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Dibutylphosphate (DBP) mediated synthesis of cyclic *N,N′*-disubstituted urea derivatives from amino esters: a comparative study

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ABSTRACT

The *N,N′*-disubstituted urea derivatives such as amino acid hydantoins and dihydrouracil derivatives were prepared starting from natural and unnatural amino acid esters using dibutylphosphate (DBP). During the attempted synthesis of N-heterocycles with larger than six-membered rings containing the *N,N′*-disubstituted urea functionalities, three unexpected products namely squamolone, *N*-methyl pyrrolidine-2-one, and diketopiperazine were isolated.

The *N,N′*-disubstituted urea functionality has recently attracted much attention as an ubiquitous moiety incorporated into the compounds with numerous biological activities and therapeutic applications,[1] such as anticonvulsant,[2] antiarrhythmic,[3] antibacterial,[4] antitumor,[5] antidiabetic,[6] and antiepileptic activity.[7] Hydantoins, dihydrouracil, quinazoline-2,4-(1*H*,3*H*)-dione, and pyrido[2,3-*d*] pyrimidine-2,4-(1*H*,3*H*)-dione derivatives are the classes of N-heterocycles containing *N,N′*-disubstituted urea linkages (Fig. 1).

Cyclic compounds containing the *N,N′*-urea linkage have great importance in synthetic organic and medicinal chemistry; consequently, various synthetic methods have been developed over time. Conventional synthetic methods involve the reaction of urea with different natural and un-natural amino acids.[8] General access to 5-mono- and 5,5-disubstituted hydantoins was provided earlier by Read[1a,9] synthesis and by Bucherer–Bergs[10] synthetic methods, respectively. Apart from the above mentioned methods, hydantoin derivatives can also be synthesized by a variety of other methods.[9c,11] However, these methods suffer from various drawbacks, such as substitution invariability, low yields, expensive substrates, and harsh reaction conditions. In order to overcome these bottlenecks, we recently reported dibutylphosphate (DBP) mediated synthesis of diversely substituted hydantoins.[11k] Encouraged by its simplicity and diverse applicability, we applied this protocol to the synthesis of various *N,N′*-disubstituted urea derivatives. In continuation of our work on bioactive molecules,[12] herein we report the synthesis of amino acid hydantoins **4a–g** starting from amino acid methyl ester hydrochlorides **1a–g** in good to excellent yield. The methodology was further extended to the synthesis of six-membered N-heterocycles containing the *N,N′*-urea linkage like dihydrouracil **9** and *N*-methyl dihydrouracil **17**. In an attempt to

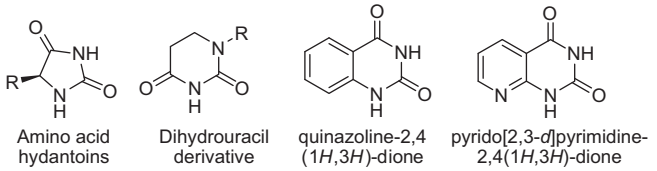
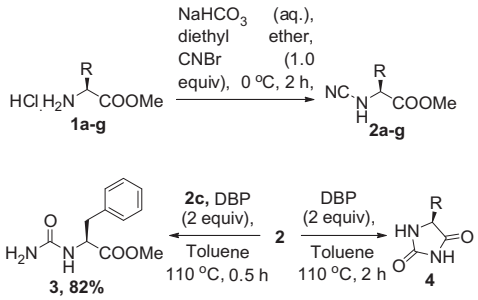


Figure 1. N-Heterocycles containing *N,N′*-disubstituted urea linkage.



Scheme 1. Synthesis of amino acid hydantoins.

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synthesize larger rings containing *N*,*N*′-urea linkages like 1,3-diazepane-2,4-dione **10** (seven-membered), 1-methyl-1,3-diazepane-2,4-dione **18** (seven-membered), and cyclic dipeptide **28** (eight-membered), we ended up with 2-oxopyrrolidine-1-carboxamide or squamolone **12** (five-membered), *N*-methyl pyrrolidine-2-one **20** (five-membered), and diketopiperazine **27** (six-membered) as unexpected products, respectively.

The initial synthetic studies are summarized in Scheme 1. Standardization of the reaction conditions was performed on phenylalanine hydantoin (**4c**). The synthesis of **4c** was achieved starting from L-phenylalanine methyl ester hydrochloride (**1c**). On treating **1c** with cyanogen bromide (*caution: cyanogen bromide is toxic; reaction should be carried out in a fume hood*) in diethyl ether: $NaHCO_3$ (aq) at 0 °C for 2 h,[11k,13] *N*-cyano phenylalanine methyl ester **2c** was isolated in good yield. Uncyclized disubstituted urea derivative **3** was obtained when **2c** was refluxed with DBP in toluene for 30 min. However, extended refluxing for 2 h gave the desired product, that is, phenylalanine hydantoin **4c**. With the optimized reaction conditions in hand, we synthesized seven amino acid hydantoins **4a**–**g** starting from amino acid methyl ester hydrochlorides **1a**–**g** (Table 1) in good to excellent yields.[11b] The mechanism for the formation of **4** from **2** proceeds by nucleophilic attack of the hydroxyl group of DBP on the electrophilic cyanamide group, as earlier described.[11k]

In order to explore the applicability of this procedure, we extended this methodology for the synthesis of six-membered N-heterocycles containing the *N*,*N*′-urea linkage, that is, dihydrouracil **9**. Conventionally, **9** is synthesized by the reaction of β-alanine with KNCO,[14] although the major limitation with this procedure lies in the synthesis of *N*-substituted dihydrouracil. In the present studies, β-alanine methyl ester hydrochloride **5** was converted into methyl 3-cyanamidopropanoate **7** by the reaction of cyanogen bromide in biphasic solution for 1 h and the crude **7** was refluxed with DBP in toluene for 5 h to give analytically pure dihydrouracil **9** (Scheme 2).

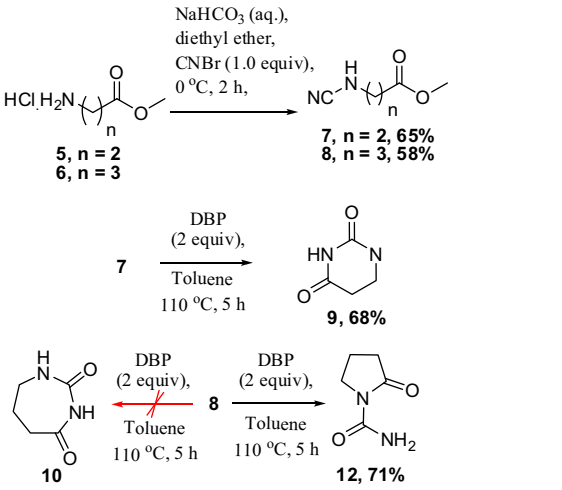
Successful synthesis of **9** by this methodology motivated us to synthesize 1,3-diazepane-2,4-dione **10**, a seven-membered cyclic compound containing the *N*,*N*′-urea linkage. Methyl 4-aminobutanoate hydrochloride **6** was cyanated to give methyl 4-cyanamidobutanoate **8**, and was used crude for the cyclization step. Refluxing **8** with DBP in toluene for 5 h resulted in the formation of **12** instead of the anticipated product **10**[15] as shown in Scheme 2 and Figure 2. From this result it was apparent that if the nucleophilic attack by NH in compound **8** or **11** cannot be prevented, then the synthesis of **10** or N-heterocycles having larger rings containing the *N*,*N*′-urea linkage may not be possible. Therefore, an alternate route was attempted for the preparation of larger rings containing the *N*,*N*′-urea linkage.

The reaction conditions were first standardized on compound **17**, that is, *N*-methyl dihydrouracil. In this method, the free amine group of **5** was protected with di-*tert*-butyl dicarbonate (Boc-anhydride) in dioxane: $NaHCO_3$ (aq) at 0 °C warming to rt for 5 h,[16] followed by N-methylation using methyl iodide and sodium hydride in DMF.[17] The resulting methyl-3-(*tert*-butoxycarbonyl (methyl)amino) propanoate **13**, was deprotected using TFA:DCM[16] and was immediately cyanated with cyanogen bromide to give methyl 3-(*N*-methylcyanamido) propanoate **15**. The resulting cyanated ester was then refluxed with DBP in toluene for 5 h to give **17** in good yield (Scheme 3). We then applied the same protocol of Boc protection, N-methylation, Boc deprotection, and

Table 1
Results for synthesized amino acid hydantoins

Entry	Product	R	Time (h)	Yield[b] (%)
1	**4a**	H	1.5[a]	75
2	**4b**	CH_3	2[a]	79
3	**4c**	CH_2Ph	2	73
4	**4d**	$CH(CH_3)_2$	2[a]	85
5	**4e**	$CH(CH_3)CH_2CH_3$	1.5	82
6	**4f**	$CH_2CH(CH_3)_2$	2	77
7	**4g**	$CH_2CO_2CH_3$	2[a]	74

[a] Reaction was carried out without solvent.
[b] Isolated yield.



Scheme 2. Synthesis of dihydrouracil and squamolone.

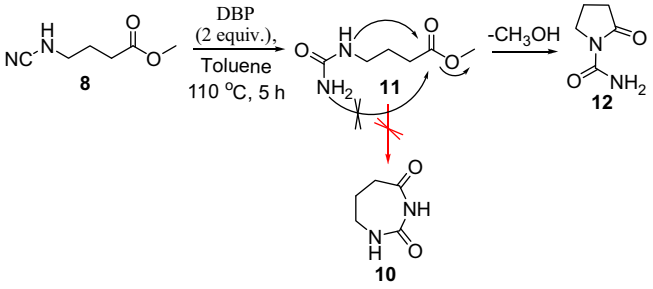
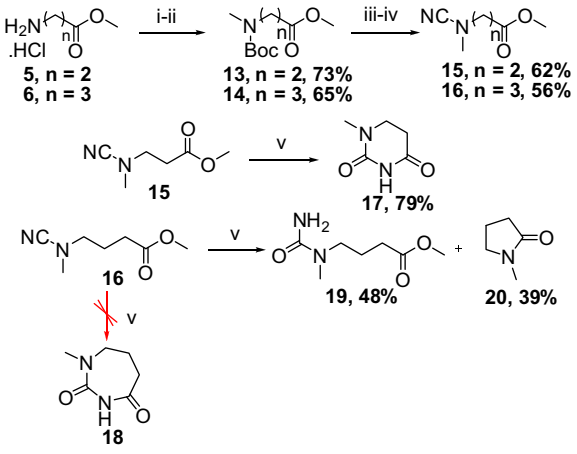


Figure 2. Plausible mechanism for the formation of squamolone.



Scheme 3. Synthesis of *N*-methyl dihydrouracil and *N*-methyl pyrrolidine-2-one. Reagents and conditions. (i) Boc_2O (1.1 equiv), dioxane: $NaHCO_3$(aq), 0 °C, rt, 5 h, (ii) CH_3I (5 equiv), DMF, NaH (2.5 equiv), 0 °C to rt, over night, (iii) TFA:DCM, 0 °C, 2 h, (iv) diethyl ether: $NaHCO_3$ (aq), CNBr (1 equiv), 0 °C, 2 h, (v) DBP (2 equiv), toluene, 110 °C, 5 h.

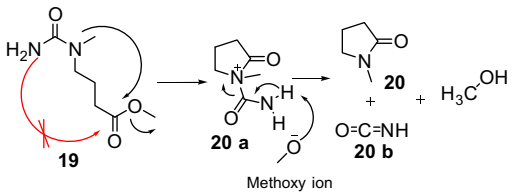
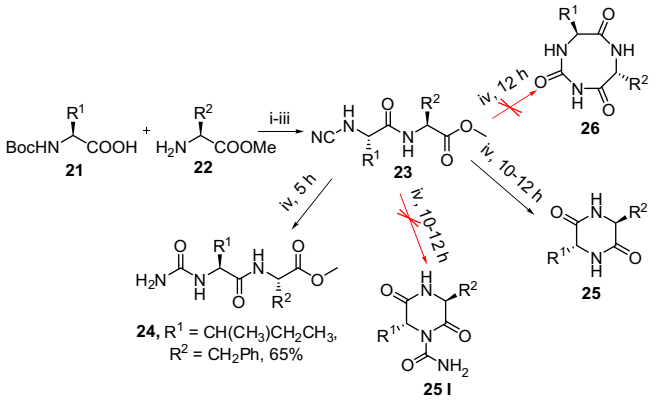


Figure 3. Plausible mechanism for the formation of *N*-methylpyrrolidine-2-one.



Scheme 4. Synthesis of diketopiperazines. Reagents and conditions. (i) CDI (1 equiv), THF, 0 °C to rt, overnight, (ii) TFA:DCM, 0 °C to rt, 2 h, (iii) diethyl ether: $NaHCO_3$ (aq), CNBr (1.0 equiv), 0 °C, 2 h, (iv) DBP (2 equiv), toluene, 110 °C, 5 h or 11–12 h.

Table 2
Results for synthesized diketopiperazines

Entry	Product	R^1	R^2	Time (h)	Yield[a] (%)
1	**25a**	Ile	Phe	11	58
2	**25b**	Ile	Val	12	62
3	**25c**	Phe	Ala	12	60
4	**25d**	Phe	Leu	12	56

[a] Isolated yield.

N-cyanation for the synthesis of seven-membered ring **18**, that is, 1-methyl-1,3-diazepane-2,4-dione. The resulting methyl 4-(*N*-methyl-cyanamido) butanoate **16** was when refluxed with DBP in toluene for 5 h to give a mixture of uncyclized urea ester, that is, methyl 4-(*N*-methylureido) butanoate **19** and a five-membered cyclic compound, that is, *N*-methylpyrrolidin-2-one **20** as an unexpected product instead of giving the desired compound **18** (Scheme 3).

A plausible mechanism for the formation of **20** instead of **18** is depicted in Figure 3. The reaction proceeds via the formation of unstable cyclic quaternary amine **20a** along with the loss of a methoxy anion. The methoxy anion abstracts a proton from the amide nitrogen and in situ forms an unexpected five-membered ring, that is, *N*-methylpyrrolidine-2-one **20** and isocyanic acid **20b**. The formation of two unexpected five-membered rings, that is, **12** and **20** prompted us to expand this protocol to dipeptides.

All dipeptides were synthesized in solution phase by using amino acids, that is, **21** (N-protected), **22** (C-protected), and carbonyldiimidazole (CDI) as coupling reagent.[18] The Boc group was deprotected[16] to give a TFA salt of the dipeptide, followed by the reaction with cyanogen bromide to give N-cyanated dipeptide esters **23a–d**. The overall yield of the crude product **23a–d** was reasonably good, that is, 55–65%. Without further purification compounds **23a–d** were refluxed with DBP in toluene for 5–8 h,

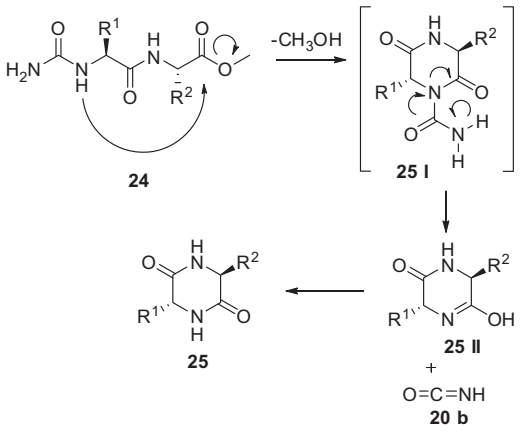


Figure 4. Plausible mechanism for the formation of diketopiperazines.

which resulted in uncyclized urea ester derivatives **24a–d**. On extended refluxing hours, diketopiperazines (DKPZ) **25a–d** were formed instead of carboxamide group containing DKPZ **25 I** (Scheme 4 and Table 2). From the above experiments it became apparent that the construction of seven-membered (**10** and **18**) and even eight-membered (**26**) ring structures containing the *N*,*N*′-urea linkage from **8**, **16**, and **23** is not feasible by this method.

A plausible mechanism for the formation of DKPZ **25** is depicted in Figure 4. The mechanism proceeds by the nucleophilic attack of nitrogen on the electrophilic carbonyl to form intermediate **25 I**. Intermediate **25 I**, on internal rearrangement, forms the more stable DKPZ **25** via another intermediate **25 II**[19] and eliminates isocyanic acid **20b**, which can easily be removed by precipitating the product with petroleum ether. All the synthesized compounds were characterized by FT-IR, ^{1}H NMR, ^{13}C NMR, and ESI-MS. The purity of the compounds was checked by HPLC analysis.

We have described a comparative study on DBP mediated synthesis of N-heterocycles containing the *N*,*N*′-urea linkage of five- to eight-membered ring systems. Various types of N-heterocycles containing *N*,*N*′-urea linkages like amino acid hydantoins, dihydrouracil, *N*-methyl dihydrouracil, and their derivatives can be synthesized by applying the presented methodology. We anticipate that the methodology can also be useful for the synthesis of two fused six-membered rings containing the *N*,*N*′-urea linkage like quinazoline-2,4-(1*H*,3*H*)-dione, pyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)-dione, and their derivatives.

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Supplementary data

Supplementary data (Details experimental procedure and characterization data of all compounds and copies of ^{1}H NMR, ^{13}C NMR spectra and HPLC chromatograms are given in supplementary material.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.083.

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