The Synthesis and Preferred Conformation of Pyridoyl Urea and Analogous Derivatives: Preparation of a Folate Analogue

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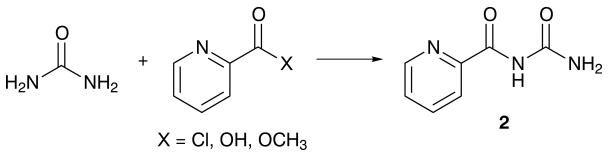
The synthesis of 2-pyridoyl urea and analogous derivatives is reported; NMR spectra show that the acylureas adopt an intramolecular H-bonded conformation.

We are interested in pyridoyl urea and analogous derivatives as monocyclic models of guanine and pterine.[1] A literature search revealed a scarcity of data on these unsubstituted acylurea derivatives and, in particular, a dearth of synthetic work.[9a,b] We have, therefore, tried a few straightforward synthetic pathways to easily obtain the desired derivatives from simple precursors (Scheme 1).

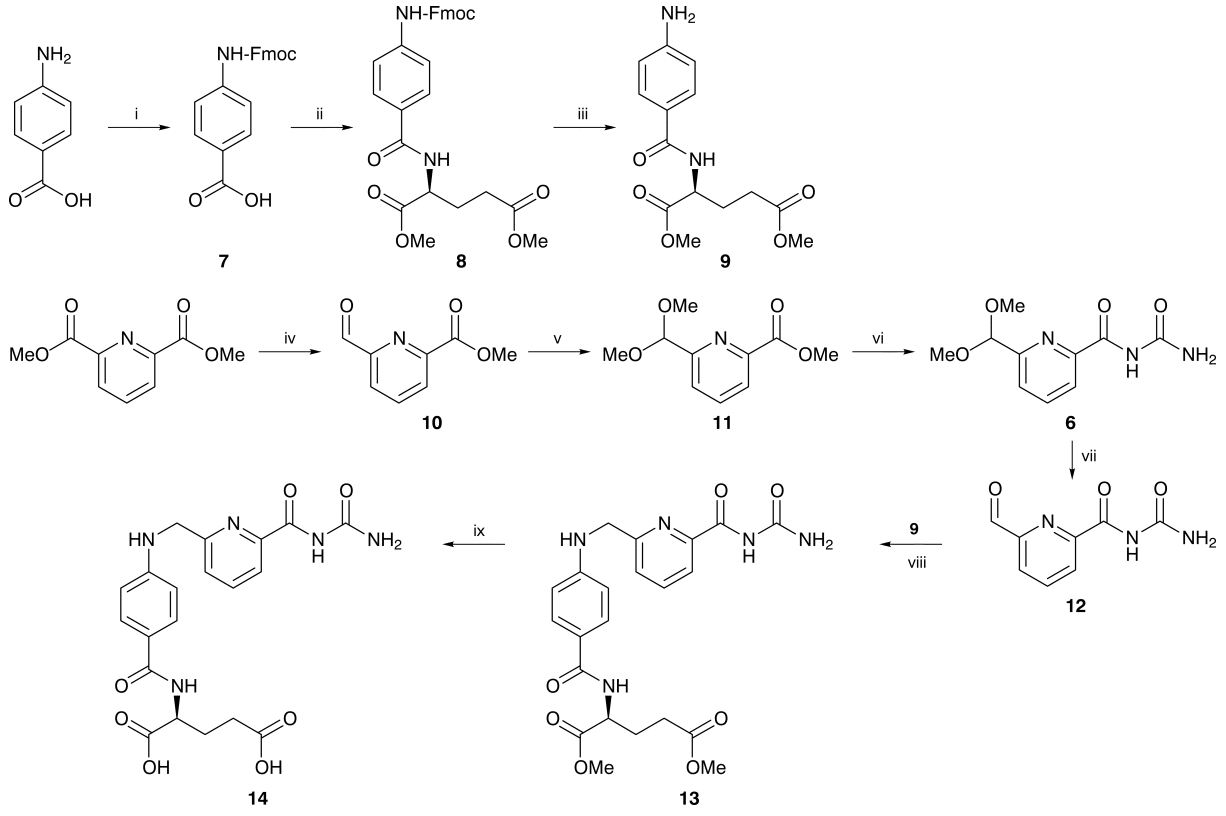


Scheme 1

The methyl ester gave the most encouraging results; specifically, when reacted with excess metallated urea (obtained in THF with KH) it gave the desired product in a 90% isolated yield. This synthetic procedure was extended to the obtainment of compounds **2**–**6** and in all cases yields >60% of isolated products were obtained (Table 1)

We decided to prepare the potentially biologically active folate analogue **14** with a pyridoyl urea in place of the pterine moiety. The synthetic pathway is described in Scheme 2.

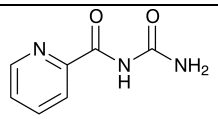
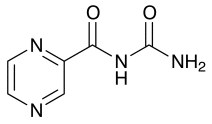
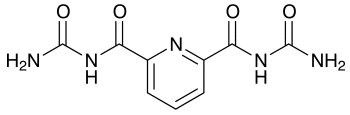
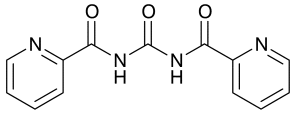
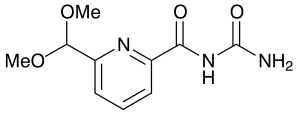
The 300 MHz ^{1}H NMR spectrum of **2** in $CDCl_3$ shows three different signals (a, b and c), corresponding to three different NH protons at 10, 8.3 and 5.3 ppm, respectively. The spectrum recorded in [$^2H_6$]DMSO at room temperature also displays three NH signals; however, signals b and c are much closer and at 60 °C they coalesce at *ca.* 7.5 ppm.



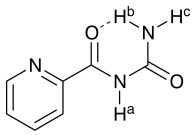
Scheme 2 *Reagents*: i, Fmoc-Cl in 10% Na_2CO_3/1,4-dioxane; ii, 2-chloro-4,6-dimethoxytriazine, *N*-methylmorpholine, L-glutamic acid dimethyl ester hydrochloride in CH_2Cl_2; iii, piperidine in CH_2Cl_2; iv, DIBAL-H in CH_2Cl_2; v, MeOH, $CH(OCH_3)_3$, PPTS; vi, KH, urea in THF; vii, H_2O, H_2SO_4, silica; viii, L-glutamic acid dimethyl ester *p*-amino-benzoate, TFA, $NaBH_3CN$ in CH_2Cl_2; ix, 1 M NaOH/THF

*To receive any correspondence.

Table 1 Yields of derivatives **2–6**

Derivative	Formula	Yield (%)
2		90
3		78
4		60
5		62
6		94

Hence, this molecule adopts the intramolecular H-bonded conformation **2b**.



2b

This structure is stable and only in the competing DMSO solvent at high temperature does exchange of the bonded and free NH_2 protons become fast on the NMR time scale.

NMR spectra of derivatives **3–6** and **13** show a similar behaviour; thus, we think that intramolecularly H-bonded structures analogous to **2b** are also the most stable for these derivatives.

In vitro anti-cancer and anti-HIV screening of compounds **3–4** and **14** is in progress.

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Techniques used: ^1H and ^{13}C NMR, IR, mass spectrometry and circular dichroism

References: 11

Schemes: 2

Table: 1

Fig. 1: The G-quartet

Fig. 2: Species composed of two or more G-quartets in the presence of K^+

Fig. 3: ^1H NMR spectra of **2**

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References cited in this synopsis

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9 (*a*) T. J. Ward and J. C. White, (*Eur. Pat.*) *Chem. Abstr.*, 1989, **112**, 118 671d; (*b*) J. W. Hanifin, Jr., R. A. Capuzzi and E. Cohen, (*US Pat.*) *Chem. Abstr.*, 1967, **67**, 116 893f.