# The aza-ene reaction of heterocyclic ketene aminals with activated carbonyl compounds: a novel and efficient synthesis of γ-lactam-fused diazaheterocycles

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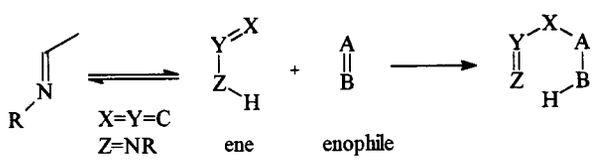
Reactions of heterocyclic ketene aminals with activated carbonyl compounds are strongly influenced by the structure of the heterocycle moiety. Six-membered heterocyclic ketene aminals with or without an *N*-methyl group such as **3** and **4** underwent efficient addition and consecutive cyclocondensation reactions with diethyl oxomalonate **9** to produce γ-lactam-fused pyrimidine derivatives **10** and **11** in moderate to excellent yield. For the five-membered enediamines, however, those compounds without any *N*-substituent such as **6** underwent the same reaction slowly and no reaction at all was observed with *N*-methyl and *N*,*N*′-dimethyl-substituted analogs **7** and **8**. Heterocyclic ketene aminals **3** also reacted with glyoxylic acid esters **17** to afford 8-aroyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidines **18** in good yield. No asymmetric induction was found, however, when (1*R*,2*S*,5*R*)-(−)-menthyl glyoxylate **17b** was employed as a chiral substrate. An aza-ene reaction mechanism involving heterocyclic ketene aminals as the aza-ene component (H–N–C=C) has been proposed. The effects of intramolecular hydrogen bonding and heterocyclic ring size on the reactivity are also discussed.



## Introduction

The ene reaction is defined as a σ-bond-forming reaction between an ene component and an enophile with a concomitant 1,5-hydrogen shift and migration of the double bond[1] (Scheme 1). According to the nature of the reactants, the ene reaction




has been divided into two categories. An "all-carbon" ene reaction takes place between an olefin bearing an allylic hydrogen atom (the carba-ene) and an activated alkene or alkyne (the carba-enophile), and a hetero-ene reaction describes that taking place between an ene and enophile, either of which contains at least one heteroatom.[2] The hetero-ene reaction can be further categorised into three sub-types; Type I reactions describe the interaction of all-carba-ene components with hetero-enophiles, Type II reactions involve a hetero-ene component and an all-carba enophile and Type III reactions include those occurring between hetero-ene components and hetero-enophiles.

Due to its synthetic potential and its intriguing reaction pathways in organic chemistry, the ene reaction has received much attention since the first report in 1943.[3] Great developments have been achieved in the past three decades. Both "all-carbon" ene reactions and Type I hetero-ene reactions employing hetero-enophiles such as carbonyl and thiocarbonyl compounds, imines, nitroso and azo compounds are well documented and have often been utilized in the synthesis of natural products. Most "all-carbon" ene reactions have been shown to proceed by a concerted mechanism through a six-membered cyclic transition state under thermal and catalytic conditions. Hetero-ene and some Lewis-acid catalyzed ene reactions can occur stepwise by way of a zwitterionic intermediate.[4]

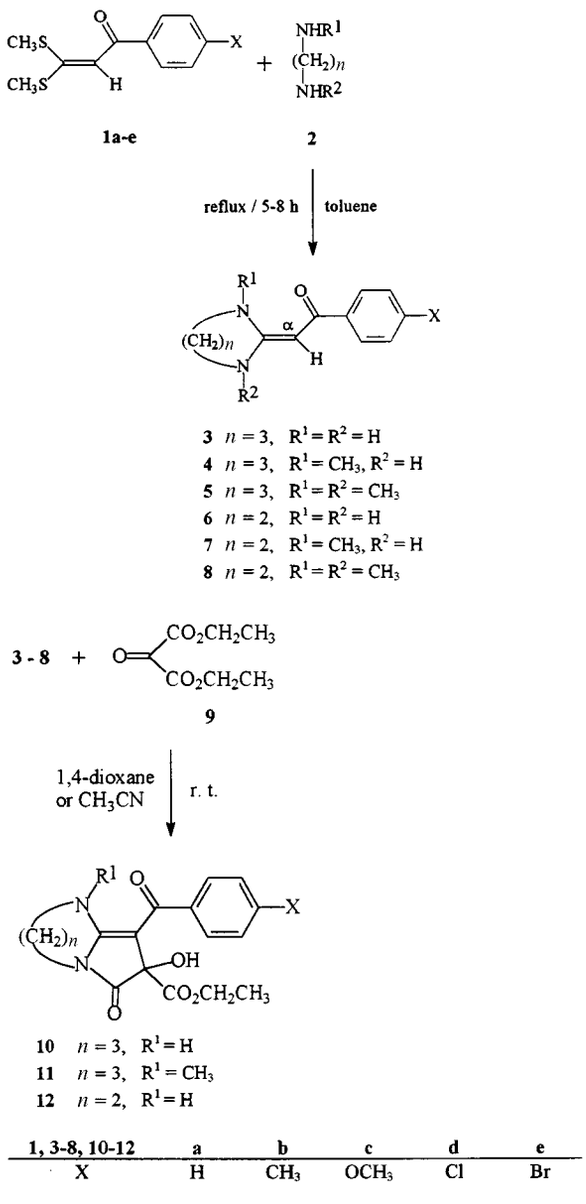
In contrast to these extensively studied "all-carbon" ene and Type I hetero-ene reactions, little is known of the ene reactions involving hetero-ene components, *i.e.* Type II and III hetero-ene reactions. This is particularly true for hetero-ene systems containing a heteroatom at the 2-position (X = Y = C, Z = heteroatom) (Scheme 1), with the exception of enols tautomerized from the corresponding ketones, which have been reported to undergo thermal intramolecular ene reactions (the Conia reaction).[5] This is not surprising, however, since hetero-ene components such as secondary enamines exist predominantly in their more stable tautomeric forms, as imines.[6] Therefore they usually act as the hetero-enophiles rather than the hetero-ene components. Nevertheless, we believe that secondary enamines or their imine tautomers would be the hetero-ene components provided that the enamine–imine tautomerism shifts to the enamine side. Moreover, the hetero-ene reactions of secondary enamines would provide novel and valuable synthetic approaches to imine intermediates, and to ketones, amines and *N*-heterocycles, respectively, upon hydrolysis, reduction and cyclization of the product imines.

Heterocyclic ketene aminals **3**–**8**, also known as cyclic 1,1-enediamines, are powerful and versatile building blocks for the synthesis of various types of compounds that are difficult to access by other synthetic methods.[7] One of the notable features of heterocyclic ketene aminals is the enhanced electron density on the α-carbon leading to higher nucleophilicity than that of nitrogen, owing to the conjugative effect of the electron-donating amino groups and the electron-withdrawing substituents.[8] Considerable effort has been made therefore during the past decade to study enaminic reactions such as nucleophilic addition[9] and substitution[10] with a variety of electrophiles and even 1,3-dipoles.[11] Most noticeably, however, heterocyclic ketene aminals bearing a secondary amino moiety have been shown recently to be a unique aza-ene component and to undergo both Type II and III aza-ene reactions readily when α,β-unsaturated carboxylic acid esters[12] and ketones[13] and the activated azo compounds[14] are used as carba- and hetero-enophiles, respectively. To examine the scope and limitations of this novel aza-ene component in organic synthesis, we have explored the aza-ene reactions of heterocyclic ketene aminals utilizing a wide range of enophiles. Herein we wish to report a

Type III aza-ene reaction of benzoyl-substituted heterocyclic ketene aminals with activated carbonyl compounds.

## Results and discussion

In order to study the effect of the structure of the enediamine on its addition to carbonyl compounds, heterocyclic ketene aminals **3**–**8** were synthesized by the cyclocondensation of ketene dithioacetals **1a**–**e** and diamines **2** by a literature method[15] (Scheme 2). Among the products prepared, 1,3-




**Scheme 2**

dimethyl-2-*para*-substituted benzoylmethylene hexahydropyrimidines **5** are notable as they have not been reported before. Their structure was confirmed by spectral data and microanalysis. It is worth noting that all these compounds show a characteristic absorption band of a carbonyl group at $\nu_{max}$ 1600 $cm^{-1}$ in the infra-red spectrum. Such a large bathochromic shift of the carbonyl group has been rationalized as the effect of a strong conjugation system involving the nitrogen atoms, the double bond and the electron-withdrawing benzoyl group.[8]

The first carbonyl reactant we chose in this study was diethyl oxomalonate **9** as it is one of the most reactive and frequently used hetero-enophiles.[16] We found that heterocyclic ketene aminals can react with it, the outcome of the reaction being strongly dependent upon the structure of the heterocycle moiety of **3**–**8** (Scheme 2). As illustrated in Table 1, the six-membered heterocyclic ketene aminals **3** underwent a rapid and efficient reaction with **9** in both non-polar and polar solvents such as 1,4-dioxane and acetonitrile at ambient temperature to afford γ-lactam-fused pyrimidines **10**. Reaction of mono-*N*-methylated analogues **4** was also effective yielding the corresponding products **11** in fairly good yield. However, when a tertiary cyclic enediamine **5** was applied, reaction gave a complicated mixture of inseparable products. Attempts were made to optimize the reaction but no characterizable products were yielded. In contrast to **3**, heterocyclic ketene aminals **6** with an imidazolidine ring were found to be much less reactive towards **9**, the reaction being sluggish and taking two days to give a low to moderate yield of pyrrolo[1,2-*a*]imidazole derivatives **12**. More significantly, *N*-methyl- and *N*,*N*′-dimethyl heterocyclic ketene aminals **7** and **8** did not react at all with **9** and most of the starting material was recovered even after a prolonged reaction period.

**Table 1** The reactions of heterocyclic ketene aminals **3**, **4** and **6** with diethyl oxomalonate **9**

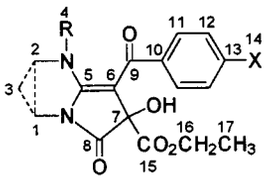
| Starting materials | *t*/h[a] | Products | Yields (%)[b] |
|---|---|---|---|
| **3a** | 2 | **10a** | 91 |
| **3b** | 2 | **10b** | 92 |
| **3c** | 2 | **10c** | 92 |
| **3d** | 2 | **10d** | 81 |
| **3e** | 2 | **10e** | 82 |
| **4a** | 5 | **11a** | 31 |
| **4b** | 5 | **11b** | 58 |
| **4c** | 5 | **11c** | 62 |
| **4d** | 5 | **11d** | 47 |
| **4e** | 5 | **11e** | 41 |
| **6a** | 48 | **12a** | 41 |
| **6b** | 48 | **12b** | 42 |
| **6c** | 48 | **12c** | 53 |
| **6d** | 48 | **12d** | 30 |
| **6e** | 48 | **12e** | 51 |

[a] In 1,4-dioxane or acetonitrile. [b] Isolated yields.

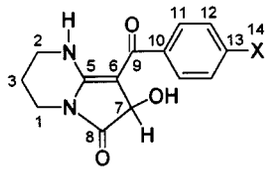
The structures of all products **10**–**12** were established on the basis of spectroscopic evidence and elemental analyses. Observation of an amide carbonyl signal around 170 ppm in the $^{13}C$-NMR spectrum (Table 2) excludes the possible structure of products such as **13** which might result from addition of the secondary amino group of the heterocyclic ketene aminals to the carbonyl of **9** followed by annulation of the enaminic carbon to an ester group. If the product had the structure of **13**, the carbonyl of the pyrrolidin-3-one moiety would give a carbon signal around 187 ppm.[17] The lactam structure was also supported by the infra-red spectrum in which an amide carbonyl vibration band was evident around 1615–1645 $cm^{-1}$. It should be noted that the methylene protons of the ester group in **10**–**12** appeared as multiple signals in the $^{1}H$–NMR spectrum. This is because the ester group is attached to a chiral center.[18] Thus the methylene protons, being non-equivalent, exhibit an AB-quartet which is further split by the adjacent methyl hydrogens.

These results suggest that an unusual substituent effect operates during the reaction. Thus, with differently substituted heterocyclic ketene aminals, reaction differed considerably. It appears essential that the secondary amino group in the heterocyclic ketene aminals add to the carbonyl compound, since the *N*,*N*′-dimethylated cyclic enediamines did not react with **9**. However, the secondary amino group does not attack the carbonyl group initially, only a *C*-adduct being produced as evidenced by structural analyses. This indicates that the 'effective reaction unit' is the secondary enamine moiety (H–N–C=C), rather than the tertiary enamine. In other words, if the reaction proceeded by way of the tertiary enamine, then *N*,*N*′-dimethyl-

**Table 2** $^{13}$C NMR Data of compounds **10**, **11**, **12** and **18**

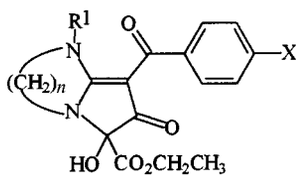


**10-12**



**18**

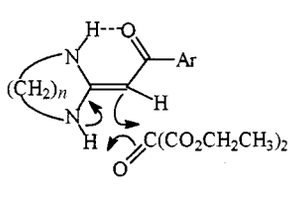
| Compound | C-1 | C-2 | C-3 | C-4 | C-5 | C-6 | C-7 | C-8 | C-9 | C-10 | C-11 | C-12 | C-13 | C-14 | C-15 | C-16 | C-17 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **10a** | 38.7 | 37.4 | 20.0 | | 159.8 | 90.8 | 77.2 | 172.0 | 187.9 | 140.6 | 127.8 | 126.9 | 130.0 | | 169.7 | 62.9 | 13.6 |
| **10b** | 38.5 | 37.2 | 19.5 | | 158.9 | 92.0 | 77.2 | 172.4 | 184.2 | 138.1 | 127.9 | 127.2 | 139.0 | 20.9 | 168.9 | 60.9 | 13.4 |
| **10c** | 38.7 | 37.3 | 19.7 | | 159.1 | 92.0 | 77.4 | 172.6 | 184.2 | 133.5 | 129.3 | 112.8 | 160.6 | 51.3 | 169.1 | 61.1 | 13.6 |
| **10d** | 38.8 | 37.3 | 19.6 | | 159.2 | 92.3 | 77.1 | 172.4 | 183.4 | 134.4 | 129.2 | 127.6 | 139.7 | | 168.9 | 61.1 | 13.6 |
| **10e** | 38.8 | 37.3 | 19.6 | | 159.2 | 92.4 | 77.1 | 172.5 | 183.5 | 140.1 | 129.4 | 130.5 | 123.2 | | 168.9 | 61.2 | 13.6 |
| **11a** | 43.7 | 37.4 | 20.3 | 49.5 | 158.7 | 91.0 | 78.8 | 171.4 | 186.6 | 141.4 | 128.1 | 127.6 | 130.6 | | 169.8 | 62.8 | 13.7 |
| **11b** | 43.7 | 37.4 | 20.3 | 49.4 | 158.5 | 90.9 | 78.9 | 171.5 | 186.7 | 138.7 | 128.3 | 128.2 | 140.9 | 21.4 | 169.9 | 62.8 | 13.8 |
| **11c** | 42.9 | 36.8 | 19.6 | 48.7 | 157.8 | 90.0 | 78.3 | 170.9 | 185.4 | 133.4 | 129.5 | 112.2 | 160.9 | 54.5 | 169.2 | 62.1 | 13.1 |
| **11d** | 43.7 | 37.4 | 20.2 | 49.5 | 159.2 | 90.5 | 78.6 | 171.4 | 185.0 | 136.5 | 129.7 | 127.8 | 139.7 | | 169.7 | 62.9 | 13.7 |
| **11e** | 43.8 | 37.5 | 20.2 | 49.6 | 159.3 | 90.6 | 78.6 | 171.5 | 185.1 | 140.1 | 129.9 | 130.8 | 125.1 | | 169.7 | 62.9 | 13.7 |
| **12a** | 49.3 | 38.3 | | | 163.0 | 90.9 | 83.7 | 169.2 | 184.6 | 140.3 | 127.8 | 127.4 | 130.1 | | 168.9 | 61.0 | 13.6 |
| **12b** | 49.2 | 38.2 | | | 162.8 | 90.8 | 83.7 | 169.2 | 184.4 | 137.5 | 128.3 | 127.6 | 139.8 | 21.1 | 169.0 | 61.0 | 13.7 |
| **12c** | 49.2 | 38.2 | | | 162.8 | 90.6 | 83.8 | 169.2 | 183.7 | 132.6 | 129.6 | 113.0 | 161.1 | 55.3 | 169.1 | 61.0 | 13.7 |
| **12d** | 49.3 | 38.3 | | | 163.1 | 90.8 | 83.5 | 169.1 | 183.2 | 134.9 | 129.4 | 127.9 | 139.0 | | 168.9 | 61.1 | 13.7 |
| **12e** | 49.3 | 38.3 | | | 163.2 | 90.8 | 83.5 | 169.1 | 183.3 | 139.4 | 129.9 | 130.8 | 123.8 | | 168.9 | 61.1 | 13.7 |
| **18a** | 38.3 | 36.6 | 19.4 | | 158.7 | 90.2 | 68.0 | 175.3 | 183.2 | 141.0 | 127.7 | 127.3 | 129.4 | | | | |
| **18b** | 38.5 | 36.8 | 19.7 | | 158.8 | 90.2 | 68.3 | 175.5 | 183.3 | 138.4 | 128.5 | 127.6 | 139.3 | 21.1 | | | |
| **18c** | 38.4 | 36.7 | 19.6 | | 158.7 | 89.8 | 68.2 | 175.3 | 182.5 | 133.4 | 129.4 | 113.0 | 160.5 | 55.2 | | | |
| **18d** | 38.4 | 36.8 | 19.5 | | 158.8 | 90.3 | 67.9 | 175.3 | 181.7 | 134.3 | 129.3 | 127.9 | 139.8 | | | | |



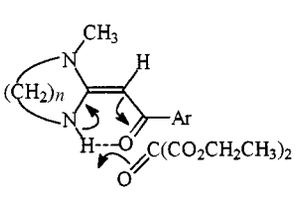
**13**

ated heterocyclic ketene aminals would give the desired addition products. It is concluded therefore that the addition most probably proceeds *via* an aza-ene reaction between the heterocyclic ketene aminals **3**, **4**, **6** and diethyl oxomalonate **9**.

The mechanism depicted in Scheme 3 can best interpret the experimental facts. The aza-ene reaction between heterocyclic ketene aminals **3**, **4** and **6**, and **9** forms an intermediate **15** which undergoes a rapid imine–enamine tautomerization to give **16**. Intramolecular cyclocondensation of **16** leads to the formation of final products **10**–**12**. Without a secondary enamine moiety (H–N–C=C) in the molecule, as in compounds **5** and **8**, no aza-addition was effected. The cyclocondensation step is much faster than the first two steps since no intermediate **15** or **16** was isolated. The great difference in reaction rate between **3** and **4** and between **6** and **7** may be attributed to the effect of intramolecular hydrogen bonds between carbonyl and secondary amine moieties in **3**, **4**, **6** and **7**. Intramolecular hydrogen bond

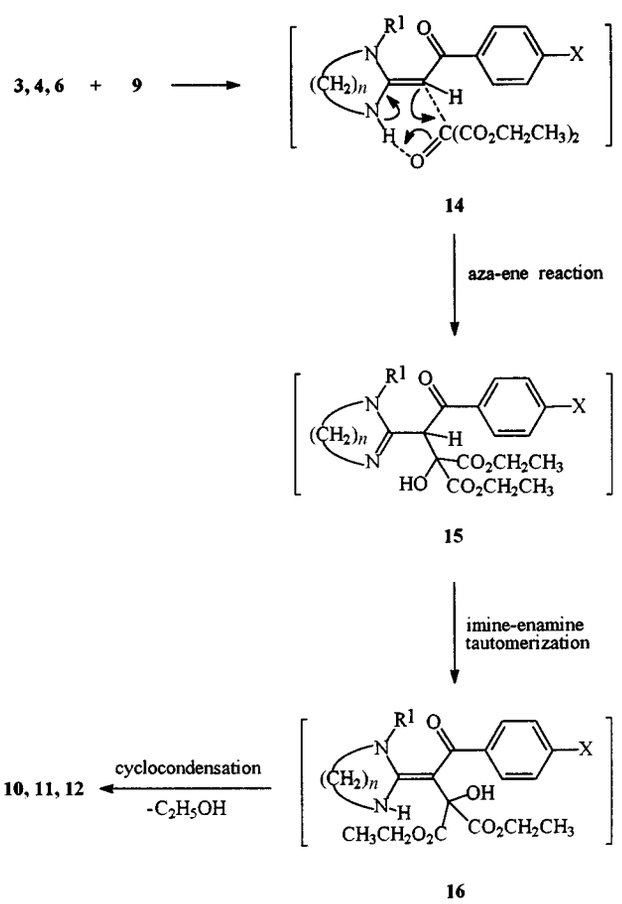


**3, 6 + 9**



**4, 7 + 9**

formation decreases the aza-ene addition rate. A similar correlation between hydrogen bonding and the rate of the aza-ene reaction has been noted previously by us when heterocyclic ketene aminals were allowed to react with ethyl propiolate.[12] It



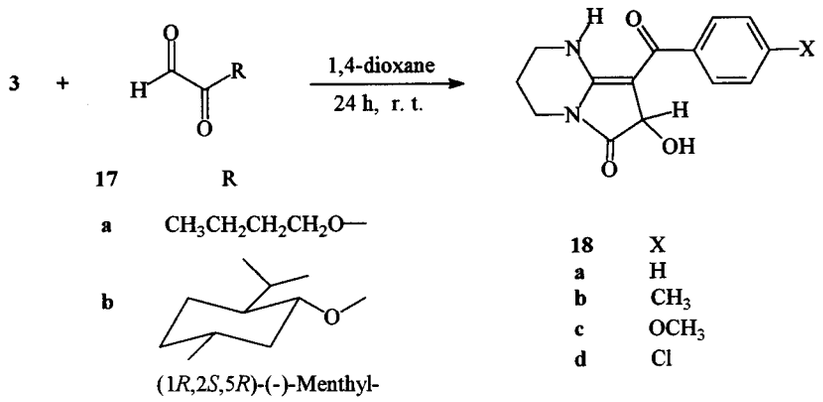
**14**

**15**

**16**

**Scheme 3**

should be stressed that although the six-membered heterocyclic ketene aminals always show higher nucleophilic reactivity than the five-membered analogs,[9–14,17] the remarkable difference in reaction velocity in this case is unexpected. A precise explanation of the effect of the size of heterocycle on the reactivity is




**Scheme 4**

still open to debate, although we may ascribe this to the difference in conjugation systems between **3** and **6**. In other words, six-membered heterocyclic ketene aminals **3** may form a better conjugation system involving amino nitrogens, double bond and aroyl moieties because of their smaller ring strain. This would lead to more extensive delocalization of the electrons and a more concentrated electron density on the α-carbon than its five-membered analogs, as evidenced by the fact that the vinyl proton of **3** resonates at higher field than that of **6** in the $^1$H–NMR spectrum.[8]

The reaction of heterocyclic ketene aminals **3**–**8** with *n*-butyl glyoxylate **17** was also investigated. Being a weaker heteroenophile compared to diethyl oxomalonate **9**, compound **17** was only attacked by the most reactive heterocyclic ketene aminal **3**. Thus, under the identical conditions as for the reaction of **3**–**8** with **9**, compound **3** underwent an aza-ene addition to **17a** and a consecutive cyclocondensation reaction to produce 8-aroyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]-pyrimidine **18** (Scheme 4). As a chiral center was created during the aza-ene addition, a chiral substrate (1*R*,2*S*,5*R*)-(−)-menthyl glyoxylate **17b** was then tested in order to prepare optically active compounds **18**. The reaction was equally efficient, but unfortunately, no asymmetric induction was observed. Glyoxylate **17b** is probably not a good chiral reagent in this case, since its chiral centers are remote from the aza-ene reaction site. The structure of **18** has been proven by spectroscopic data and microanalyses. Interestingly in the $^1$H NMR spectrum, the signal of the proton at the 7-position appears as a pseudo-triplet while its adjacent hydroxy proton appears as a doublet ($J \sim 8$ Hz). After treating the sample with $D_2O$, the former signal becomes a singlet and the hydroxy signal disappears. Also to disappear is the secondary amino proton which had been observed as a broad peak around 10 ppm. Apparently, the proton at the 7-position couples with the hydroxy proton, and furthermore is also probably correlated with the amino proton through a long range '*zig zag*' coupling.

In conclusion, heterocyclic ketene aminals are good aza-ene components and undergo Type III hetero-ene reactions readily and efficiently with activated carbonyl compounds. By the reaction of **3**, **4** and **6** with diethyl oxomalonate **9** and glyoxalic acid esters **17**, we have provided a novel and efficient synthetic route to γ-lactam-fused diazaheterocycles.

## Experimental

Melting points, which are uncorrected, were determined using a Reichert Kofler hot-stage apparatus. Infrared spectra were obtained on a Perkin-Elmer 782 instrument as KBr discs or liquid films. NMR spectra were recorded in $CDCl_3$ or [$^2H_6$]-DMSO solution with $SiMe_4$ as internal standard on a Varian Unity 200 spectrometer. Chemical shifts are reported in ppm while the coupling constant *J* values are in Hz. Mass spectra were measured on a AEI MS-50 mass spectrometer and microanalyses were carried out at the Analytical Laboratory of the Institute.

### Preparation of 1,3-dimethyl-2-[(4-substituted benzoyl)methylene]perhydropyrimidines 5

Mixtures of benzoyl-substituted ketene dithioacetals **1a**,**c**,**d** and *N*,*N*′-dimethylpropane-1,3-diamine **2** were refluxed in toluene for 5–8 h to give **5a**,**c**,**d**.[15]

**2-Benzoylmethylene-1,3-dimethylperhydropyrimidine 5a.** Yield, 78%; mp 153–155 °C (Found: C, 73.32; H, 7.52; N, 12.11. $C_{14}H_{18}N_2O$ requires C, 73.01; H, 7.88; N, 12.17%); $\nu_{max}$(KBr)/cm$^{-1}$ 1590; $\delta_H$($CDCl_3$) 7.86 (2H, m, ArH), 7.34 (3H, m, ArH), 4.82 (1H, s, =CH–), 3.32 (4H, t, *J* 5.1, 2 × $CH_2$), 3.14 (6H, s, 2 × $NCH_3$) and 2.04 (2H, quintet, *J* 5.1, $CH_2$); *m*/*z* (EI) 230 ($M^+$, 68%), 213 (100), 202 (23), 153 (50), 125 (69) and 105 (48).

**1,3-Dimethyl-2-[(4-methoxybenzoyl)methylene]perhydropyrimidine 5c.** Yield, 73%; mp 114–116 °C (Found: C, 68.83; H, 7.33; N, 10.53. $C_{15}H_{20}N_2O_2$ requires C, 69.20; H, 7.75; N, 10.76%); $\nu_{max}$(KBr)/cm$^{-1}$ 1590; $\delta_H$($CDCl_3$) 7.84 (2H, d, *J* 8.9, ArH), 6.88 (2H, d, *J* 8.9, ArH), 4.80 (1H, s, =CH–), 3.82 (3H, s, $OCH_3$), 3.30 (4H, t, *J* 5.2, 2 × $CH_2$), 3.12 (6H, s, 2 × $NCH_3$) and 2.02 (2H, quintet, *J* 5.2, $CH_2$); *m*/*z* (EI) 260 ($M^+$, 69%), 243 (100), 232 (19), 153 (28), 135 (48) and 125 (78).

**2-[(4-Chlorobenzoyl)methylene]-1,3-dimethylperhydropyrimidine 5d.** Yield, 68%; mp 44–46 °C (Found: $M^+ + 1$ (FAB) 265.1108. $C_{14}H_{18}ClN_2O$ requires 265.1102); $\nu_{max}$(KBr)/cm$^{-1}$ 1590; $\delta_H$($CDCl_3$) 7.80 (2H, d, *J* 6.6, ArH), 7.32 (2H, d, *J* 6.9, ArH), 4.76 (1H, s, =CH–), 3.32 (4H, t, *J* 5.3, 2 × $CH_2$), 3.14 (6H, s, 2 × $NCH_3$) and 2.04 (2H, quintet, *J* 5.3, $CH_2$); *m*/*z* (EI) 264 ($M^+$, 53%), 247 (91), 236 (24), 153 (45), 139 (45) and 125 (100).

### General procedure for the preparation of pyrrolo[1,2-*a*]pyrimidine derivatives 10a–e, 11a–e and pyrrolo[1,2-*a*]imidazole derivatives 12a–e

To a solution of heterocyclic ketene aminals **3a**–**e**, **4a**–**e**, **6a**–**e** (3 mmol) in 1,4-dioxane or acetonitrile (20 cm$^3$) was added dropwise diethyl 2-oxomalonate **9**[19] (3.5 mmol). The mixture was stirred at room temperature under argon and the reaction was monitored by TLC. Product **10a**–**e** precipitated directly from the mixture while **11a**–**e** and **12a**–**e** were obtained after removal of solvent under vacuum. Recrystallization from the appropriate solvent gave pure **10**, **11** and **12**.

**8-Benzoyl-7-ethoxycarbonyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 10a.** Mp 190–192 °C (absolute ethanol) (Found: C, 61.84; H, 5.61; N, 8.55. $C_{17}H_{18}N_2O_5$ requires C, 61.81; H, 5.49; N, 8.48%); $\nu_{max}$(KBr)/cm$^{-1}$ 3340, 3200 (OH, NH), 1760, 1735 and 1640 (C=O); $\delta_H$($CDCl_3$) 10.30

(1H, s, NH), 7.30–7.73 (5H, m, ArH), 4.36 (1H, s, OH), 3.80–3.96 (2H, m, $CH_2$), 3.68 (2H, t, *J* 5.9, $CH_2$), 3.56 (2H, t, *J* 5.9, $CH_2$), 2.14 (2H, quintet, *J* 5.9, $CH_2$) and 0.88 (3H, t, *J* 10.7, $CH_3$); *m*/*z* (EI) 330 ($M^+$, 8%), 312 (50), 283 (10), 266 (23) and 257 (100).

**7-Ethoxycarbonyl-7-hydroxy-8-(4-methylbenzoyl)-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 10b.** Mp 203–205 °C (absolute ethanol and acetonitrile) (Found: C, 62.74; H, 6.00; N, 8.25. $C_{18}H_{20}N_2O_5$ requires C, 62.78; H, 5.85; N, 8.14%); $\nu_{max}$(KBr)/$cm^{-1}$ 3340, 3200 (OH, NH), 1760, 1735 and 1640 (C=O); $\delta_H$($[^2H_6]$DMSO) 10.20 (1H, s, NH), 7.66 (2H, d, *J* 10.7, ArH), 7.12 (2H, d, *J* 10.7, ArH), 6.68 (1H, s, OH), 3.60–3.90 (2H, m, $CH_2$), 3.58 (2H, t, *J* 6.8, $CH_2$), 3.46 (2H, t, *J* 6.8, $CH_2$), 2.28 (3H, s, $CH_3$), 1.96 (2H, quintet, *J* 6.8, $CH_2$) and 0.70 (3H, t, *J* 8.5, $CH_3$); *m*/*z* (EI) 344 ($M^+$, 9%), 326 (42), 297 (8), 280 (33), 271 (74), 255 (38), 243 (17) and 179 (100).

**7-Ethoxycarbonyl-7-hydroxy-8-(4-methoxybenzoyl)-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 10c.** Mp 196–198 °C (absolute ethanol and acetonitrile) (Found: C, 60.07; H, 5.57; N, 7.72. $C_{18}H_{20}N_2O_6$ requires C, 59.96; H, 5.59; N, 7.78%); $\nu_{max}$(KBr)/$cm^{-1}$ 3330, 3200 (OH, NH), 1760, 1735 and 1645 (C=O); $\delta_H$($[^2H_6]$DMSO) 10.24 (1H, s, NH), 7.82 (2H, d, *J* 9.0, ArH), 6.84 (2H, d, *J* 9.0, ArH), 6.74 (1H, s, OH), 3.60–3.90 (2H, m, $CH_2$), 3.76 (3H, s, $OCH_3$), 3.58 (2H, t, *J* 4.8, $CH_2$), 3.48 (2H, t, *J* 4.8, $CH_2$), 1.96 (2H, quintet, *J* 4.8, $CH_2$) and 0.70 (3H, t, *J* 8.5, $CH_3$); *m*/*z* (EI) 360 ($M^+$, 8%), 342 (42), 296 (29), 287 (37), 271 (35), 179 (91) and 135 (100).

**8-(4-Chlorobenzoyl)-7-ethoxycarbonyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 10d.** Mp 202–204 °C (absolute ethanol and acetonitrile) (Found: C, 56.01; H, 4.87; N, 7.92. $C_{17}H_{17}ClN_2O_5$ requires C, 55.97; H, 4.70; N, 7.68%); $\nu_{max}$(KBr)/$cm^{-1}$ 3350, 3320 (OH, NH), 1760, 1735 and 1640 (C=O); $\delta_H$($[^2H_6]$DMSO) 10.16 (1H, s, NH), 7.76 (2H, d, *J* 9.0, ArH), 7.38 (2H, d, *J* 8.7, ArH), 6.78 (1H, s, OH), 3.60–3.90 (2H, m, $CH_2$), 3.58 (2H, t, *J* 8.3, $CH_2$), 3.48 (2H, t, *J* 8.3, $CH_2$), 1.98 (2H, quintet, *J* 8.3, $CH_2$) and 0.75 (3H, t, *J* 5.1, $CH_3$); *m*/*z* (EI) 366 ($[M + 2]^+$, 3%), 364 ($M^+$, 9), 346 (37), 291 (80), 275 (47) and 179 (100).

**8-(4-Bromobenzoyl)-7-ethoxycarbonyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 10e.** Mp 203-205 °C (absolute ethanol and acetonitrile) (Found: C, 49.80; H, 4.40; N, 6.88. $C_{17}H_{17}BrN_2O_5$ requires C, 49.89; H, 4.19; N, 6.85%); $\nu_{max}$(KBr)/$cm^{-1}$ 3340, 3200 (OH, NH), 1760, 1735 and 1640 (C=O); $\delta_H$($[^2H_6]$DMSO) 10.16 (1H, s, NH), 7.68 (2H, d, *J* 8.9, ArH), 7.50 (2H, d, *J* 8.3, ArH), 6.78 (1H, s, OH), 3.60–3.90 (2H, m, $CH_2$), 3.58 (2H, t, *J* 6.9, $CH_2$), 3.46 (2H, t, *J* 6.9, $CH_2$), 1.96 (2H, quintet, *J* 6.9, $CH_2$) and 0.72 (3H, t, *J* 5.1, $CH_3$); *m*/*z* (EI) 410 ($[M + 2]^+$, 6%), 408 ($M^+$, 6), 390 (29), 346 (16), 335 (66), 319 (44), 183 (51) and 179 (100).

**8-Benzoyl-7-ethoxycarbonyl-7-hydroxy-1-methyl-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 11a.** Mp 133–135 °C (ethyl acetate) (Found: C, 62.49; H, 5.76; N, 8.09. $C_{18}H_{20}N_2O_5$ requires C, 62.78; H, 5.85; N, 8.14%); $\nu_{max}$(KBr)/$cm^{-1}$ 3320 (OH), 1745, 1710 and 1625 (C=O); $\delta_H$($CDCl_3$) 7.30–7.75 (5H, m, ArH), 4.36 (1H, s, OH), 3.80–4.00 (3H, m, $CH_2$, C*H*H), 3.30–3.65 (3H, m, CH*H*, $CH_2$), 3.18 (1H, s, $NCH_3$), 2.16 (2H, quintet, *J* 4.8, $CH_2$) and 1.10 (3H, t, *J* 7.6, $CH_3$); *m*/*z* (EI) 344 ($M^+$, 2%), 271 (16), 255 (22), 193 (11), 151 (10), 122 (65) and 105 (100).

**7-Ethoxycarbonyl-7-hydroxy-1-methyl-8-(4-methylbenzoyl)-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 11b.** Mp 146–148 °C (ethyl acetate and ethanol) (Found: C, 63.65; H, 6.13; N, 7.84. $C_{19}H_{22}N_2O_5$ requires C, 63.67; H, 6.19; N, 7.82%); $\nu_{max}$(KBr)/$cm^{-1}$ 3380 (OH), 1755, 1740 and 1615 (C=O); $\delta_H$($CDCl_3$) 7.62 (2H, d, *J* 8.0, ArH), 7.15 (2H, d, *J* 8.0, ArH), 4.38 (1H, s, OH), 3.80–4.00 (3H, m, $CH_2$, C*H*H), 3.30–3.65 (3H, m, CH*H*, $CH_2$), 3.15 (1H, s, $NCH_3$), 2.35 (3H, s, $CH_3$), 2.15 (2H, quintet, *J* 5.1, $CH_2$) and 1.10 (3H, t, *J* 7.4, $CH_3$); *m*/*z* (EI) 358 ($M^+$, 2%), 342 (3), 285 (38), 269 (25), 193 (26), 151 (16), 136 (64), 119 (87) and 91 (100).

**7-Ethoxycarbonyl-7-hydroxy-1-methyl-8-(4-methoxybenzoyl)-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 11c.** Mp 135–137 °C (ethyl acetate and ethanol) (Found: C, 60.92; H, 5.87; N, 7.45. $C_{19}H_{22}N_2O_6$ requires C, 60.95; H, 5.92; N, 7.48%); $\nu_{max}$(KBr)/$cm^{-1}$ 3370 (OH), 1735, 1710 and 1625 (C=O); $\delta_H$($CDCl_3$) 7.72 (2H, d, *J* 8.4, ArH), 6.84 (2H, d, *J* 8.4, ArH), 4.40 (1H, s, OH), 3.80–4.00 (3H, m, $CH_2$, C*H*H), 3.82 (3H, s, $OCH_3$), 3.30–3.65 (3H, m, CH*H*, $CH_2$), 3.15 (1H, s, $NCH_3$), 2.15 (2H, quintet, *J* 4.5, $CH_2$) and 1.08 (3H, t, *J* 6.6, $CH_3$); *m*/*z* (EI) 374 ($M^+$, 3%), 358 (4), 301 (13), 285 (23), 193 (43), 152 (76) and 135 (100).

**8-(4-Chlorobenzoyl)-7-ethoxycarbonyl-7-hydroxy-1-methyl-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 11d.** Mp 136–138 °C (ethyl acetate and ethanol) (Found: C, 56.98; H, 4.97; N, 7.40. $C_{18}H_{19}ClN_2O_5$ requires C, 57.07; H, 5.06; N, 7.40%); $\nu_{max}$(KBr)/$cm^{-1}$ 3400 (OH), 1760, 1740 and 1615 (C=O); $\delta_H$($CDCl_3$) 7.68 (2H, d, *J* 8.4, ArH), 7.30 (2H, d, *J* 8.4, ArH), 4.34 (1H, s, OH), 3.80–4.00 (3H, m, $CH_2$, C*H*H), 3.30–3.65 (3H, m, CH*H*, $CH_2$), 3.20 (1H, s, $NCH_3$), 2.15 (2H, quintet, *J* 4.9, $CH_2$) and 1.08 (3H, t, *J* 7.1, $CH_3$); *m*/*z* (EI) 378 ($M^+$, 1%), 362 (2), 205 (19), 289 (16), 193 (13), 156 (60) and 139 (100).

**8-(4-Bromobenzoyl)-7-ethoxycarbonyl-7-hydroxy-1-methyl-6-oxo-1,2,3,4,6,7-hexahydropyrrolo[1,2-*a*]pyrimidine 11e.** Mp 133–135 °C (ethyl acetate) (Found: C, 51.38; H, 4.45; N, 6.60. $C_{18}H_{19}BrN_2O_5$ requires C, 51.08; H, 4.52; N, 6.62%); $\nu_{max}$(KBr)/$cm^{-1}$ 3400 (OH), 1760, 1740 and 1615 (C=O); $\delta_H$($CDCl_3$) 7.60 (2H, d, *J* 8.4, ArH), 7.46 (2H, d, *J* 8.4, ArH), 4.35 (1H, s, OH), 3.80–4.00 (3H, m, $CH_2$, C*H*H), 3.30–3.65 (3H, m, CH*H*, $CH_2$), 3.22 (1H, s, $NCH_3$), 2.15 (2H, quintet, *J* 5.0, $CH_2$) and 1.08 (3H, t, *J* 5.3, $CH_3$); *m*/*z* (EI) 424 (2%), 422 ($M^+$, 2), 406 (2), 349 (19), 333 (15), 200 (78), 193 (17) and 183 (100).

**7-Benzoyl-6-ethoxycarbonyl-6-hydroxy-5-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole 12a.** Mp 201-203 °C (absolute ethanol and acetonitrile) (Found: C, 60.72; H, 5.00; N, 8.78. $C_{16}H_{16}N_2O_5$ requires C, 60.75; H, 5.10; N, 8.86%); $\nu_{max}$(KBr)/$cm^{-1}$ 3340, 3280 (OH, NH), 1760, 1735 and 1660 (C=O); $\delta_H$($[^2H_6]$DMSO) 9.10 (1H, br. s, NH), 7.25–7.75 (5H, m, ArH), 6.70 (1H, s, OH), 4.00 (2H, t, *J* 5.9, $CH_2$), 3.60–3.90 (4H, m, 2 × $CH_2$) and 0.70 (3H, t, *J* 5.9, $CH_3$); *m*/*z* (EI) 316 ($M^+$, 3%), 298 (18), 243 (66), 225 (8), 215 (27), 165 (14) and 105 (100).

**6-Ethoxycarbonyl-6-hydroxy-7-(4-methylbenzoyl)-5-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole 12b.** Mp 203–205 °C (absolute ethanol and acetonitrile) (Found: C, 61.71; H, 5.64; N, 8.68. $C_{17}H_{18}N_2O_5$ requires C, 61.81; H, 5.49; N, 8.48%); $\nu_{max}$(KBr)/$cm^{-1}$ 3350, 3290 (OH, NH), 1755, 1730 and 1655 (C=O); $\delta_H$($[^2H_6]$DMSO) 9.10 (1H, br s, NH), 7.68 (2H, d, *J* 8.0, ArH), 7.14 (2H, d, *J* 8.0, ArH), 6.70 (1H, s, OH), 4.02 (2H, t, *J* 7.6, $CH_2$), 3.70–3.95 (4H, m, 2 × $CH_2$), 2.32 (3H, s, $CH_3$) and 0.78 (3H, t, *J* 5.1, $CH_3$); *m*/*z* (EI) 330 ($M^+$, 3%), 312 (20), 257 (45), 229 (16), 165 (38) and 119 (100).

**6-Ethoxycarbonyl-6-hydroxy-7-(4-methoxybenzoyl)-5-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole 12c.** Mp 192–194 °C (absolute ethanol and acetonitrile) (Found: C, 58.82; H, 5.36; N, 7.99. $C_{17}H_{18}N_2O_6$ requires C, 58.95; H, 5.24; N, 8.09%); $\nu_{max}$(KBr)/$cm^{-1}$ 3340, 3280 (OH, NH), 1750, 1720 and 1650 (C=O); $\delta_H$($[^2H_6]$DMSO) 9.10 (1H, br s, NH), 7.84 (2H, d, *J* 8.4, ArH), 6.90 (2H, d, *J* 8.4, ArH), 6.76 (1H, s, OH), 4.04 (2H, t, *J* 7.6, $CH_2$), 3.70–3.95 (4H, m, 2 × $CH_2$), 3.80 (3H, s, $OCH_3$)

and 0.80 (3H, t, *J* 6.3, $CH_3$); *m*/*z* (EI) 346 ($M^+$, 2%), 328 (22), 273 (17), 255 (11), 165 (37) and 135 (100).

**7-(4-Chlorobenzoyl)-6-ethoxycarbonyl-6-hydroxy-5-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole 12d.** Mp 205–207 °C (absolute ethanol and acetonitrile) (Found: C, 54.99; H, 4.66; N, 7.95. $C_{16}H_{15}ClN_2O_5$ requires C, 54.78; H, 4.31; N, 7.99%); $\nu_{max}$(KBr)/$cm^{-1}$ 3340, 3285 (OH, NH), 1750, 1725 and 1650 (C=O); $\delta_H$([$^2H_6$]DMSO) 9.10 (1H, br s, NH), 7.68 (2H, d, *J* 9.1, ArH), 7.40 (2H, d, *J* 9.1, ArH), 6.84 (1H, s, OH), 4.05 (2H, t, *J* 6.3, $CH_2$), 3.70–3.95 (4H, m, 2 × $CH_2$) and 0.80 (3H, t, *J* 6.5, $CH_3$); *m*/*z* (EI) 350 ($M^+$, 3%), 332 (22), 277 (64), 259 (12), 249 (21), 165 (34) and 139 (100).

**7-(4-Bromobenzoyl)-6-ethoxycarbonyl-6-hydroxy-5-oxo-2,3,5,6-tetrahydro-1*H*-pyrrolo[1,2-*a*]imidazole 12e.** Mp 203–205 °C (absolute ethanol and acetonitrile) (Found: C, 48.79; H, 4.25; N, 7.03. $C_{16}H_{15}BrN_2O_5$ requires C, 48.62; H, 3.83; N, 7.09%); $\nu_{max}$(KBr)/$cm^{-1}$ 3300, 3290 (OH, NH), 1750, 1720 and 1650 (C=O); $\delta_H$([$^2H_6$]DMSO) 9.10 (1H, br s, NH), 7.72 (2H, d, *J* 6.4, ArH), 7.56 (2H, d, *J* 6.4, ArH), 6.84 (1H, s, OH), 4.06 (2H, t, *J* 6.7, $CH_2$), 3.70–3.95 (4H, m, 2 × $CH_2$) and 0.80 (3H, t, *J* 6.4, $CH_3$); *m*/*z* (EI) 396 (4%), 394 ($M^+$, 3), 376 (33), 348 (9), 321 (88), 305 (22), 393 (16) and 183 (100).

**General procedure for the preparation of pyrrolo[1,2-*a*]-pyrimidines 18a–d.** A mixture of heterocyclic ketene aminals **3a**–**d** (3 mmol) and *n*-butyl glyoxylate **17a**[20] (3.5 mmol) or (1*R*,2*S*,5*R*)-(−)-menthyl glyoxylate **17b**[21] (3.5 mmol) in 1,4-dioxane (20 $cm^3$) was stirred at room temperature for 24 h. The crude products precipitated after partial removal of the solvent under reduced pressure. Recrystallization from the appropriate solvent gave pure **18a**–**d**.

**8-Benzoyl-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydropyrrolo-[1,2-*a*]pyrimidine 18a.** Yield, 91%; mp 155–157 °C (ethanol and acetonitrile) (Found: C, 65.10; H, 5.65; N, 10.78. $C_{14}H_{14}N_2O_3$ requires C, 65.10; H, 5.46; N, 10.85%); $\nu_{max}$(KBr)/ $cm^{-1}$ 3400, 3200 (OH, NH), 1755 and 1645 (C=O); $\delta_H$([$^2H_6$]DMSO) 10.06 (1H, br s, NH), 7.30–7.88 (5H, m, ArH), 5.78 (1H, d, *J* 7.9, OH), 4.75 (1H, t, *J* 5.1, CH), 3.39–3.57 (4H, m, 2 × $CH_2$) and 1.94 (2H, quintet, *J* 5.6, $CH_2$); *m*/*z* (EI) 258 ($M^+$, 2%), 240 (100), 211 (42) and 183 (47).

**7-Hydroxy-8-(4-methylbenzoyl)-6-oxo-1,2,3,4,6,7-hexahydro-pyrrolo[1,2-*a*]pyrimidine 18b.** Yield, 55%; mp 167–169 °C (ethyl acetate and ethanol) (Found: C, 65.86; H, 6.04; N, 10.11. $C_{15}H_{16}N_2O_3$ requires C, 66.16; H, 5.92; N, 10.29%); $\nu_{max}$(KBr)/ $cm^{-1}$ 3400, 3200 (OH, NH), 1750 and 1635 (C=O); $\delta_H$([$^2H_6$]-DMSO) 10.06 (1H, br s, NH), 7.78 (2H, d, *J* 6.8, ArH), 7.18 (2H, d, *J* 6.8, ArH), 5.78 (1H, d, *J* 7.6, OH), 4.79 (1H, t, *J* 4.6, CH), 3.38–3.52 (4H, m, 2 × $CH_2$), 2.32 (3H, s, $CH_3$) and 1.92 (2H, quintet, *J* 6.7, $CH_2$); *m*/*z* (EI) 272 ($M^+$, 2%), 254 (100), 225 (24), 211 (22) and 197 (21).

**7-Hydroxy-8-(4-methoxybenzoyl)-6-oxo-1,2,3,4,6,7-hexa-hydropyrrolo[1,2-*a*]pyrimidine 18c.** Yield, 78%; mp 153–155 °C (ethanol and acetonitrile) (Found: C, 62.58; H, 5.58; N, 9.75. $C_{15}H_{16}N_2O_4$ requires C, 62.49; H, 5.59; N, 9.72%); $\nu_{max}$(KBr)/ $cm^{-1}$ 3340, 3190 (OH, NH), 1760 and 1635 (C=O); $\delta_H$([$^2H_6$]-DMSO) 10.10 (1H, br s, NH), 7.90 (2H, d, *J* 6.4, ArH), 6.90 (2H, d, *J* 6.7, ArH), 5.80 (1H, d, *J* 8.0, OH), 4.79 (1H, t, *J* 4.0, CH), 3.80 (3H, s, $OCH_3$), 3.36–3.55 (4H, m, 2 × $CH_2$) and 1.94 (2H, quintet, *J* 5.1, $CH_2$); *m*/*z* (EI) 288 ($M^+$, 1%), 271 (64), 244 (42), 137 (87) and 135 (100).

**8-(4-Chlorobenzoyl)-7-hydroxy-6-oxo-1,2,3,4,6,7-hexahydro-pyrrolo[1,2-*a*]pyrimidine 18d.** Yield, 49%; mp 156–158 °C (ethanol) (Found: C, 57.70; H, 4.63; N, 9.54. $C_{14}H_{13}ClN_2O_3$ requires C, 57.44; H, 4.48; N, 9.57%); $\nu_{max}$(KBr)/ $cm^{-1}$ 3360, 3210 (OH, NH), 1765 and 1640 (C=O); $\delta_H$([$^2H_6$]DMSO) 10.04 (1H, br s, NH), 7.88 (2H, d, *J* 9.6, ArH), 7.44 (2H, d, *J* 8.9, ArH), 5.82 (1H, d, *J* 8.3, OH), 4.80 (1H, s, CH), 3.38–3.57 (4H, m, 2 × $CH_2$) and 1.94 (2H, quintet, *J* 6.2, $CH_2$); $\delta_H$([$^2H_6$]-DMSO + $D_2O$) 7.76 (2H, d, *J* 8.0, ArH), 7.47 (2H, d, *J* 8.0, ArH), 4.88 (1H, s, CH), 3.34–3.60 (4H, m, 2 × $CH_2$) and 1.97 (2H, quintet, *J* 6.2, $CH_2$); *m*/*z* (EI) 294 ([$M^+$ + 2], 2%), 292 ($M^+$, 5), 274 (100), 245 (25), 218 (56) and 211 (59).

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*Paper 8/08328B*