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Highly efficient dialkylphosphate-mediated syntheses of hydantoins and a bicyclohydantoin under solvent-free conditions

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ABSTRACT

Diversely substituted hydantoins have been synthesized by new strategy from cyanamide based precursor, that is, methyl *N*-cyano-*N*-alkyl/arylaminoacetate. Dialkylphosphates were employed as the mild reagent to hydrolyze and cyclize the substrate in one step to give quantitative yields of the desired products. Syntheses of multivalent hydantoins viz bis-hydantoin, bicyclohydantoin have potentially widened the scope and applicability of the present method. Solvent-free conditions and very easy work-up procedure make the reaction convenient and eco-friendly. Single crystal structures of some of the representative compounds are also reported.

The discovery of hydantoin and the prospects of developing novel hydantoin based drugs for the treatment of tumor, viral, convulsion, diabetes, and arrhythmic, has generated worldwide interests among researchers.[1] Hydantoin scaffolds are also an important structural unit found in agrochemicals.[2] Acid-, base, and enzyme catalyzed hydrolysis of hydantoin lead to unnatural and natural amino acids.[3] Recent use of hydantoin derivatives as markers of oxidative cell damage, which could find applications in cancer, aging, and neurological disorders.[4] This has further invoked the research interests to develop a simple, rapid, convenient, and eco-friendly method for the substituted hydantoin.

Realizing the importance of hydantoin in organic and medicinal chemistry, various methods have been developed[5] which have essentially constructed hydantoin ring substituted at different positions. Among these, the Bucherer–Bergs synthesis[6] and the Reed synthesis[7] are the most commonly used protocols. The major limitations in using these methods are associated with solubility problem of the substrates and difficult reaction conditions, moreover, the resulting hydantoin ring possesses substitution invariably at C-5 position. In order to overcome the drawbacks associated with these two reactions, researchers have developed new methods/techniques that include the use of solid phase synthesis,[8] microwave synthesis,[9] and typical catalyst/synthetic strategy,[10] however, yields and the desired substituted products are still a major concern. Keeping in view of this, there is a need to develop a method which can produce a variety of hydantoin derivatives with substituents at the desired positions. Poor yields, difficult reaction conditions, expensive substrates, and environmental concern are still the most relevant aspects, which encourage us to develop a better and practical method for hydantoin synthesis.

While exploring the chemistry and applications of cyanamides,[11] we recently investigated cyanamide based new precursor, that is, methyl *N*-cyano-*N*-alkyl/arylaminoacetate **1** for the synthesis of hydantoin.[12] Upon closer examination, we observed a major bottleneck to follow this synthetic strategy. Fifty percent of H_2SO_4 was used for the hydrolysis and cyclization, which is very harmful and highly corrosive. More importantly, most of the acid sensitive functional groups such as halides, nitriles, ethers, alcohols, double bond, and triple bond have difficulty to survive under this harsh condition. As a result, hydantoin containing these functionalities could not be synthesized, which are the essential requirements to incorporate structural diversity in hydantoin. In an attempt to overcome these bottlenecks, we explored dialkylphosphates as the most suitable and 'mild reagents'. The reagent can bring about the hydrolysis and cyclization of **1** in one step without affecting the acid sensitive moieties. Herein, we report a very simple, rapid, highly efficient, and environmentally benign synthesis of hydantoins **3** which overcame the disadvantages associated with the previous methods. The transformation of methyl *N*-cyano-*N*-alkyl/arylaminoacetate **1** into hydantoin **3** was facilitated by commercially available dibutyl phosphate **4**. Formation of **3** took place at 100 °C under solvent-free conditions. In this reaction, **2** got converted into butyl pyrophosphate **4** (Scheme 1) which can easily

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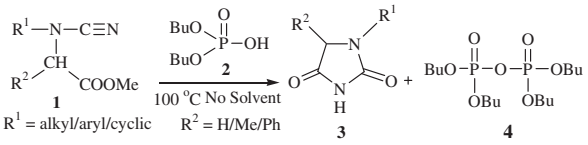
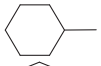
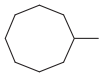
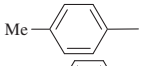
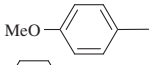
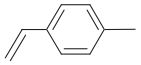
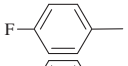
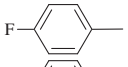
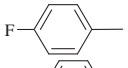
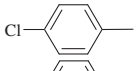
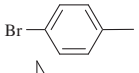
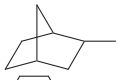
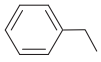


Scheme 1. Synthesis of hydantoins.

be removed from the reaction mixture by precipitating the products with petroleum ether (40–60 °C). The scope and generality of this method was demonstrated by the synthesis of wide varieties of hydantoins having alkyl (primary, secondary, and tertiary), aryl with electron donating and electron withdrawing groups, and cyclic groups in ring system. The products were formed in excellent yields with reasonably good purity. The results and reaction conditions are summarized in Table 1. The reaction was performed with various dialkylphosphates and their performance against **1** was found to be almost at par with dibutyl phosphate. However, **2** was chosen due to their commercial/economical viability and easy preparation method. Furthermore the pyrophosphate **4** formed in the reaction is easily removable without compromising the yields of the products. All products were characterized by NMR, MS, IR, and elemental analysis. In order to substantiate our spectroscopic data, recrystallization of some of representative products (Table 1, entries 6 and 9) in $CHCl_3$ was carried out to obtain single crystals, whose X-ray structures are given in Figure 1.

Table 1
Various hydantoins from **1**[13]

Entry	Products	R_1	R_2	Time (h)	Yield (%)[a]
1	**3a**		H	1	92
2	**3b**		H	1	92
3	**3c**	^{n}octyl—	H	1.5	88
4	**3d**		H	1	90
5	**3e**		H	1	88
6	**3f**		H	2	85
7	**3g**		H	2	82
8	**3h**		Me	2	80
9	**3i**		H	1.5	84
10	**3j**		H	2	80
11	**3k**		H	1.5	83
12	**3l**		H	2	90
13	**3m**		Me	2	91
14	**3n**		Ph	2	88
15	**3o**		H	2	85
16	**3p**		H	2	86
17	**3q**		Ph	2	75
18	**3r**		H	1	89

[a] Isolated yields.

The exact mechanism for the formation of **3** and role of **2** still needs to be investigated. However, the plausible explanation has been assigned in Scheme 2. In this reaction, electrophilic center in cyanamide group of **1** is attacked by the nucleophilic hydroxyl group of dibutyl phosphate resulting in an unstable intermediate **5**. This further reacts with second molecule of dibutyl phosphate to form an ureido derivative that isomerizes into stable urea derivative **6**.

The intermediate **6**, under the influence of heat, cyclizes into **3** with the loss of MeOH. The attempts to isolate the intermediate **5**, a 1:1 reaction of substrate and dibutyl phosphate were performed. However, it did not yield any characterizable product even after heating the reaction mixture for 12 h. Some amount of **1** invariably remains unreacted while **2** was completely consumed to form pyrophosphate. This study further confirmed that the reaction can be completed in 1:2 mole ratios of **1** and **2**.

In an attempt to assess the reactivity of nitrile (C–CN) and nitrile functionality in cyanamide group (N–CN) in **1** toward the hydrolysis by **2**, we have chosen a substrate **7** (where -CN group lies at 3 and 4 position of aromatic ring). The reaction is depicted in Scheme 3 where **7** possess nitrile and cyanamide functionalities in a single molecule. This was reacted with **2** under the given sets of reaction conditions. Surprisingly, **2** did not affect nitrile group (C–CN) and resulted in the formation of 1-(3-cyanophenyl) hydantoin **8** and 1-(4-cyanophenyl) hydantoin **9**.

Bicyclohydantoin alone[15] or coupled with arylpiperazine moiety represents one of the most important classes of the 5-HT1A receptor ligands which have been the most attractive targets for medicinal chemists.[16] This inspired us to explore this method for the synthesis of bicyclohydantoin. Retro-synthetic analysis based on our method indicated that bicyclohydantoin **11** can be synthesized from precursor **10** (Scheme 4). By following our previous strategy,[12] we cannot prepare **10** because of the intricacies involved in its designing, however, it can be prepared easily from the reaction of proline methyl ester and cyanogen bromide.

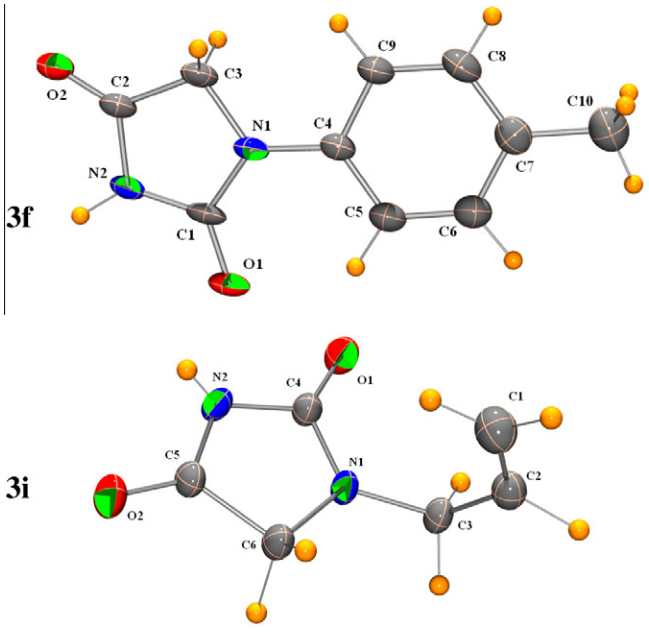
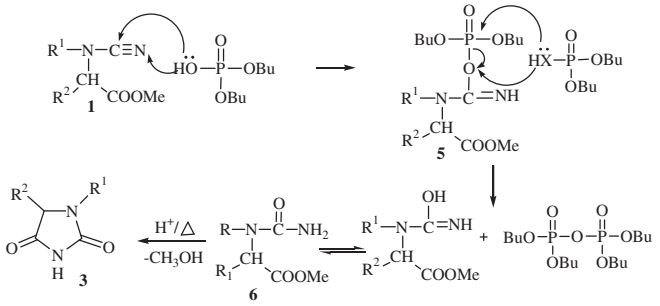
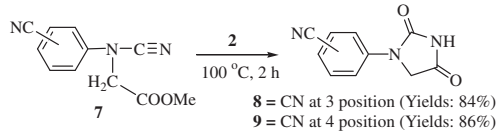


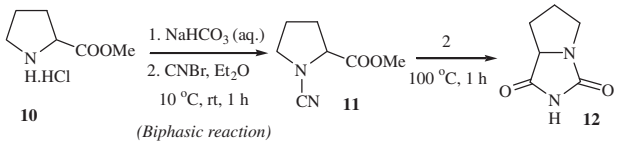
Figure 1. ORTEP diagram of compounds **3f** and **3i**.[14]



Scheme 2. Mechanism for the formation of **3**.



Scheme 3. Comparative reactivity of nitrile and cyanamide group.

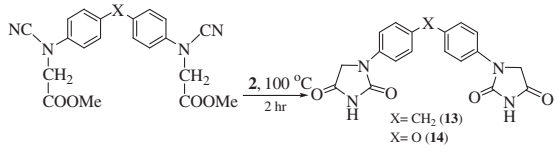


Scheme 4. Synthesis of bicyclohydantoin **12**.

As, it is evident that the free amino acid esters are known to be susceptible to undergo self-condensation to form diketopiperazines and polycondensation products due to the intramolecular reaction between amine and ester group.[17] In an alternative approach, proline methyl ester was in situ converted into **11** from **10** without isolation. In biphasic reaction, proline methyl ester hydrochloride and cyanogen bromide were dissolved in water and diethyl ether, respectively.[18] To this immiscible solution, a saturated solution of sodium bicarbonate was added to neutralize **10** into proline methyl ester which reacts with cyanogen bromide in organic layer to give **11**. Conversion of **11** into **12** was carried out by following our present method (Scheme 4).[19]

We have also successfully attempted to synthesize bis-hydantoins. Bis-hydantoin with methylene (**13**) and ether (**14**) pivotal was synthesized with good yields under similar reaction conditions as shown in Scheme 5. This indicates the expansion of our method for the development of chemically useful products which could find its application in supramolecular chemistry.[20]

In summary, a new strategy for the synthesis of hydantoins has been developed to give the products in quantitative yields with high purity. Synthesis of wide varieties of hydantoins with primary, secondary, tertiary, cyclic, and aryl groups represents an impressive library. The reaction is also of practical importance for the synthesis of bis-hydantoins and bicyclohydantoin which may open attractive avenues in supramolecular chemistry and medicinal chemistry. The important features of the reaction are solvent-free conditions and easy work-up procedure which make the reaction convenient and eco-friendly.



Scheme 5. Synthesis of bis-hydantoins.

Supplementary data

Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.029.

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13. *General procedure for the synthesis of hydantoins* (**3**). Methyl *N*-alkyl/arylaminoacetate **1** (0.0025 mol) and dibutyl phosphate **2** (0.005 mol) were heated at 100 °C as per the reaction time specified in Table 1. The reaction mixture was cooled and then petroleum ether (40–60 °C) (10 mL) was added. Product was precipitated which was again washed with petroleum ether (10 mL × 2) to get pure crystalline solid with good purity. Methyl *N*-alkyl/arylaminoacetates were synthesized from our reported method.[12] Spectral data of compounds **3a**–**3f**, **3r,** and **14** were matched with already known data[12] so not given here. The spectral data of other compounds are given in Supplementary data.
14. X-ray crystallographic data of **3f** and **3i** (CCDC No. 764753 and 764754) reported in this Letter can be found in Supplementary data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/datarequest/cif.
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18. *Synthesis of N-cyano proline methyl ester (**11**).* In a biphasic reaction, proline methyl ester hydrochloride and cyanogen bromide were dissolved in water and diethyl ether, respectively. To this immiscible solution, a saturate solution of sodium bicarbonate was added at 10 °C to release proline methyl ester which reacts with cyanogen bromide to give *N*-cyano proline methyl ester. The reaction was stirred for 2 h. Progress of reaction was monitored by TLC. The organic layer was washed with water, dried, and evaporated in vacuo to give viscous liquid in 60% yields. IR (KBr): ν 2957, 2888, 2215, 1744, 1440, 1352, 1285, 1214, 1165 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ = 1.75–2.21 (m, 4H, CH_2CH_2), 3.44 (m, 2H, CH_2), 3.69 (s, 3H, CH_3), 4.37 (1H, CH); ^{13}C NMR (100 MHz, DMSO-d6): δ = 23.9, 29.5, 50.7, 52.3, 61.4, 115.9, 171.1: TOF-MS (ESI, M+H): m/z = 156.6.
19. *Synthesis of bicyclohydantoin (**12**).* *N*-cyano proline methyl ester **11** (0.5 g, 0.0032 mol) and dibutyl phosphate **2** (0.0064 mol) were heated at 100 °C for 1 h. Solid product formed was washed with petroleum ether (10 mL × 2) to get pure crystalline solid in 55% overall yields. White crystalline solid; mp 156–160 °C; IR (KBr): ν 3190, 3065, 1759, 1728, 1403, 1344, 1231, 1080 cm^{-1}; ^1H NMR (400 MHz, DMSO-d6): δ = 1.59–1.68 (m, 1H, CH), 1.88–1.98 (m, 2H, CH_2), 2.00–2.09 (m, 1H, CH), 3.01–3.06 (m, 1H, CH), 3.42–3.49 (m, 1H, CH), 4.08–4.12 (t, 1H, CH), 10.73 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d6): δ = 26.6, 26.7, 444.9, 64.0, 161.0, 175.4; MS (ESI, M+H): m/z = 141.5 Anal. calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99%; Found: C, 51.46; H, 5.72; N, 20.7%.
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