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An efficient multi-component synthesis of *N*-1-alkylated 5-nitrouracils from α-amino acids

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ABSTRACT

The preparation of *N*-1 selectively alkylated uracil intermediates usually requires selective protection at *N*-3 followed by alkylation at *N*-1 and subsequent removal of the protecting group. In this Letter, we show the limitations of this approach when quaternary C centres at *N*-1 became a key target for the programme. To access this key substructure, we developed an efficient multi-component reaction (MCR) from readily available α-amino acid precursors.

During a recent project on an undisclosed target, we targeted the uracil core scaffold from which to explore the 3 key vectors from *N*-1 & *N*-3 and C-5 to deliver the target design set. Retrosynthetic analysis gave the obvious synthon 5-nitrouracil. From which we envisaged a selective alkylation strategy to introduce the alkyl groups at *N*-1 and *N*-3 followed by reduction of the nitro group and amide bond formation (Fig. 1).

Consequently, our first strategy relied upon selective *N*-3-protection of 5-nitrouracil with the benzhydryl group[1] followed by *N*-1 alkylation to prepare **2** in acceptable yields.[2] Subsequent deprotection of the benzhydryl group under hydrolytic conditions[1] gave access to **3** for exploration from the *N*-3 vector. Alkylation of *N*-3 followed by reduction of the nitro group under dissolving metal conditions[3] and subsequent amide bond formation using COMU (1-cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate)[4] as the coupling agent afforded our key scaffold **5** (Scheme 1).

From Table 1, alkylation with unhindered alkyl bromides such as ethyl bromoacetate (entry 1) afforded consistently high yields of selectively *N*-1 alkylated product with no signs of O-alkylation as determined by NMR. After screening several conditions, we found that alkylation with triflate derived lactate derivatives (entries 2 and 3)[5] proceeded in acceptable yields and little epimerisation during the process as confirmed by chiral HPLC.[6] However, all attempts to introduce a quaternary C centre under classical alkylation (entry 4)[7] or *Mitsunobu*-type[8] conditions from ethyl 2-hydroxy-2-methylpropanoate (entry 5)[9] failed affording no signs of alkylated product.

Disappointed by the fact that we failed to apply alkylation chemistry often cited for phenolic substrates,[5,9] we focused our efforts on the preparation of the more accessible cyclopropyl derivative **8** following established protocol to prepare 1-aminocyclopropane-1-carboxylic acid starting from phthalimide.[10] Alkylation of **1** with either the triflate or the alcohol, under *Mitsunobu* conditions, proceeded in acceptable yields to afford **6**. Ring-opening of the resulting lactone **6** with HBr followed by esterification of the resulting carboxylic acid moiety afforded **7**. Subsequent cyclisation to the cyclopropyl derivative proceeded in acceptable yields in the presence of NaH after significant optimisation. Finally, cleavage of the benzhydryl group under acidic conditions and N-alkylation with Me-I afforded **8** albeit in just 1.2% overall yield. Furthermore, attempts to exploit **8** to prepare our desired libraries failed whereby saponification led to ring opening of the cyclopropyl moiety to afford **9** and hydrolysis of the ester worked but also led to cleavage of the amide vector affording **11** (Scheme 2).

Next, we turned our attention to an alternative cyclisation strategy[10] starting from α-amino acid ester precursors. We envisaged that we could access the desired scaffold **3** using ethyl nitroacetate as the key starting material depending on a 3 MCR (multi-component reaction) with just the primary urea precursor (**12**) to prepare from readily-available amino acid substrates **13** using either TMS-isocyanate[11] or potassium cyanate (Fig. 2).[12]

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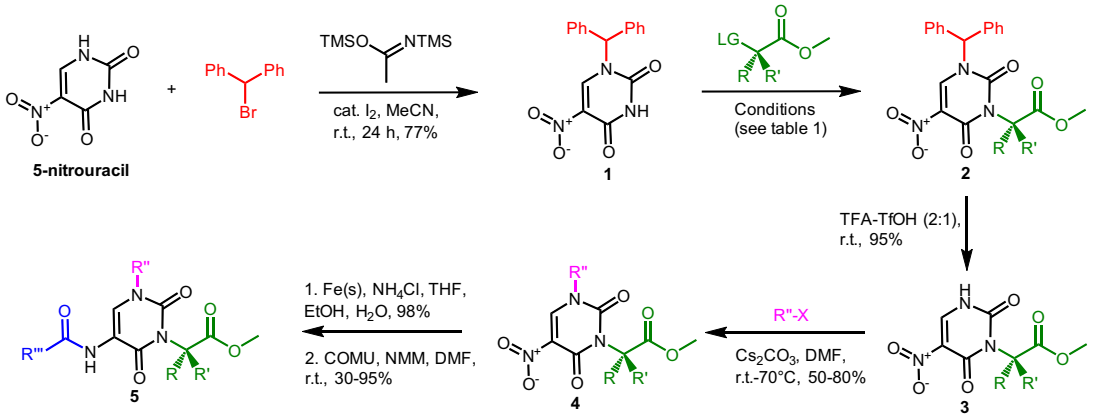


Scheme 1. General scheme developed to access the scaffold **5**.

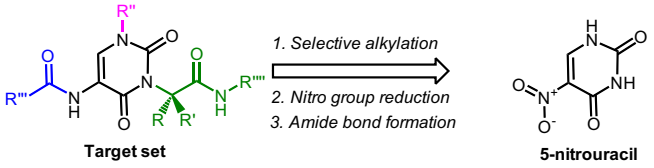


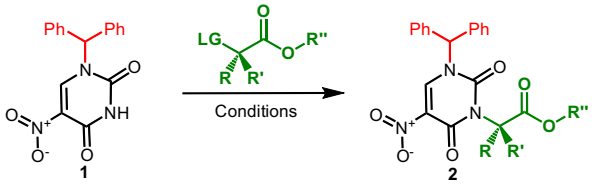
Figure 1. Retrosynthetic analysis of key scaffolds.

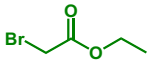
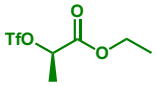
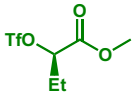
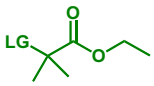
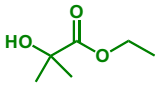
The preparation of the primary urea components **15**–**22** was fast and required no chromatography. Starting from α-amino acid esters **13**, we used TMS-isocyanate affording yields 73–95% (Scheme 3; Table 2, entries 1, 2, 5 and 7).[11] From α-amino acids **14**, we adopted a 2-step process using potassium cyanate followed by protection of the carboxylic acid moiety by alkylation (Scheme 3; Table 2, entries 3, 4 and 8).[12] Condensation of the urea intermediates **15**–**22** with ethyl nitroacetate in the presence of triethylorthoformate afforded consistently good yields of the surprisingly stable intermediates **23**–**30** (*E*/*Z* ratio ~ 6:4) that could be purified by normal phase chromatography if necessary, but often they were pure enough to be used in the cyclisation step without further purification (Table 2, entries 1–8).

With the precursors **23**–**30** in hand, we turned our attention to finding appropriate cyclisation conditions. Looking in the literature there exists several reported cyclisation conditions published for simple symmetrical urea substrates under strongly basic[10,13] or acidic conditions.[14] Table 3 shows a selection of conditions that were screened using the cyclopropyl derivative **26** as the substrate (entry 4, Table 2).

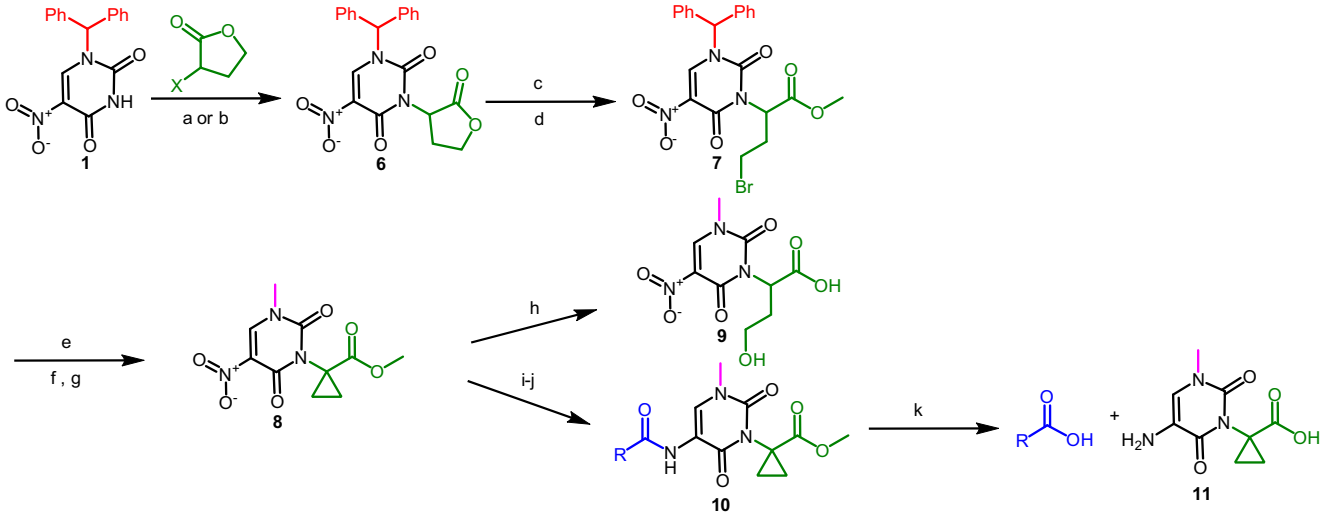
With the isolated advanced intermediate **26** in hand and just one step from the uracil derivative, we were surprised by how difficult it was to obtain the cyclised uracil product based on literature precedent.[10,13,14] Briefly, the results from screening a large

Table 1
First generation of conditions employed to alkylate **1**



Entry	Alkylating agent	Conditions*	Yield % (e.r.)
1		K_2CO_3, DMF, rt	96
2		K_2CO_3, MeCN, rt	64 (97/3)
3		K_2CO_3, MeCN, rt	61 (95/5)
4		Extensive base & solvent screen, rt to 150 °C in the microwave using various leaving groups (LG)	–
5		*Mitsunobu*: DTAD, TPP, toluene, rt to 120 °C or *Mitsunobu-Tsunoda*: CMPP or CMBP, toluene, 120 °C	–

* DTAD = di-tert-butyl azodicarboxylate; TPP = triphenylphosphine; CMPP = cyanomethyltriphenylphosphorane; CMBP = cyanomethyltributylphosphorane.



Scheme 2. Preparation of cyclopropyl analogue **8**. Conditions: (a) when X = OTf, K_2CO_3, MeCN, rt, 42%; (b) when X = OH, DIAD, TPP, DCM, rt, 40%; (c) HBr in AcOH, 70 °C, 75%; (d) cat. Sulfuric acid, MeOH-DME, 45%; (e) NaH 60%, THF, rt, 1 h, 82%; (f) TFA, TfOH, rt, 10 min, 50%; (g) CH_3I, K_2CO_3, DMF, rt, 3 h, 21%; (h) 1 M LiOH (aq), THF, 100%; (i) H_2, Pd-C, EtOAc, rt, 74%; (j) RCOOH, HATU, DIPEA, DMF, rt, 65%; (k) 2 M HCl (aq) EtOH, reflux, 16 h.

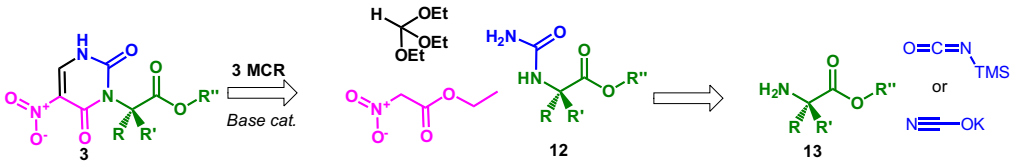
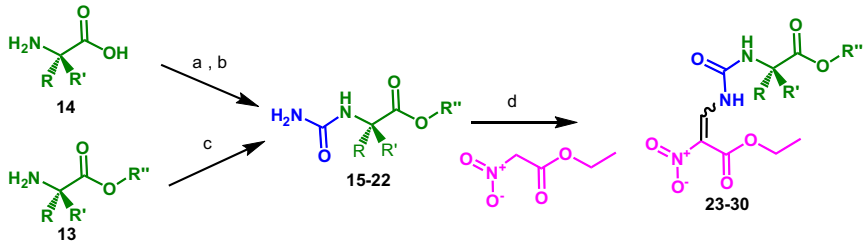


Figure 2. Retrosynthetic analysis proposed to access scaffold **3** with hindered quaternary C centres at *N*-1.



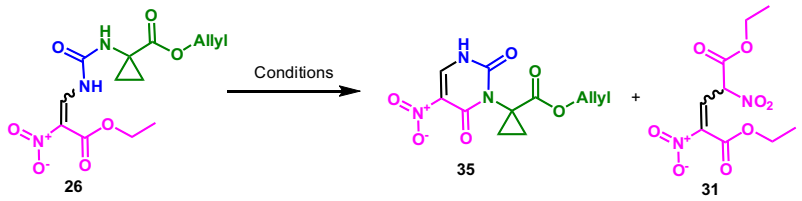
Scheme 3. Preparation of intermediates **23**–**30**. Reagents and conditions: (a) 3–5 equiv KOCN, water, reflux, 3–5 h; (b) R-X, DIPEA, DMF, rt, 16 h, 33–42%; (c) TMS-isocyanate, DCM, rt, 16 h, 71–95%; (d) triethylorthoformate, toluene, 90 °C to reflux, 3–16 h, 46–93%.

Table 2
Results for the preparation of cyclisation precursor **23**–**30**

Entry	R′, R″	R	Urea step(s) yield (%)	Compound	Condensation step yield (%)	Compound
1[*]	H,H	Et	80	**15**	93	**23**
2	H, CH_3 (S)	Et	73	**16**	55	**24**
3	$-(CH_2)_2-$	Me	71	**17**	46	**25**
4	$-(CH_2)_2-$	Allyl	39	**18**	97	**26**
5	$-(CH_2)_2-$	*t*-Bu	87	**19**	92	**27**
6	$-(CH_2)_3-$	Me	33	**20**	82	**28**
7	CH_3, CH_3	Me	95	**21**	46	**29**
8	CH_3, CH_3	Allyl	42	**22**	62	**30**

[*] Compound **15** was prepared from ethyl isocyanatoacetate and a solution of NH_3 in IPA.

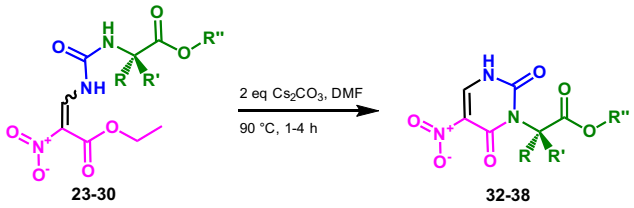
Table 3
Selected results from the cyclisation screening



Entry	Conditions	Yield of **35** (%)	Yield of **31**[*] (%)
1	2 equiv NaH, DMF, rt to 80 °C	–	**67**
2	2 equiv *t*-BuOK, DMF, rt to 90 °C	–	**35**
3	2 equiv DIPEA, DMF, rt to 120 °C	–	–
4	2 equiv DBU, DMF, rt to 90 °C	–	**52**
5	2 equiv K_2CO_3, DMF, rt to 90 °C	Traces	**75**
6	AcOH, rt to reflux	–	–
7	$BF_3{\cdot}Et_2O$, DCM, rt to reflux	–	**35**
8	2 equiv Cs_2CO_3, toluene, rt to 120 °C	**5**	**56**
9	2 equiv Cs_2CO_3, MeCN, rt–reflux, 2 h	**78**	**6**
10	2 equiv Cs_2CO_3, DMF, rt to 95 °C, 2 h	**84**	**5**

[*] Only **31** was clearly identified as a major impurity by LCMS and ^{1}H NMR.

Table 4
Selected results for the preparation of *N*-1 alkylated uracils



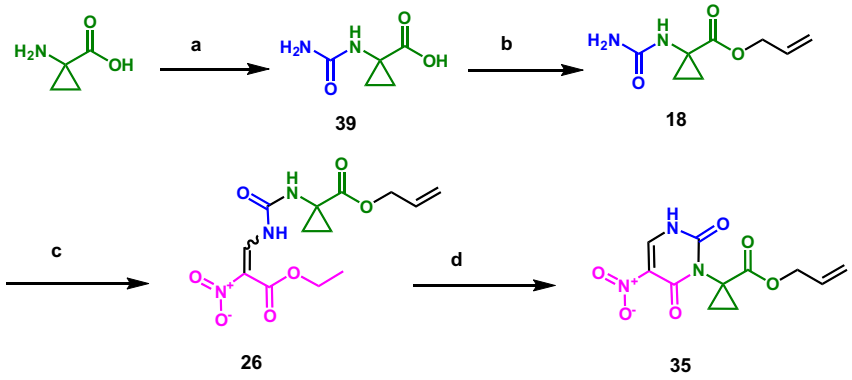
Entry	Compound	R′, R″	R	Dilution (volumes)	Yield (%) [S/R]
1	**32**	H,H	Et	10	95
2	**33**	H, CH_3 (S)	Et	10	84 [78:22]
3	**33**	H, CH_3 (S)	Et	20	84 [91:9]
4	**33**	H, CH_3 (S)	Et	20[*]	79 [94:6]
5	**33**	H, CH_3 (S)	Et	40[*]	66 [95:5]
6	**33**	H, CH_3 (S)	Et	60[*]	58 [>99:1]
7	**34**	$-(CH_2)_2-$	Me	10	84
8	**35**	$-(CH_2)_2-$	Allyl	10	97
9	**36**	$-(CH_2)_2-$	*t*-Bu	10	92
10	**37**	$-(CH_2)_3-$	Me	10	82
11	**38**	CH_3, CH_3	Me	10	25
12		CH_3, CH_3	Allyl	10	0

[*] Reactions carried out using MeCN as solvent.

panel of conditions identified Cs_2CO_3 as the most effective base in either DMF or MeCN as the solvent (Table 3, entries 9, and 10). All the other conditions afforded, at best, only trace quantities of the desired product **35**. The ethyl nitroacetate dimer **31** was the only major impurity that we identified which we believe was coming from decomposition **26** in situ.

Table 4 confirms that the cyclisation process is very sensitive to steric hindrance at *N*-1. As steric hindrance increases (entries 1–11), the process becomes less efficient. This was particularly evident for the case of the *gem*-dimethyl intermediate (entries 11 and 12) whereby only poor yields were obtained despite extensive conditions' screening looking at solvent and base combinations. In addition, we demonstrate that we can control epimerisation during the cyclisation process (entries 2–6). Briefly, by diluting the process by 2 fold in DMF we reduce the undesired R enantiomer by 13% (entries 2 vs 3). Switching from DMF to MeCN also reduced epimerisation (entries 3 vs 4). Finally, by further diluting the process to 60 volumes, we managed to eliminate epimerisation albeit with a 16% loss in chemical yields (entries 4–6).[7]

Finally, to check the robustness of our process we performed the synthesis of **35** on a 100 g scale (Scheme 4). The synthesis started with 200 g of 1-aminocyclopropane carboxylic acid using KOCN in refluxing water; crystallisation of the intermediate acid was performed by addition of concentrated hydrochloric acid at 3 °C to afford the acid **39** in 80% yield. To avoid use of CMR solvents such as DMF, alkylation with allyl bromide was performed in a mixture of THF-water retaining DIPEA as a base. The MCR reaction was performed as described and **26** was crystallised by adding heptane to yield a stable yellow amorphous powder in 79% yield. For the cyclisation step, we managed to replace DMF with MeCN while maintaining a comparable isolated yield and an operating temperature of below 100 °C. The latter point was particularly



Scheme 4. Large-scale preparation of **35**. Reagents and conditions: (a) KOCN, water, reflux, 78%; (b) Allyl bromide, DIPEA, THF–H_2O (10:1), reflux, 18 h, 68%; (c) ethyl nitroacetate, triethyl orthoformate, toluene, reflux, 16 h, 79%; (d) Cs_2CO_3, MeCN, reflux, 30 min, 73%.

important as safety assessment of compounds **26** and **35** by DSC (differential scanning calorimetry) showed a decomposition enthalpy of about −800 J/g starting at 188 °C and 250 °C, respectively.[15] In conclusion, we obtained an overall yield of 30.6% over 4 steps without any chromatography.

In conclusion, we have discovered an efficient way to prepare selectively *N*-1-alkylated 5-nitrouracils with quaternary carbon centres in poor to excellent yields from readily available α-amino acids. Work is currently ongoing to improve the substrate scope of the cyclisation step.

Supplementary data

Supplementary data (full experimental procedures and supporting LCMS and ^{1}H NMR characterisation data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.04.039.

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6. Real time chiral analysis was carried out by coupling the chiral column to the *iChem Explorer* (http://www.ichemexplorer.com/). Conditions: Column = IB Chiralpak 4.6 × 250, 5 μM; solvent = heptane/EtOH (9/1) + 0.3% TFA; flow rate = 1.4 mL/min; temperature of column oven = 35 °C; run time = 20 min.
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15. DSC thermograms of isolated compounds are visible in the Supplementary information.