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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

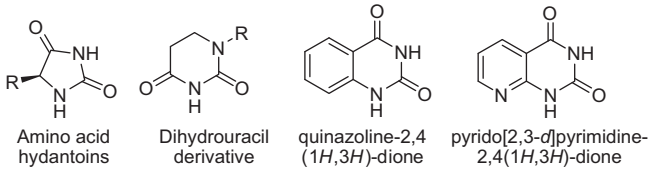
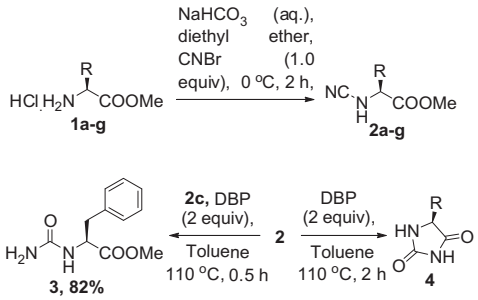


Figure 1. N-Heterocycles containing *N,N′*-disubstituted urea linkage.



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).

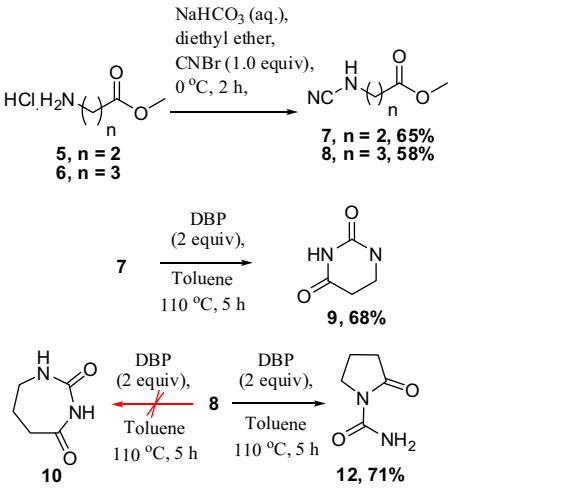
Successful synthesis of **9** by this methodology motivated us to synthesize 1,3-diazepane-2,4-dione **10**, a seven-membered cyclic compound containing the *N*,*N*′-urea linkage. Methyl 4-aminobutanoate hydrochloride **6** was cyanated to give methyl 4-cyanamidobutanoate **8**, and was used crude for 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.

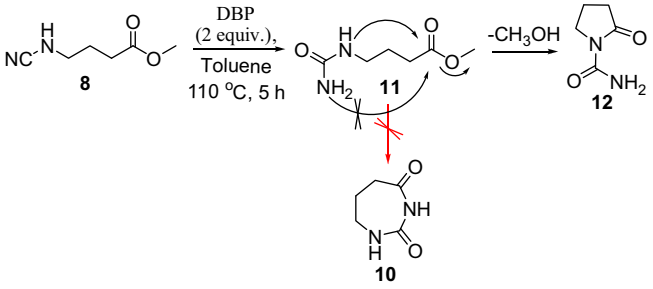
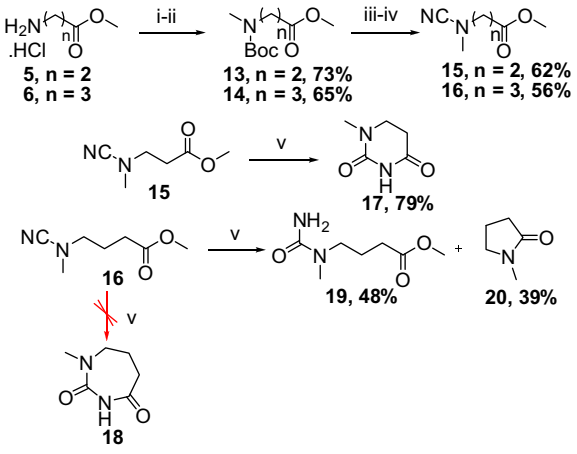


Figure 2. Plausible mechanism for the formation of squamolone.



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.