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A simple desymmetrisation approach to unsymmetric N,N'-disubstituted cyclic ureas

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Abstract

The bis-enolate derived from 1,3-di-isobutyryl-*trans*-4,5-tetramethylene-imidazolidin-2-one 8 is unstable and deacylates to afford dianion 11 which can be regioselectively alkylated to afford unsymmetric cyclic urea 17 in good yield. Subsequent deacylation of 17 and methylation on nitrogen affords unsymmetric 1-benzyl-3-methyl-*trans*-4,5-tetramethyleneimidazolidin-2-one 19 in good yield. © 1999 Elsevier Science Ltd. All rights reserved.

While established methodology for the synthesis of symmetric, and unsymmetric acyclic ureas is well documented,¹ versatile synthetic routes for the preparation of cyclic ureas are less common. The majority of synthetic efforts within this area have been directed towards preparing pharmacologically active symmetric cyclic urea's such as 1 and 2,² and the corresponding unsymmetric cyclic urea 3,³ all of which show promise as potential drug candidates against HIV infection. Cyclic ureas have also proved useful as chiral auxiliaries in asymmetric synthesis, where we, and others, have reported that the enolates of *N*-acylated-ureas such as 4,⁴ 5,⁵ and 6^6 efficiently control stereoselectivity during enolate alkylation/aldol reactions (Fig. 1).



Figure 1.

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Strategy 1 Cyclisation of N,N-disubstituted ureas



Figure 2.

As part of ongoing studies into the development of efficient chiral auxiliaries for asymmetric synthesis we required a versatile synthesis of orthogonally protected N,N'-bis-protected cyclic ureas. A survey of the literature revealed that existing synthetic approaches to this class of compound could be classified according to the strategy employed to desymmetrise the urea fragment (Fig. 2). These different approaches included the formation of cyclic ureas via treatment of unsymmetric N,N'-bis-protected diamines with phosgene (or a synthetic equivalent, Strategy 1);^{3a,7} base catalysed intramolecular cyclisation of bis-*N*-carbamoyl protected diamines (Strategy 2);⁸ mono-deprotection of symmetric bis-benzylated cyclic ureas using sodium in liquid ammonia (Strategy 3);^{3b} or desymmetrisation of urea fragments via formation and *N*-monoprotection of cyclic isoureas (Strategy 4).^{3a} We now wish to report on a simple 'one-pot' procedure which can efficiently desymmetrise N,N'-bis-protected C_2 -symmetric cyclic ureas such as 1,3-di-isobutyryl-*trans*-4,5-tetramethylene-imidazolidin-2-one **12** (Strategy 3). This class of urea **12** is a versatile synthetic intermediate since it may be easily converted into orthogonally *N,N'*-bis-protected cyclic ureas such as 1-benzyl-3-methyl-*trans*-4,5-tetramethylene-imidazolidin-2-one **19** in excellent yield.

Deprotonation of (rac)-trans-4,5-tetramethyleneimidazolidin-2-one 7 with *n*-BuLi in THF at $-78^{\circ}C$, ^{4a,b} followed by addition of isobutyryl chloride gave the desired 1,3-di-isobutyryl-trans-4,5-tetramethylene-imidazolidin-2-one 8 in 89% yield. Treatment of cyclic urea 8 with 2 equivalents of KHMDS at $-78^{\circ}C$ in THF, followed by warming to room temperature over 2 h, gave the desired 1-isobutyryl-trans-4,5-tetramethylene-imidazolidin-2-one 12 in quantitative yield (Scheme 1).

Further experiments revealed that this mono-deprotection reaction required 2 equivalents of KHMDS as base, since deprotonation of 8 with one equivalent of KHMDS quantitatively afforded recovered starting material 8 in excellent yield. Furthermore, changing the counterion of the base employed for deprotonation of 8 from potassium to lithium, by substituting 2 equivalents of LHMDS for KHMDS, once again only afforded recovered starting material 8 in good yield. These experimental observations are consistent with a reaction mechanism where one of the N-acyl fragments of 8 is initially deprotonated to afford an enolate 9 which is stabilised by chelation of its K^+ counterion to the central urea oxygen. Subsequent deprotonation of the remaining N-acyl group of 9 affords a bis-enolate fragment 10 which has a conformation with one of its enolate fragments stabilised by chelation of the K⁺ counterion to the





Scheme 1.

urea carbonyl, and the other enolate fragment in an open chain form. As a result of this conformation the uncoordinated enolate fragment is highly reactive and rapidly decomposes via loss of ketene, to afford the stable bis-anion 11 which was protonated on work-up to afford mono-deprotected urea 12. It was reasoned that the enolate fragment of 11 was stabilised towards further fragmentation not only because of chelation of its K⁺ counterion to the urea carbonyl, but also because decomposition of 11 via a ketene elimination pathway would result in a highly disfavoured bis-anionic urea fragment 13 containing two formal negative charges within the same five membered ring. Furthermore, it is interesting to contrast the instability of bis-enolate 10 with the previously reported potassium bis-enolate (Z,Z)-14 which is sufficiently stable to react smoothly with two equivalents of electrophile, in a highly diastereoselective manner, to afford the C_2 -symmetric urea 15 in excellent yield (Scheme 2).⁴ We believe that this observed difference in enolate stability between 10 and 14 arises because decomposition of the uncoordinated enolate of bis-enolate 10 is promoted by release of A^(1,3) allylic strain between the urea fragment and the isopropyl group of the uncoordinated enolate fragment.



Scheme 2.

We next considered whether the inherent steric bias of the isopropyl enolate fragment of bis-anion 11 could be exploited in order to selectively monoalkylate the nitrogen of the urea ring system with an electrophile. A 'one-pot' procedure was devised, involving treatment of 8 with 2 equivalents of KHMDS in THF at -78° C to afford dianion 10, followed by addition of benzyl bromide, giving orthogonally N,N'-diprotected 1-isobutyryl-3-benzyl-*trans*-4,5-tetramethylene-imidazolidin-2-one 17 as a single product in 65% yield (Scheme 3).



Scheme 3.

Urea 17 was easily deprotected by reductive removal of the isobutyryl protecting group using Super Hydride[®] in THF to give monobenzylated urea 18 in 78% yield. This intermediate urea 18 could be further functionalised via deprotonation with KHMDS in THF and alkylated with MeI to afford 1-benzyl-3-methyl-*trans*-4,5-tetramethyleneimidazolidin-2-one 18 in 97% yield (Scheme 4).



Scheme 4.

In summary, we have demonstrated that unsymmetric cyclic ureas such as 18 can be prepared using a novel 'one-pot' in situ deprotection strategy from C_2 -symmetric cyclic ureas such as 7 in an overall 44% yield. We are currently investigating the scope and limitation of this strategy for the synthesis of novel chiral auxiliaries and these studies will be reported in due course. All new compounds were fully characterised.

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