C_{30}H_{36}N_2O_{10}$: C, 61.63; H, 6.21; N, 4.79. Found: C, 61.43; H, 6.42; N, 4.80. *Crystal data for* **16b**: $C_{30}H_{36}N_2O_{10}$, M=584.6, monoclinic, $P2_1/c$ (no. 14), a=10.402(1), b=9.352(1), c=15.569(1) Å, β=105.67(1)°, V=1458.2(1) Å^3, Z=2 (C_i symmetry), D_c=1.331 g cm^{-3}, μ (Cu Kα)=0.84 mm^{-1}, T=293 K, pale yellow prisms; 2415 independent measured reflections, F^2 refinement, R_1=0.043, wR_2=0.108, 2056 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq128°$], 193 parameters. CCDC 172562.

4.4.3. Compound 16c. White crystals from methanol–ethyl acetate–petroleum: mp 221–223°C; ^{1}H NMR (DMSO-d_6) (25°C) δ 5.81 (1H, t, J=6.5 Hz), 4.10 (2H, q, J=7.1 Hz), 3.32 (2H, s), 3.21 (2H, br), 2.74 (2H, t, J=7.7 Hz), 2.21 (4H, br), 1.61 (4H, br), 1.17 (3H, t, J=7.1 Hz); ^{1}H NMR (DMSO-d_6) (80°C) δ 5.77 (1H, br, C═CH), 4.13 (2H, q, J=7.1 Hz, OCH_2), 3.52 (2H, br, NCH_2), 3.23 (2H, t, J=7.9 Hz, CH_2C═C), 2.73 (2H, t, J=8.3 Hz, CH_2COO), 2.30 (2H, br, CH_2CO), 2.20 (2H, q, J=6.5 Hz, CH_2C═C), 1.66 (2H, br, CH_2), 1.46 (2H, br, CH_2), 1.20 (3H, t, J=7.1 Hz, CH_3); ^{13}C NMR ($CDCl_3$) δ 175.5, 171.0, 166.7, 165.1, 136.8, 132.0, 109.0, 61.2, 47.8, 29.5, 29.4, 28.3, 27.7, 26.9, 24.6, 14.9; IR (KBr) 1840, 1720, 1660, 1650 cm^{-1}; MS (EI) *m/z* 612 (M^+, 6%), 348 (100), 349 (30). Anal. Calcd for $C_{32}H_{40}N_2O_{10}$: C, 62.73; H, 6.58; N, 4.57. Found: C, 62.46; H, 6.26; N, 4.39. *Crystal data for* **16c**: $C_{32}H_{40}N_2O_{10}$, M=612.7, triclinic, $P\bar{1}$ (no. 2), a=9.643(6), b=9.744(1), c=10.445(3) Å, α=112.37(2), β=116.90(3), γ=92.83(2)°, V=779.6(5) Å^3, Z=1 (C_i symmetry), D_c=1.305 g cm^{-3}, μ (Cu Kα)=0.81 mm^{-1}, T=293 K, colourless rhombs; 2483 independent measured reflections, F^2 refinement, R_1=0.053, wR_2=0.143, 2218 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq128°$], 204 parameters. CCDC 172563.

4.5. General procedure for the reaction of 1a–c with phthaloyl dichloride

Under a nitrogen atmosphere, the phthaloyl dichloride (15 mmol) was added to the solution of DABCO (15 mmol) in dry dichloromethane (20 mL) at −15°C to form a white mixture. To it was added dropwise the solution of enamines **1a–c** in dichloromethane (40 mL) cooled in an ice-bath. The colour of the reaction mixture turned yellow. After being stirred under refluxing for about 20–22 h, the mixture was poured into water (about 30 mL) and neutralised with saturated $NaHCO_3$ solution. The products were extracted by chloroform and dried over $MgSO_4$. After removal of the solvent under vacuum, the pure products **17–19** were obtained from column chromatography and further recrystallisation.

4.5.1. 11-Ethoxycarbonyl-10-(2-ethoxycarbonylmethyl-enepyrrolidin-1-yl)-2,3-dihydro-5*H*-pyrrolo[1,2-*b*][2]-benzazepine-5-one 17a. Yellow crystals from ethyl acetate–petroleum ether: mp 168–170°C; ^{1}H NMR (DMSO-d_6) δ 8.23 (1H, d, J=6.7 Hz), 7.53 (1H, t, J=7.3 Hz), 7.48 (1H, t, J=7.4 Hz), 6.96 (1H, d, J=7.8 Hz), 5.52 (1H, t, J=3.4 Hz, C=CH), 4.40 (1H, s, C=CH), 4.14 (2H, q, J=7.1 Hz, OCH_2), 4.21 and 4.05 (2H, m, NCH_2), 3.90 (2H, q, J=7.1 Hz, OCH_2), 3.47 (2H, m, NCH_2), 3.10 (2H, m, CH_2C=C), 2.58 (2H, m, CH_2C=C), 2.10 and 1.90 (2H, m, CH_2), 1.19 (3H, t, J=7.1 Hz, CH_3) 1.10 (3H, t, J=7.0 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 168.4, 165.1, 164.8, 162.2, 135.3, 134.5, 133.8, 133.4, 132.4, 131.6, 130.9, 129.6, 128.6, 120.7, 83.0, 62.6, 58.6, 54.0, 52.0, 31.8, 27.1, 22.5, 15.3, 14.5. MS (FAB) m/z 423 (M+1, 38%), 349 (100); IR (KBr) 1730, 1680, 1620, 1610, 1590 cm^{-1}. Exactly MS: 423.1909, $C_{24}H_{27}N_2O_5$ requires 423.1914.

4.5.2. Compound 18. Yellow crystals from ethyl acetate–petroleum ether: mp 198–200°C; ^{1}H NMR (DMSO-d_6) (25°C) δ 7.99 (1H, d, J=7.2 Hz), 7.84 (1H, t, J=7.5 Hz), 7.73 (2H, t, J=7.2 Hz), 7.65 (1H, d, J=7.3 Hz), 7.60 (1H, t, J=7.1 Hz), 7.53 (1H, d, J=7.4 Hz), 7.49 (1H, bs), 5.41 (1H, s), 5.25 (1H, s), 4.24 (1H, m), 4.10 (3H, m), 3.26 (1H, br), 3.17 (1H, br), 2.99–3.34 (2H, br), 2.32 (2H, br), 1.98 (3H, br), 1.85 (1H, br), 1.67 (1H, br), 1.60 (1H, br) 1.21 (3H, t, J=7.1 Hz), 1.06 (3H, t, J=6.8 Hz); ^{1}H NMR (DMSO-d_6) (80°C) δ 7.92 (1H, d, J=7.6 Hz), 7.80 (1H, t, J=8.1 Hz), 7.67–7.72 (3H, m), 7.58 (1H, d, J=7.8 Hz), 7.55 (1H, t, J=7.1 Hz), 7.42 (1H, t, J=7.9 Hz), 5.34 (1H, t, J=4.0 Hz, CH=C), 5.31 (1H, t, J=4.2 Hz, CH=C), 4.20 (2H, q, J=7.1 Hz, OCH_2), 4.16 (2H, q, J=7.2 Hz, OCH_2), 3.61 (2H, br, NCH_2), 3.33 (2H, t, J=5.3 Hz, NCH_2), 2.35 (2H, m, CH_2C=C), 2.00 (4H, m, CH_2C=C and CH_2), 1.68 (2H, m, CH_2), 1.24 (3H, t, J=7.2 Hz, CH_3), 1.14 (3H, t, J=7.2 Hz, CH_3); ^{13}C NMR (DMSO-d_6) δ 167.3, 166.2, 165.8, 165.2, 150.4, 149.1, 137.8, 137.1, 136.1, 135.5, 134.2, 132.5, 131.6, 131.0, 130.9, 130.2, 126.2, 125.6, 124.6, 123.5, 117.0, 115.3, 114.8, 62.8, 61.1, 52.0, 24.2, 24.1, 23.3, 22.3, 14.9, 14.2. IR (KBr) 1800, 1740, 1650, 1600 cm^{-1}; MS (FAB) m/z 581 (M+1, 40%), 507 (100). Anal. Calcd for $C_{34}H_{32}N_2O_7$: C, 70.33; H, 5.55; N, 4.82. Found: C, 70.25; H, 5.54; N, 4.89. *Crystal data for* **18**: $C_{34}H_{32}N_2O_7$, M=580.6, triclinic, $P\bar{1}$ (no. 2), a=9.788(2), b=10.672(2), c=15.600(2) Å, α=109.19(2), β=102.65(2), γ=92.43(1)°, V=1490.1(5) Å^3, Z=2, D_c=1.294 g cm^{-3}, μ (Mo Kα)=0.09 mm^{-1}, T=293 K, yellow blocks; 5135 independent measured reflections, F^2 refinement, R_1=0.049, wR_2=0.113, 3583 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq 50°$], 387 parameters. CCDC 172564.

4.5.3. Compound 19. White crystals from acetone–ethyl acetate–petroleum ether: mp 195–197°C; ^{1}H NMR (DMSO-d_6) (35°C) δ 7.11–8.08 (8H, m), 6.07 (0.55H, t, J=6.4 Hz), 5.87 (0.45H, t, J=5.9 Hz), 4.42 (1.1H, q, J=7.1 Hz), 4.13 (0.9H, q, J=7.0 Hz), 3.64–3.75 (2H, m), 3.40–3.48 (4H, m), 2.40–2.69 (4H, m), 1.55–1.87 (10H, m), 1.32 (1.65H, t, J=7.1 Hz), 1.20 (1.35H, t, J=6.9 Hz), 0.60–0.68 (3H, m). ^{1}H NMR (DMSO-d_6) (90°C) δ 7.93–7.80 (2H, m), 7.81 (1H, t, J=7.3 Hz), 7.70 (1H, t, J=7.4 Hz), 7.15–7.40 (4H, m), 5.94 (1H, t, J=5.5 Hz), 4.32 (2H, br), 3.75 (2H, q, J=7.1 Hz), 3.71 (2H, br), 3.44 (2H, t, J=4.2 Hz), 2.61 (2H, br), 2.45 (2H, m), 1.54–1.78 (10H, m), 1.31 (3H, t, J=7.0 Hz), 0.74 (3H, t, J=7.2 Hz); ^{13}C NMR (DMSO-d_6) δ 174.8, 170.3, 166.2, 166.1, 165.7, 148.7, 147.1, 137.5, 137.1, 136.2, 135.7, 132.9, 132.5, 132.3, 128.8, 128.3, 127.8, 126.3, 126.1, 125.7, 125.6, 116.0, 62.4, 62.0, 59.9, 50.7, 47.8, 44.3, 44.1, 30.2, 30.0, 29.8, 28.8, 28.3, 27.6, 25.0, 24.0, 14.7, 14.6, 14.1; IR (KBr) 1800, 1720, 1700, 1660, 1640, 1600 cm^{-1}; MS (FAB) m/z: 627 (M+1, 4%), 314(90), 96 (100). Anal. Calcd for $C_{36}H_{38}N_2O_8$: C, 69.00; H, 6.11; N, 4.47. Found: C, 68.91; H, 6.08; N, 4.51. *Crystal data for* **19a**: $C_{36}H_{38}N_2O_8$, M=626.7, monoclinic, $P2_1/n$ (no. 14), a=9.595(1), b=13.370(1), c=25.479(1) Å, β=93.38(1)°, V=3262.8(2) Å^3, Z=4, D_c=1.276 g cm^{-3}, μ (Cu Kα)=0.74 mm^{-1}, T=293 K, colourless platy prisms; 5079 independent measured reflections, F^2 refinement, R_1=0.072, wR_2=0.197, 3883 independent observed reflections [$|F_o|>4\sigma(|F_o|)$, $2\theta\leq 124°$], 420 parameters. CCDC 172565.

5. Supporting material

X-Ray data for compounds **16b**, **16c**, **18** and **19**.

Acknowledgements

We thank the National Natural Science Foundation of China and SRF for ROCS, SEM 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., Int. Ed. Engl.* **1964**, *3*, 490–496.
2. Taguchi, H.; Yazawa, H.; Arnett, J. F.; Kishi, Y. *Tetrahedron Lett.* **1977**, 627–630.
3. Danishefsky, S.; Etheredge, S. J. *J. Org. Chem.* **1974**, *39*, 3430–3432.
4. Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. *J. Org. Chem.* **1993**, *58*, 611–617.
5. Snyder, L.; Shen, W.; Bornmann, W. G.; Danishefsky, S. *J. Org. Chem.* **1994**, *59*, 7033–7037.
6. Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859–2866 and references cited therein.
7. Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662–4663.
8. Buchanan, J. G.; Jigajinni, V. B.; Singh, G.; Wightman, R. T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2377–2384.
9. Paulvannan, K.; Stille, J. R. *J. Org. Chem.* **1994**, *59*, 1613–1620.
10. Saliou, C.; Fleurant, A.; Celerier, J. P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 3365–3368.
11. Fleurant, A.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1993**, *4*, 1429–1430.
12. Thanh, G. V.; Celerier, J. P.; Lhommet, G. *Tetrahedron: Asymmetry* **1996**, *7*, 2211–2212.
13. Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170–8182.
14. Brunerie, P.; Celerier, J. P.; Petit, H.; Lhommet, G. *J. Heterocycl. Chem.* **1986**, *23*, 1183–1188.

15. Bahaji, El.H.; Refouvelet, B.; Couquelet, J.; Tronche, P. *C. R. Acad. Sci. II* **1986**, *303*, 455–458.
16. Nagasaka, T.; Inoue, H.; Ichimura, M.; Hamaguchi, F. *Synthesis* **1982**, 848–850.
17. Brunerie, P.; Celerier, J. P.; Huche, M.; Lhommet, G. *Synthesis* **1985**, 735–738.
18. Wang, M.-X.; Miao, W.-S.; Cheng, Y.; Huang, Z.-T. *Tetrahedron* **1999**, *55*, 14611–14622.
19. For a useful review, see: Roeder, E. *Curr. Org. Chem.* **1999**, *3*, 557.
20. For the synthesis of hydroxylated indolizidine alkaloidal compounds, see: Maggini, M.; Prato, M.; Ranelli, M.; Scorrano, G. *Tetrahedron Lett.* **1992**, *33*, 6537–6540. Cordero, F. M.; Cicchi, S.; Goti, A.; Brandi, A. *Tetrahedron Lett.* **1994**, *35*, 949–952. Cicchi, S.; Goti, A.; Brandi, A. *J. Org. Chem.* **1995**, *60*, 4743–4748.
21. Part of this work appeared as preliminary communications: Cheng, Y.; Yang, H.-B.; Hung, Z.-T.; Wang, M.-X. *Tetrahedron Lett.* **2001**, *42*, 1757–1759.
22. Dannhardt, G.; Meindl, W.; Gussmann, S.; Ajili, S.; Kappe, T.; Eur *J. Med. Chem.* **1987**, *22*, 505–510.
23. Celerier, J. P.; Deloisy, E.; Lhommet, G.; Maitte, P. *J. Org. Chem.* **1979**, *44*, 3089.
24. Celerier, J. P.; Eskenazi, C.; Maitte, P.; Lhommet, G. *J. Heterocycl. Chem.* **1979**, *16*, 953–955.
25. Kappe, T.; Hariri, M.; Soliman, F. S. G. *Arch. Pham.* **1976**, *309*, 684–687.