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Piperazine-2,3,5-triones in the synthesis of constrained peptides

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Abstract

Amino acid amides react with diethyl oxalate and sodium ethoxide to yield 6-substituted piperazine-2,3,5-triones, which can be mono-alkylated at N^4, bis-alkylated at N^4 and C^6, or tris-alkylated at N^4, N^1, and C^6 under mild basic conditions; this provides access to i) α,α-disubstituted cyclic peptide derivatives; ii) constrained peptides *via* C(α)-N bond formation; iii) DKP analogues.

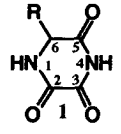
Keywords: amino acids and derivatives, peptide analogues/mimetics, piperazines/piperazinones

Peptides constitute one of the most important classes of pharmaceutical lead compounds, and efficient routes to unusual amino acids, peptides, and constrained peptide analogues are in great demand. We report herein some preliminary studies on the use of piperazine-2,3,5-triones **1** for accessing unusual peptide analogues with the following features:

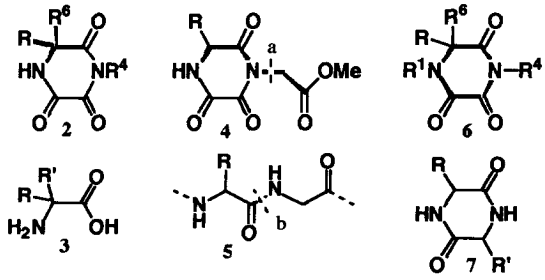
i) The targets contain α,α-dialkylated residues (i.e. **2** c.f. **3**);

ii) The methodology employs unusual N→C(α) bond formation, rather than the more usual N→C=O bond formation (bond **a** in **4**; c.f. bond **b** in **5**);

iii) The procedure allows selective alkylation to produce a wide range of targets **6**, which complement DKP derivatives **7** with biological or catalytic properties.



For consistency throughout this paper, additional substituents on the 2,3,5-piperazine trione are labelled $R^{1\text{-}6}$, depending on their position on the heterocyclic ring. Although the parent heterocycle **1** is a 2,3,5-piperazine trione with the amide nitrogen as N^1, peptidic derivatives (e.g. **4**) are formally 2,3,6-triones numbered from the imide nitrogen as N^1.



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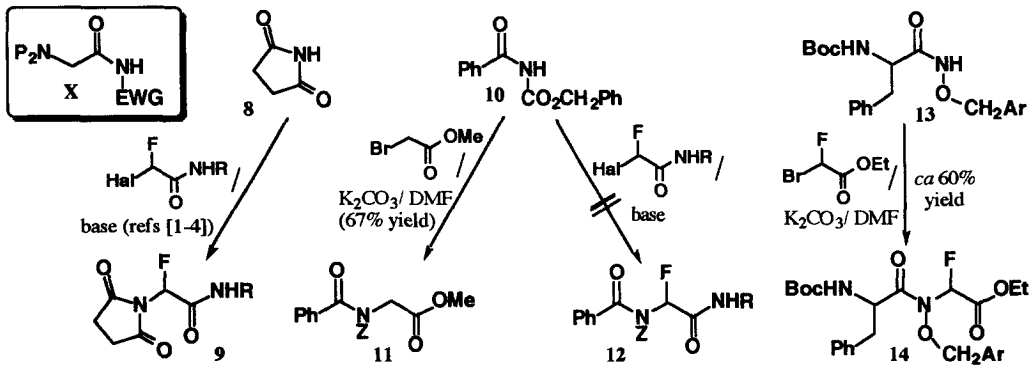
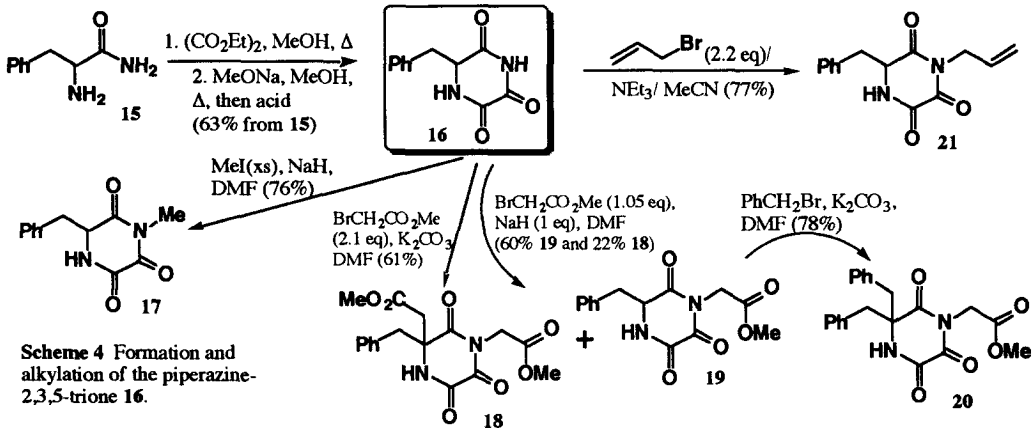
Our research into piperazine-2,3,5-triones arose because of an interest in peptides that would not be accessible through standard N→C=O peptide bond formation. For example, we hoped to prepare α-fluoropeptides by finding a suitably activated amino acid amide derivative that could react with α-fluoro-α-halo carboxamides. Our initial studies[1-4] had shown how simple nitrogen nucleophiles, such as succinimide, phthalimide etc., could be successfully used to displace iodide from α-fluoro-α-iodocarboxamides (Scheme 1). We then looked for related substrates of the type **X** (see box) that would give us compounds possessing a true dipeptide skeleton. Despite some limited success with various acyclic compounds as 'amide anion equivalents' (Schemes 2 and 3), poor yields led us to consider cyclic derivatives instead.



Scheme 1 Scheme 2 Scheme 3

We decided to study the phenylalanine derived piperazine-2,3,5-trione **16** as a model system, expecting it to react similarly to succinimide/phthalimide. It can be made from phenylalaninamide and diethyl oxalate,[5,6] and this class of compound seemed an ideal candidate for our purposes, as selective cleavage of the (O)C^3-N^4 bond should be possible at a later stage if required. Indeed Person and Le Corre have shown the 3-oxo group in **16** is sufficiently reactive to undergo selective methylenation with Wittig reagents.[6]



Scheme 4 Formation and alkylation of the piperazine-2,3,5-trione **16**.

As shown in Scheme 4, N^4-methylation of **16** was achieved using sodium hydride (1 mole equiv.) and methyl iodide to give **17** (76%), but to our surprise when the alkylating agent

employed was methyl bromoacetate (1.05 mol. eq.) we isolated the bis-alkylated species **18** (22%) as well as the expected product **19** (60%); the bis-alkylated product **18** could be obtained from **16** in 61% yield by using potassium carbonate/DMF and 2.1 equiv. of bromoacetate. Derivative **19** could be further alkylated selectively at C^6 using benzyl bromide and potassium carbonate to give **20** (78%). In contrast, we observed clean mono-alkylation when **16** was treated with excess allyl bromide in MeCN using triethylamine as the base, giving **21**.

However, when **16** was treated with potassium carbonate and methyl bromoacetate, only bis-alkylation was observed (no mono-alkylation), and this led to a mild general route to bis-alkylated piperazine triones - see Scheme 5 and Table 1. We could also tris-allylate **16** in a one-pot reaction using K_2CO_3/phase transfer catalyst ($Bu_4N^+Br^-$) (c.f. ref. 7) in MeCN giving rapid alkylation at N^4 and C^6, plus slower alkylation at N^1; the structure of the piperazinetrione **23** was confirmed by single crystal X-ray structure determination.[8]

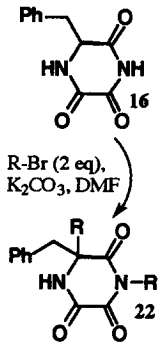
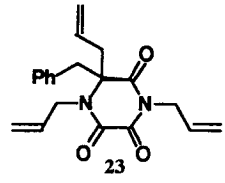


Table 1 Yields of **22**

R	Yield
CH_2CO_2Me	61%
CH_2Ph	59%
$CH_2CH{=}CH_2$	57%
$CH_2CH{=}CH{-}Ph$	57%



Scheme 5 Synthesis of bis-alkylated piperazine triones **22** from **16**.

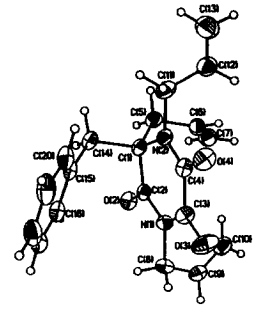
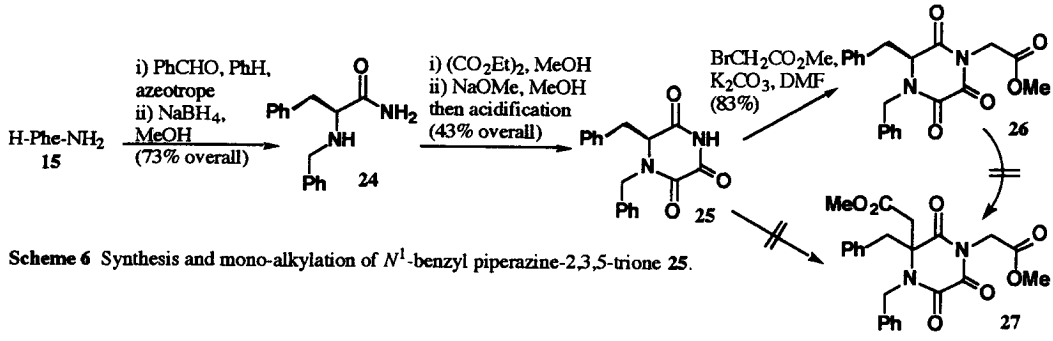


Figure 1 X-Ray crystal structure of the tris-allylated derivative **23**.

It was important for us to have access to piperazinetriones alkylated at only the 4-position, and we wondered whether (reversible) alkylation of the N^1-position might prevent C^6-alkylation. Accordingly, the N^1-blocked trione **25** was synthesised from *N*-benzyl phenylalaninamide (Scheme 6), and this compound underwent clean alkylation with $BrCH_2CO_2Me/K_2CO_3$ only at N^4 giving **26** (83%); no C^6 alkylation was observed. This tactic therefore provides a mild route to N^4-alkylated piperazine triones, including constrained peptides.



Scheme 6 Synthesis and mono-alkylation of N^1-benzyl piperazine-2,3,5-trione **25**.

We have therefore shown that piperazine-2,3,5-triones can be selectively alkylated:
i) At N^4, by using N^1-benzyl derivative **25**, or using NEt_3 in MeCN with **16**;
ii) At N^4 and C^6, using K_2CO_3/DMF and excess alkylating agent with **16**;
iii) At N^4, N^1 and C^6, by adding a PTC to K_2CO_3 in MeCN.

Of particular importance are the α,α-bis-alkylated α-amino acid derivatives, because of their increasing use as biological probes, and DKP analogues because of their biological[9] and catalytic[10] properties. Our procedure is notable because it is simple, cheap, and mild (c.f. α-bis-alkylation of chiral[11-14] and achiral[15-17] cyclic amides). Although vigorous hydrolysis of our final products should yield quaternary amino acids, of particular note are preliminary results under milder conditions, in which only the N^4-C^3 bond of **22** (R = CH_2Ph) was hydrolysed using 1% TFA in 10% aqueous THF at reflux; similar oxalates are found in new HIV-1 anti-infective agents[18] and in natural products[19].

In conclusion, these model studies have demonstrated that the 6-substituted piperazine-2,3,5-trione heterocyclic system is readily accessed, and that our model heterocycle **16** can be alkylated under mild, selective conditions, providing routes to a range of constrained peptide analogues, including α,α-bis-alkylated residues and DKP analogues.

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8. Crystal data for **23** – colourless crystal (0.80 x 0.52 x 0.16 mm) from MeCN coated with nujol mounted on a glass fibre, $C_{20}H_{22}N_2O_3$, M = 338.40, monoclinic, space group $P2_1/c$, a = 8.813(8), b = 11.418(12). c = 18.102(17) Å, β = 103.540(7)°, V = 1770.9(4) $Å^3$, Z = 4, D_C = 1.269 g cm^{-3}, μ = 0.086 mm^{-1}. $R1$ = 0.0372, for 2579 unique observed [I > 2σ(I)] data; $R1$ = 0.0476, $wR2$ = 0.1010 and goodness of fit 1.022 for all 3115 data and 226 parameters. Full data has been deposited with the Cambridge Crystallographic Data Centre.
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