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Reactions of alkylidenepyrrolidines with α-chlorooximes and α-chlorohydrazones

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ABSTRACT

The reactions of alkylidenepyrrolidines with α-chlorooximes give isoxazoles via an acylation reaction followed by ring isomerisation. In contrast, and in line with a previous report, the corresponding α-chlorohydrazones give the simple acylation products, although in one instance a cycloadduct was also obtained.

α-Chlorooximes and α-chlorohydrazones are widely used in organic synthesis, mainly as precursors of nitrile oxide and nitrilimine dipoles for use in cycloaddition chemistry.[1] However, they can also be considered as highly functionalised electrophiles.[2] We have recently reported the reaction of alkylidenepyrrolidine **1** with nitrolic acids **2**, in which the HNO_2 that is eliminated from the nitrolic acid nitrosates the alkylidenepyrrolidine double-bond. Two cycloaddition reactions then take place to give the observed products **3** (Scheme 1).[3]

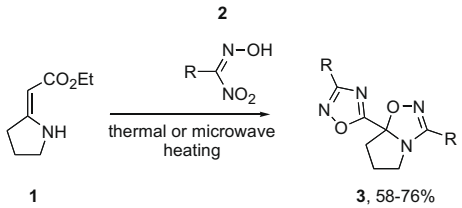
The reaction of alkylidenepyrrolidines such as **1** with α-chlorohydrazones **4** has been reported to give products **5**, by simple acylation of the alkylidenepyrrolidine double-bond (Scheme 2).[4]

This preference for C-acylation is unsurprising.[5] The possibility that the products **5** could isomerise to give the corresponding pyrazoles was mentioned by the authors, although it was not observed in this instance. However, the formation of isoxazoles has been reported following the reaction of alkylidenepyrrolidine ketones with hydroxylamine.[6] The reaction of alkylidenepyrrolidine **1** with α-chlorooximes **6** has not been reported, and would appear to have more in common with the former case. We therefore reacted alkylidenepyrrolidine **1** with a range of α-chlorooximes **6**. Products **7** were obtained in good yields (Scheme 3; Table 1),[7] presumably by initial acylation to give compound **8** followed by isomerisation to give **9** and a rapid second acylation to give the observed products. Use of a single equivalent of the α-chlorooxime gave the same products, but in lower yield and with some alkylidenepyrrolidine left unreacted. Mass spectrometry confirmed that compounds **7** are 1:2 adducts with loss of two equivalents of HCl. NMR data for these compounds are similar to those reported by Dannhardt et al.[6] for analogues lacking the ester and side-chain acylation, although as would be expected, the chemical shifts of the methylene groups adjacent to nitrogen and to the isoxazole ring are slightly higher in compounds **7**.

Isoxazoles possess a range of useful biological activity.[8] In particular, a variety of compounds (e.g., **10**, Fig. 1) closely related to **7** are ghrelin receptor modulators, having potential for the treatment of various eating disorders.[9] Therefore a new method for the formation of such compounds from readily available starting materials is noteworthy. The reverse of the ring transformation depicted in Scheme 3 is known, leading to the formation of aromatic pyrrole compounds from suitably substituted isoxazoles.[10]

Surprisingly, when the 3-nitrophenyl chlorooxime **6e** was used, compound **11** was obtained as the sole product (Scheme 4).[11] This result is entirely reproducible, although it is not clear why the oxime cyclises onto the ester in this case, but onto the alkylidenepyrrolidine ring in other cases.

Reactions of alkylidenepyrrolidine **1** with α-chlorohydrazones do proceed with simple acylation as previously reported.[4] However, in one instance (with α-chlorohydrazone **12**), in addition to the expected compound **13**, we were also able to obtain compound **14**, this being formed by 1,3-dipolar cycloaddition onto the imine tautomer of the alkylidenepyrrolidine (Scheme 5). The failure of compound **13** to undergo conversion into the pyrazole, in a manner analogous to the corresponding oximes, can most likely be attrib-



Scheme 1.

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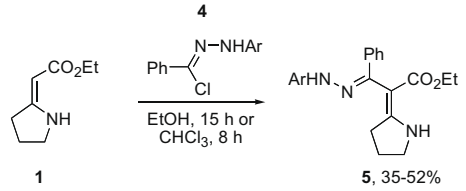
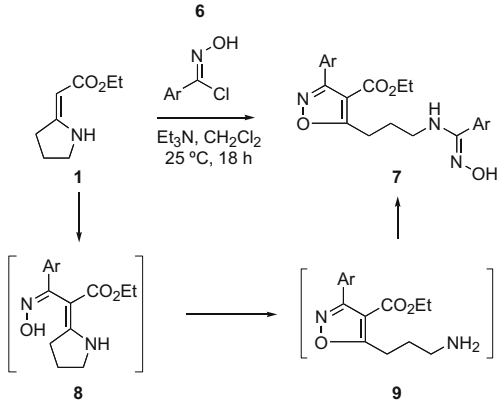
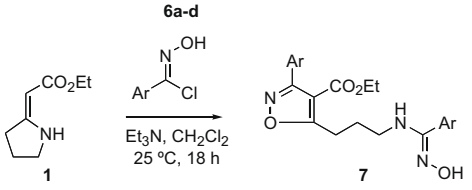


Scheme 2.

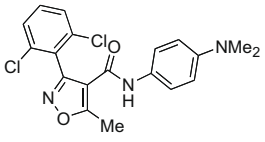


Scheme 3.

Table 1
Formation of adducts **7**

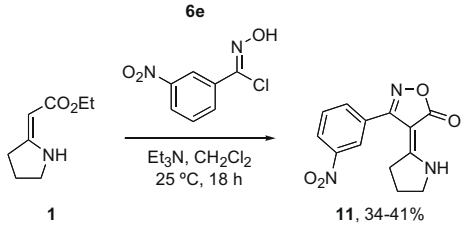


Product	Ar	Yield (%)
7a	2,6-Dichlorophenyl	69
7b	2,4-Dichlorophenyl	67
7c	Phenyl	68
7d	2-Nitrophenyl	56

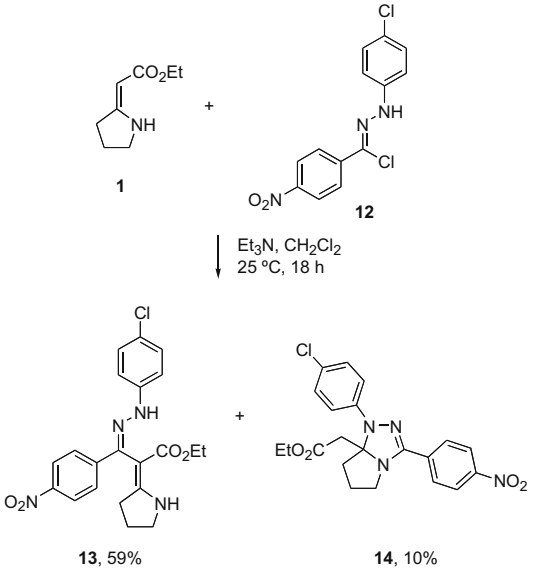


10

Figure 1.



Scheme 4.



Scheme 5.

uted to steric hindrance and to the lower nucleophilicity of the arylated nitrogen.

Acknowledgements

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7. *Ethyl 5-(3-(2,6-dichloro-N′-hydroxybenzimidamido)propyl)-3-(2,6-dichlorophenyl) isoxazole-4-carboxylate* (**7a**): The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of α-chloroaldoxime **6a** (448 mg, 2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise over 2 min and the reaction mixture was stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated in vacuo and purified by flash column chromatography (eluent 2:1 petroleum ether/EtOAc) to give the *title*

compound (366 mg, 69%) as a colourless solid, mp 122–123 °C (Found: MH^+, 530.0182. $C_{22}H_{20}N_3O_4{}^{35}Cl_4$ requires M, 530.0208); ν_{max} (KBr disc) 3372, 2922, 1721, 1644, 1457, 1377, 1297, 910, 784 and 732 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.39–7.11 (6H, m, aromatic CH), 5.57 (1H, br s, NH), 4.01 (2H, q, *J* 7.1, OCH_2), 3.13 (2H, t, *J* 7.4, $CH_2CH_2CH_2N$), 2.88 (2H, poorly resolved app. q, *J* 5.1, $CH_2CH_2CH_2N$), 1.88 (2H, app. quintet, *J* 7.0, $CH_2CH_2CH_2N$) and 0.90 (3H, t, *J* 7.1, CH_2CH_3); δ_C (100 MHz; $CDCl_3$) 178.1 (C), 170.0 (C), 158.6 (C), 150.4 (C), 136.0 (2×C–Cl), 135.4 (2×C–Cl), 131.3 (CH), 131.0 (CH), 129.5 (C), 128.3 (C), 128.1 (2×CH), 127.7 (2×CH), 109.3 (C), 60.8 (CH_2), 42.0 (CH_2), 28.0 (CH_2), 24.6 (CH_2) and 13.6 (CH_3); *m*/*z* (TOF ES^+) 532 (MH^+, 100%) (isotopic distribution consistent with 4×Cl).

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11. *3-(3-Nitrophenyl)-4-(pyrrolidin-2-ylidene)isoxazol-5(4H)-one* (**10**): The alkylidenepyrrolidine **1** (155 mg, 1 mmol) in CH_2Cl_2 (5 mL) was added to a solution of *N*-hydroxy-3-nitrobenzimidoyl chloride **6e** (400 mg, 2 mmol) in CH_2Cl_2 (5 mL). Triethylamine (250 mg, 2.5 mmol) was added dropwise over 2 min and the reaction mixture was stirred at ambient temperature for 18 h. The crude reaction mixture was filtered through a short plug of silica gel to remove triethylamine hydrochloride, then concentrated in vacuo and purified by flash column chromatography (eluent 1:1 petroleum ether/EtOAc) to give the *title compound* (193 mg, 41%) as a yellow solid, mp 144–146 °C (Found: M^+, 273.0750; $C_{13}H_{11}N_3O_4$ requires M, 273.0750); ν_{max} (KBr disc) 3284, 2926, 1691, 1599 and 1351 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 10.11 (1H, br s, NH), 8.38 (1H, dd, *J* 8.2, 2.3), 8.31 (1H, app. br s), 8.00 (1H, d, *J* 7.6), 7.80 (1H, app. t, *J* 8.0), 3.62 (2H, t, *J* 7.0, CH_2N), 2.53–2.47 (2H, m, CH_2C) and 1.89 (2H, app. quintet, *J* 7.2, CH_2CH_2N); δ_C (100 MHz; $CDCl_3$) 173.9 (C), 170.0 (C), 161.2 (C), 148.1 (C), 135.8 (CH), 132.6 (C), 130.7 (CH), 125.0 (C), 123.9 (CH), 85.2 (C), 49.6 (CH_2), 33.8 (CH_2) and 20.8 (CH_2); *m*/*z* (TOF EI^+) 273 (M^+, 58%), 230 (100), 200 (93) and 184 (73).