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An Efficient Approach for the Synthesis of N-1 Substituted Hydantoins

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An efficient three-step route for the synthesis of N-1 alkyl/aryl-substituted hydantoins was developed from inexpensive commercially available substrates. The reaction of amines with cyanogen bromide takes place to give monoalkyl/aryl cyanamides. This on treatment with methyl bromoacetate in the presence of sodium hydride in tetrahydrofuran affords methyl *N*-cyano-*N*-alkyl/arylaminoacetate, which undergoes hydrolysis and cyclization in the presence of 50 % H_2SO_4 to afford N-1 substituted hydantoins in very good-to-excellent yields. Wide varieties of final products having primary, secondary, tertiary, and aryl substituents at the N-1 position were successfully synthesized by this method.

Introduction

Hydantoin and its derivatives (Figure 1) are of considerable interest both from chemical and biological points of view.[1] Several compounds of this class have shown pharmaceutically useful activity such as antitumor,[2] antiarrhytmic,[3] anticonvulsant,[4] herbicidal,[5] and others[6] that lead in some case to clinical applications. Moreover, hydantoins are key intermediates during the synthesis of optically pure natural and unnatural amino acids.[7]

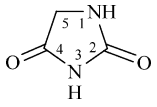

Figure 1. Generic structure of hydantoin and its numbering scheme.

Because of their biological significance, a large number of solution-phase, as well as solid-phase, preparative methods for the synthesis of hydantoin derivatives have been developed.[1] The solution-phase synthesis includes the reaction of (i) amino acids or related compounds with cyanates and thiocyanates (Reed synthesis),[8] (ii) α-dicarbonyl compounds with ureas (Bucherer–Bergs synthesis),[9] (iii) carbonyl compounds with potassium cyanide and ammonium carbonates,[10] and (iv) amino acids or esters with isocyanates.[1a,11] Various derivatives of hydantoin have also been synthesized with the use of solid supports by utilizing the more-or-less basic chemistry involved in the solution-phase synthesis.[12] By employing these methodologies, several chemically and pharmaceutically useful hydantoins substituted at different positions have successfully been synthesized. To improve upon the drawbacks associated with the previously existing methods, recently various routes/methods have been reported.[13] Unfortunately, in spite of a myriad of routes/methods for the construction of the hydantoin ring, there are very few practical methods available in the literature for the synthesis of N-1 substituted hydantoins, specifically with aryl and secondary and tertiary alkyl groups. Substitution in the hydantoin ring at the N-1 position is generally achieved by long and tedious processes that take place over the following three steps: (i) protection of the more reactive N-3 position, (ii) alkylation at the N-1 position, and (iii) removal of the protecting groups by controlled acid- or base-catalyzed hydrolysis;[14] this in general reduces the yields of the final products. Moreover, this method is not applicable for the synthesis of hydantoins with aryl and secondary and tertiary alkyl groups substituted at the N-1 position. Reed synthesis[8] and Bucherer–Bergs synthesis[9] are the most widely used protocols, but the major limitation of these methods is the nonavailability of the precursors; thus, they must be synthesized by long and complexed procedures. As we were interested in N-1 substituted hydantoins for our research program on the synthesis of phosphorylated hydantoins and their bioactivity, there was an urgent need for the development of a new and practical method for the synthesis of the title compounds. In this paper, we wish to report a route for the direct synthesis of N-1 substituted hydantoins from commercially available starting materials in very good yields.

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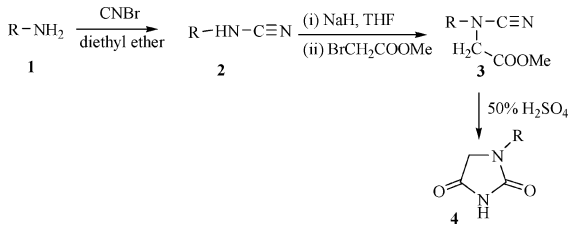
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

Results and Discussion

The method presented in this paper is based on retrosynthetic analysis, which indicates that the hydantoin ring may be generated starting from an N–C–N building block. This linkage is usually obtained from any of the moieties such as urea, (iso)cyanates, and carbodiimides.[15] We thought to incorporate this moiety from cyanamide (NH_2CN), as our interests were involved in cyanamide chemistry,[16] and it can easily be synthesized from amines.[17] Our retrosynthetic approach leads to an efficient route to N-1 alkyl/aryl hydantoins. The synthetic procedure involves three steps as outlined in Scheme 1 and gave overall yields of 65–85%. As far as we know, a route for the synthesis of **4** has not been reported in the literature.[1]



Scheme 1. Synthetic route for N-1 substituted hydantoins.

Table 1. Synthesis of N-1 substituted hydantoins.

Entry	Product **2**	Time [h]	Yield [%]	Product **3**	Time [h]	Yield [%]	Product **4**	Time [h]	M.p. [°C]	Yield [%]
a	*n*PrNHCN	1	70	*n*Pr–N(CH2COOMe)–C≡N	2	92	*n*Pr	7	124–127	80
b	*n*-octyl–NHCN	1	92	*n*-octyl–N(CH2COOMe)–C≡N	2	90	*n*-octyl	7	64–66	90
c	NHCN	1	96	N(CH2COOMe)–C≡N	2	94		0.5	183–184	88
d	NHCN	1	90	N(CH2COOMe)–C≡N	2	90		2	188–190	92
e	NHCN	1	94	CH2–N(CH2COOMe)–C≡N	2	95		2	138–140	82
f	Me, Me, NHCN, Me	1	95	Me, Me, N(CH2COOMe)–C≡N, Me	2	92	Me, Me, Me	0.5	196–198	93
g	NHCN	12	92	N(CH2COOMe)–C≡N	4	93		2	191–192	92
h	NHCN, CH3	4	95	H3C, N(CH2COOMe)–C≡N	3	92	CH3	3	212–214	85
i	NHCN, Me	6	93	Me, N(CH2COOMe)–C≡N	4	94	Me	3	164–168	90
j	NHCN	12[a]	80	N(CH2COOMe)–C≡N	8	92		7[a]	>300 (dec.)	85

[a] Reactions were carried out in THF.

In the first step, monoalkyl/aryl cyanamides **2** were synthesized by the reaction of amines with cyanogen bromide in 92–95%.[17] In the next step, reaction of **2** takes place with methyl bromoacetate in the presence of sodium hydride to afford methyl *N*-cyano-*N*-alkyl/arylaminoacetate **3** in 90–94%yields. Upon treatment with 50% H_2SO_4 at 0–25 °C, hydrolysis and cyclization of **3** occurs to give N-1 alkyl/aryl hydantoins in yields of 80–93%. The ease and convenience of this preparation stimulated us to prepare a large number of hydantoins substituted at the N-1 position. A library of hydantoins generated by this route is summarized in Table 1 and includes the formation of hydantoins with various substituents such as primary, secondary, and tertiary alkyl, cyclic, and aryl groups. Even sterically hindered hydantoins, such as N-1 *tert*-butylhydantoin (Table 1, Entry f), were easily synthesized, which is seldom seen by conventional methods. Furthermore, the introduction of a fluorogenic group, such as anthracenyl (Table 1, Entry j), into the hydantoin ring was conveniently achieved to afford 1-(2-anthracenyl)hydantoin, which can be used in bioassays and pharmacokinetics of hydantoin-based drugs.

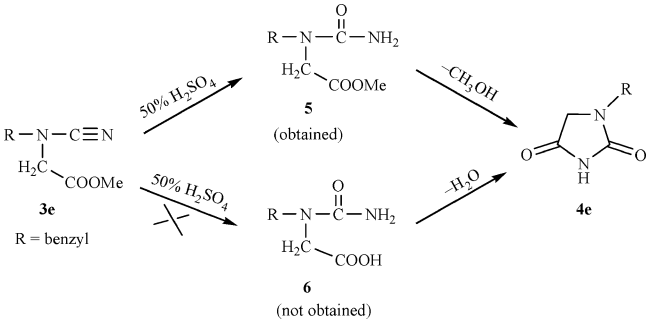
Monoalkyl/aryl cyanamides **2** were prepared by known methods,[16] in which the reaction of two molecules of aliphatic, as well as aromatic, amines with cyanogen bromide takes place in diethyl ether or tetrahydrofuran depending upon the solubility of the amines; one molecule reacts with cyanogen bromide to give cyanamides **2**, whereas the other molecule acts as a scavenger for the hydrogen bromide that is generated in the reaction to give ammonium hydrobromide as a precipitate. Other organic bases may also be used as a scavenger, but it is advisable to use substrates as the proton abstractor to avoid undesired side product formation. Because of poor nucleophilicity, the reaction of aromatic amines with cyanogen bromide is slower than that of aliphatic amines.

Formation of key compounds **3** was also found to be clean, and they were obtained by treatment of **2** with sodium hydride at 0 °C under a nitrogen atmosphere. This generated the sodium salts of the cyanamides, to which methyl bromoacetate was added at 0 °C. The solution was stirred for 1 h at the same temperature and then at room temperature for a specific time, as mentioned in Table 1, to give the desired products in 90–95% yields. In most cases, this reaction was complete in 2–4 h.

Compounds **3** were easily hydrolyzed and cyclized into hydantoins **4** upon treatment with 50% H_2SO_4 at room temperature in diethyl ether or tetrahydrofuran depending on the solubility. In our studies, we also demonstrated that the formation of N-1 cyclooctylhydantoin (**4d**, 2 h) from **3d** took place more rapidly relative to the formation of N-1 *n*-octylhydantoin (**4b**, 7 h) from **3b**. This indicates that steric hindrance helps in the cyclization step, which therefore enhances the rate of the reaction.

The structure of all the products was confirmed by ^1H and ^{13}C NMR spectroscopy. In the ^1H NMR spectrum of **3g**, three signals were observed at δ = 3.81 (–OCH_3), 4.34 ppm (–CH_2–), and multiplets for the aromatic ring protons. The ^1H-decoupled ^{13}C NMR spectrum of **3g** exhibited signals at δ = 50.95 (–OCH_3), 53.21 (–CH_2–), 113.85 ppm (–C≡N), and distinct peaks for the aromatic ring carbon atoms. Similarly, **4g** showed ^1H NMR signals at δ = 4.46 ppm (–CH_2–) and multiplets for the aromatic protons. However, the ^{13}C NMR spectrum of **4g** contained peaks at δ = 51.75 ppm (–CH_2–), two peaks for the imidic carbonyl groups at δ = 155.31 (2 C=O), 170.22 ppm (4 C=O), and multiple peaks for the aromatic ring carbon atoms. Disappearance of certain peaks of **3g** such as the –OCH_3 peak at δ = 3.81 ppm in the ^1H NMR spectrum and at δ = 50.95 ppm in the ^{13}C NMR spectrum of **4g** and the appearance of two new peaks for the imidic carbonyl groups at δ = 155.31, 170.22 ppm indicated that hydrolysis and cyclization of **3g** into **4g** had taken place in one single step.

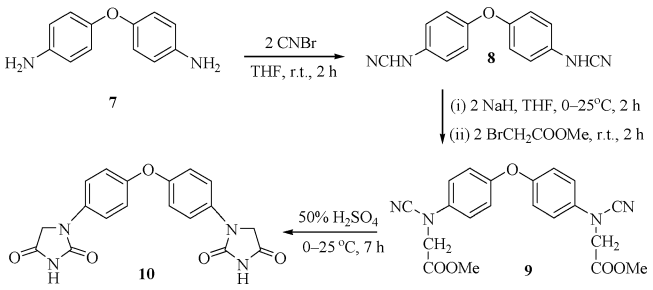
The mechanism for the formation of hydantoins **4** from compounds **3** was found to be consistent with our experimental observations (Scheme 2), which confirm that **3** undergoes partial hydrolysis of the cyanamide group to generate methyl 1-benzylhydantoate (**5**). Compound **5** then eliminates a molecule of methanol, followed by cyclization to give 1-benzylhydantoin (**4e**). This mechanism was also confirmed by the isolation of methyl 1-benzylhydantoate (**5**, m.p. 122–24 °C) from the hydrolytic intermediate of methyl *N*-cyano-*N*-benzylaminoacetate (**3e**) under controlled reaction conditions. The ^1H NMR spectrum confirmed the formation of **5** by the appearance of a new peak at δ = 6.10 ppm for the NH_2 group, whereas the peak at δ = 3.89 ppm for the –OCH_3 group remained unaffected. When the reaction mixture was allowed to react for a longer time with periodic monitoring, a new peak at δ = 10.86 ppm appeared for the imidic NH of N-1 benzylhydantoin (m.p. 138–40 °C) with simultaneous disappearance of peak at δ = 3.89 ppm for the –OCH_3 group and no sign of formation of 1-benzylhydantoic acid (**6**), which should have been obtained by the complete hydrolysis of **3e** into **6**. Therefore, it is evident that intermediate methyl hydantoates can be conveniently isolated from the reaction mixtures if necessary.



Scheme 2. Mechanism for the formation of **4** from **3**.

Multivalent structures have the unique place in molecular recognition and signal transduction process. To show the convenience of our approach for the synthesis of multivalent hydantoins, we designed and synthesized bis(hydantoin) **10** by starting from 4,4′-diaminodiphenyl ether (**7**) through the formation of 4,4′-bis(cyanamino)diphenyl ether

(**8**) and 4,4′-bis(methyl *N*-cyanoaminoacetate)diphenyl ether (**9**). The reactions proceeded smoothly in a similar sequence of steps, and compound **10** [m.p. >300 (dec.)] was obtained in 80% yield (Scheme 3), which thus shows the capability for generating multivalent structures by this route. The successful synthesis of **10** will also be useful to incorporate the hydantoin moiety into large molecules for molecular recognition studies owing to the presence of multiple binding sites in the hydantoin ring, and this work is in progress.



Scheme 3. Synthesis of bis(hydantoin) **10**.

Conclusions

We described an efficient synthetic route leading to N-1 substituted hydantoins from inexpensive commercially available substrates. Formation of a wide range of hydantoins with primary, secondary, and tertiary alkyl, cyclic, and aryl groups is one of the most striking features of this method. Extension of this method for the synthesis of bis-(hydantoin)s proves that a number of hydantoin rings may be generated in a large molecule, which is an added advantage of our methodology. Hydantoins were synthesized in very good yields with high purity. These procedures will also allow easy access to further diversified hydantoin-based natural products.

Experimental Section

Chemicals were purchased from Acros, Sigma–Aldrich, and Merck (India) and used without further purification; solvents were distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded with a Bruker (400and 100 MHz, respectively) spectrometer against TMS as an internal standard. IR spectra as KBr pellets were obtained with a Perkin–Elmer model BXII FTIR spectrophotometer. HRMS analysis was performed with a Q-TOF Micromass (Water).

General Procedure for Products 2: A solution of the appropriate amine (5.0 g) in diethyl ether/tetrahydrofuran (50 mL) was added dropwise to a solution of cyanogen bromide (0.6 equiv.) (*CAUTION: cyanogen bromide*[18] *is toxic. Reactions should be carried out in the fumehood*) at 0 °C in diethyl ether/tetrahydrofuran (100 mL), and the mixture was stirred for the specific time given in Table 1. A precipitate of the amine hydrobromide appeared and was removed by filtration. This filtrate was washed with water (2 × 100 mL) and dried with anhydrous Na_2SO_4. The solvent was removed under reduced pressure to give respective cyanamides **2**.

***n*-Propyl Cyanamide (2a):** Colorless liquid. IR (neat): $\tilde{\nu}$ = 3195, 2935, 2858, 2218, 1452 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 1.10 (t, J = 7.3 Hz, 3 H), 1.68 (m 2 H), 2.95 (q, J = 7.3 Hz, 2 H) 6.74 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.00, 19.82, 46.34, 116.98 ppm.

***n*-Octyl Cyanamide (2b):** Pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 3204, 2927, 2860, 2220, 1461 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 0.84–1.45 (m, 15 H), 2.90 (q, J = 5.6 Hz, 2 H), 6.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.18, 22.72, 26.38, 29.20, 29.24, 29.79, 31.85, 46.20, 117.05 ppm.

Cyclohexyl Cyanamide (2c): Colorless liquid. IR (neat): $\tilde{\nu}$ = 3197, 2935, 2217 1445 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20–1.94 (m, 10 H), 3.08–3.10 (t, J = 4.3 Hz, 1 H), 3.93 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.41, 25.26, 32.85, 54.69, 115.54 ppm.

Cyclooctyl Cyanamide (2d): Pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 3176, 2921, 2230, 1604, 1488 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12–1.88 (m, 14 H), 3.33–3.36 (m, 1 H), 3.89 (m 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.00, 25.12, 27.21, 31.55, 56.30, 116.32 ppm.

Benzyl Cyanamide (2e): Colorless liquid. IR (neat): $\tilde{\nu}$ = 3368, 2221, 1610, 1460 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.15–4.29 (t, J = 13.36 Hz, 2 H), 4.12–4.15 (1 H, NH), 7.31–7.39 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.14, 116, 128.03, 128.60, 129.11, 136.54 ppm.

***tert*-Butyl Cyanamide (2f):** Colorless liquid. IR (neat): $\tilde{\nu}$ = 3200, 2975, 2212 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (s, 9 H), 3.69 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.27, 53.63, 114.99 ppm.

Phenyl Cyanamide (2g): White solid. IR (neat): $\tilde{\nu}$ = 3172, 3005, 2227, 1608, 1482 cm^{-1}. ^{1}H NMR (400 MHz, CD_3OD): δ = 4.59 (br. s, 1 H, NH), 6.96–7.60 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.20, 115.43, 122.99, 129.55, 138.25 ppm.

4-Methylphenyl Cyanamide (2h): White solid. IR (KBr): $\tilde{\nu}$ = 3166, 3077, 2958, 2224, 1610, 1515, 1456, 1243 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.24 (s, 3 H), 6.85–7.16 (m, 4 H), 9.99 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.66, 111.63, 115.30, 131.21, 133.25, 134.52 ppm.

3-Methylphenyl Cyanamide (2i): Colorless oil. IR (neat): $\tilde{\nu}$ = 3174, 3003, 2920, 2229, 1603, 1484 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 2.29 (s, 3 H), 6.75–7.24 (m, 4 H), 10.04 (s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.40, 112.18, 112.52, 115.96, 124.24, 129.46, 137.35, 139.85 ppm.

2-Anthracenyl Cyanamide (2j): Green solid. IR (KBr): $\tilde{\nu}$ = 3302, 3043, 2224, 1633, 1498, 1459, 1216 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]-DMSO): δ = 6.93–8.53 (m, 9 H), 10.48 (br. s 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 103.58, 112.66, 118.08, 121.65, 125.67, 125.82, 126.46, 126.66, 127.22, 127.70, 128.25, 130.91, 131.21, 132.09, 136.57 ppm.

4,4′-Bis(cyanamino)diphenyl Ether (8): Cream solid. IR (KBr): $\tilde{\nu}$ = 3149, 3074, 2952, 2224, 1619, 1504, 1229 cm^{-1}. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 10.09 (br. s, 1 H, NH), 6.95–7.02 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 113.42, 117.43, 120.85, 129.25, 135.23 ppm. HRMS (ESI, MeOH): calcd. for $C_{14}H_{10}N_4O$ [M + H]$^+$ 251.0933; found 191.2623.

General Procedure for Products 3: To a solution of the appropriate cyanamide (2.0 g) in dry tetrahydrofuran (50 mL), was added NaH (60% oil suspension, 1.1 equiv.) in three portions at 0 °C under a nitrogen atmosphere. The reaction mixture was stirred for 1 h at

the same temperature to form the sodium salt of the cyanamides. Methyl bromoacetate (1.0 equiv.) in dry tetrahydrofuran (10 mL) was then added at 0 °C, and the mixture was stirred for the specific time given in Table 1. After completion of the reaction as monitored by TLC, the reaction mixture was filtered. The filtrate was evaporated to one-half its total volume and dichloromethane (50 mL) was added. The combined organic layer was washed with water (2 × 50 mL) and dried with anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure to give **3** in excellent yields.

Methyl *N*-Cyano-*N*-*n*-propylaminoacetate (3a): Pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 2964, 2882, 2216, 1751, 1434, 1214 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.99 (t, J = 7.3 Hz, 3 H), 1.71 (m 2 H), 3.06 (t, J = 7.3 Hz, 2 H), 3.79 (s, 3 H), 3.80 (s 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.05, 21.00, 52.44, 52.71, 53.93, 117.00, 168.58 ppm.

Methyl *N*-Cyano-*N*-*n*-octylaminoacetate (3b): Yellow liquid. IR (neat): $\tilde{\nu}$ = 2927, 2859, 2217, 1752, 1454, 1213 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 084–1.75 (m, 13 H), 3.00–3.04 (t, J = 7.2 Hz, 2 H) 3.69 (s 3 H), 4.01 (s 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.23, 22.75, 26.52, 27.64, 29.25, 31.87, 46.40, 52.30, 52.48, 52.72, 117.03, 168.58 ppm.

Methyl *N*-Cyano-*N*-cyclohexylaminoacetate (3c): Pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 2932 2857, 2209, 1749, 1440, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.85–2.02 (m, 10 H), 2.84 (m, 1 H), 3.79 (s, 3 H), 3.82 (2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.52, 24.67, 30.53, 50.30, 52.25, 59.28, 115.60, 168.52 ppm.

Methyl *N*-Cyano-*N*-cyclooctylaminoacetate (3d): Pale-yellow liquid. IR (neat): $\tilde{\nu}$ = 2923, 2858, 2209, 1751, 1455, 1209 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.52–1.78 (m 14 H), 3.11 (m, 1 H), 3.79 (s 3 H), 3.81 (s 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.62, 25.41, 27.03, 30.35, 51.39, 52.68, 116.53, 168.90 ppm.

Methyl *N*-Cyano-*N*-benzylaminoacetate (3e): Colorless oil. IR (neat): $\tilde{\nu}$ = 3027, 2948, 2216, 1746, 1609, 1549, 1506, 1447, 1215 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.69 (s, 3 H), 4.07 (s, 2 H), 4.26 (s, 2 H), 7.37–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.38, 52.61, 55.94, 117.25, 128.82, 128.94, 129.02, 133.51, 168.26 ppm.

Methyl *N*-Cyano-*N*-*tert*-butylaminoacetate (3f): Colorless oil. IR (neat): $\tilde{\nu}$ = 2979, 2205, 1749, 1462 cm^{-1}. ^1H NMR (400 MHz, [D_6]-DMSO): δ = 1.21 (s, 9 H), 3.69 (s, 3 H), 4.01 (s, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.27, 47.43, 52.30, 52.91, 115.85, 168.94 ppm.

Methyl *N*-Cyano-*N*-phenylaminoacetate (3g): White solid. M.p. 64–66 °C. IR (KBr): $\tilde{\nu}$ = 3030, 2956, 2225, 1749, 1614, 1514, 1430, 1129 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.81 (s, 3 H), 4.35 (s, 2 H), 7.06–7.38 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 50.95, 53.21, 113.35, 115.77, 124.4, 130.01, 139.51, 167.71 ppm.

Methyl *N*-Cyano-*N*-4-methylphenylaminoacetate (3h): White solid. M.p. 58–60 °C. IR (KBr): $\tilde{\nu}$ = 3004, 2956, 2222, 1741, 1594, 1498, 1437, 1226, 1182 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.31 (s, 3 H), 3.80 (s, 3 H), 4.31 (s 2 H), 6.95–7.16 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.60, 50.92, 52.95, 113.59, 115.75, 130.23, 134.16, 136.89, 167.88 ppm.

Methyl *N*-Cyano-*N*-3-methylphenylaminoacetate (3i): White solid. M.p. 52–54 °C. IR (KBr): $\tilde{\nu}$ = 3030, 2957, 2224, 1751, 1599, 1499, 1431, 1221, 1174 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3 H), 3.81 (s, 3 H), 4.33 (s, 2 H), 6.81–7.26 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.24, 30.66, 50.38, 52.69, 112.10, 112.99, 116.07, 129.26, 138.90, 139.76, 167.28 ppm.

Methyl *N*-Cyano-*N*-(2-anthracenyl)aminoacetate (3j): Greenish solid. IR (KBr): $\tilde{\nu}$ = 3045, 2952, 2224, 1750, 1632, 1453, 1215 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.84 (s, 3 H), 4.50 (s, 2 H), 7.40–8.40 (m, 9 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 49.78, 52.73, 102.77, 113.28, 116.70, 121.01, 125.20, 125.49, 126.26, 126.46, 127.14, 127.82, 128.24, 130.73, 131.08, 132.09, 136.52, 168.48 ppm.

4,4′-Bis(methyl *N*-Cyanoaminoacetate)diphenyl Ether (9): Creamy solid. IR (KBr): $\tilde{\nu}$ = 3052, 2226, 1754, 1434, 1230 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.72 (s, 6 H), 4.72 (s, 4 H), 7.05–7.17 (m, 8 H) 6.95–7.02 (m, 8 H) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 50.36, 52.01, 113.05, 117.47, 119.78, 135.80, 153.55, 168.02 ppm. HRMS (ESI, MeOH): calcd. for $C_{20}H_{18}N_4O_5$ $[M + H]^+$ 395.1355; found 417.2520 $[M + Na]^+$.

General Procedure for Products 4: To an ice-cooled solution of methyl *N*-cyano-*N*-alkyl/arylaminoacetate **3** (1.0 g) in diethyl ether or tetrahydrofuran depending upon its solubility (5 mL) was dropwise added 50% H_2SO_4 (5 mL) at 0 °C. The reaction mixture was stirred at the same temperature for 30 min and then at room temperature for a period as mentioned in Table 1. The completion of the reaction was monitored by TLC. This solution was poured into the ice-cold water to precipitate the product, which was then washed thoroughly with cold water to remove traces of sulfuric acid. The products were dried with calcium chloride vacuum desiccators.

***n*-Propylhydantoin (4a):** Compound **4a** from **3a** was synthesized by following the general procedure with a difference in the extraction procedure as follows: After completion of the reaction as monitored by TLC, the solution containing the product was neutralized with 10% sodium hydrogen carbonate and then extracted with dichloromethane (2 × 50 mL). The organic layer was finally washed with water (2 × 50 mL) and dried with sodium sulfate. Removal of solvent under reduced pressure gave the pure product in 80% yield. White crystalline solid. M.p. 124–127 °C. IR (KBr): $\tilde{\nu}$ = 3191, 2938, 1767, 1713, 1483 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 0.81 (t, J = 7.4 Hz, 3 H), 1.46 (m, 2 H), 3.16 (t, J = 7.2 Hz, 2 H) 3.91 (s, 2 H), 10.69 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]-DMSO): δ = 10.96, 20.40, 43.06, 50.29, 156.80, 171.88 ppm. HRMS (ESI, MeOH): calcd. for $C_6H_{10}N_2O_2$ $[M + H]^+$ 143.0821; found 143.1151.

1-*n*-Octylhydantoin (4b): White crystalline solid. M.p. 64–66 °C. IR (KBr): $\tilde{\nu}$ = 3196, 2924, 1759, 1702, 1464 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.49–1.64 (m, 14 H), 3.88 (s, 2 H), 4.01 (m, 1 H), 10.65 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.74, 22.27, 26.24, 27.33, 28.81, 31.39, 42.06, 50.35, 155.97, 170.19 ppm. HRMS (ESI, MeOH): calcd. for $C_{11}H_{20}N_2O_2$ $[M + H]^+$ 213.1603; found 213.4020.

1-Cyclohexylhydantoin (4c): White crystalline solid. M.p. 183–184 °C. IR (KBr): $\tilde{\nu}$ = 3163, 3027, 2928, 2770, 1775, 1702, 1479 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 0.82–1.74 (m, 10 H), 3.64 (m, 1 H), 3.88 (s 2 H), 10.67 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.34, 25.44, 30.88, 47.20, 50.94, 155.90, 171.01 ppm. HRMS (ESI, MeOH): calcd. for $C_9H_{14}N_2O_2$ $[M + H]^+$ 183.1134; found 183.3560 and 205.3676 $[M + Na]^+$.

1-Cyclooctylhydantoin (4d): White crystalline solid. M.p. 188–190 °C. IR (KBr): $\tilde{\nu}$ = 3159, 3041, 2928, 1770, 1697, 1468 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 1.49–1.64 (m, 14 H), 3.88 (s, 2 H), 4.01 (m, 1 H), 10.65 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.48, 25.86, 26.65, 31.41, 47.43, 51.71, 155.57, 170.96 ppm. HRMS (ESI, MeOH): calcd. for $C_{11}H_{18}N_2O_2$ $[M + H]^+$ 211.1447; found 211.4210 and 233.4402 $[M + Na]^+$.

1-Benzylhydantoin (4e): White crystalline solid. M.p. 138–140 °C. IR (KBr): $\tilde{\nu}$ = 3180, 3053, 2923, 27.81, 1766, 1691, 1470 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.83 (s, 2 H), 4.43 (s, 2 H), 7.25–7.38 (m, 4 H), 10.86 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.58, 50.40, 128.34, 128.50, 129.28, 135.35, 156.69, 170.46 ppm. HRMS (ESI, MeOH): calcd. for $C_{10}H_{10}N_2O_2$ [M + H]$^+$ 191.0821; found 191.3321.

1-*tert*-Butylhydantoin (4f): White crystalline solid. M.p. 196–198 °C. IR (KBr): $\tilde{\nu}$ = 3166, 3035, 2979, 2771, 1778, 1692, 1451 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (s, 9 H), 4.00 (s, 2 H), 10.57 (br. s, 1 H NH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.12, 49.76, 54.52, 156.22, 170.63 ppm. HRMS (ESI, MeOH): calcd. for $C_7H_{12}N_2O_2$ [M + H]$^+$ 157.0977; found 157.2625.

1-Phenylhydantoin (4g): White crystalline solid. M.p. 191–192 °C. IR (KBr): $\tilde{\nu}$ = 3173, 3056, 2935, 1831, 1744, 1595, 1503, 1449, 1405 cm^{-1}. ^1H NMR (400 MHz, CD_3COCD_3): δ = 4.46 (s, 2 H), 7.11–7.69 (m, 5 H), 9.97 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, CD_3COCD_3): δ = 51.75, 119.00, 124.31, 129.82, 139.62, 155.31, 170.12 ppm. HRMS (ESI, MeOH): calcd. for $C_9H_8N_2O_2$ [M + H]$^+$ 177.0764; found 177.2992 and 196.3017 [M + Na]$^+$.

1-(4-Methylphenyl)hydantoin (4h): White crystalline solid. M.p. 212–214 °C. IR (KBr): $\tilde{\nu}$ = 3172, 3053, 2921, 1740, 1617, 1517, 1444 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.26 (s, 3 H), 4.40 (s, 2 H), 7.16–7.48 (m, 4 H) 11.11 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 20.75, 51.42, 118.74, 129.73, 132.90, 136.13, 154.67, 169.94 ppm. HRMS (ESI, MeOH): calcd. for $C_{10}H_{10}N_2O_2$ [M + H]$^+$ 191.0821; found 191.3321.

1-(3-Methylphenyl)hydantoin (4i): White crystalline solid. M.p. 164–168 °C. IR (KBr): $\tilde{\nu}$ = 3152, 3039, 2925, 1732, 1593, 1495, 1416 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 2.30 (s 3 H), 4.41 (s, 2 H), 6.91–7.42 (m, 4 H) 11.14 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 21.82, 51.49, 115.97, 119.59, 125.86, 129.37, 139.62, 153.97, 168.80 ppm. HRMS (ESI, MeOH): calcd. for $C_{10}H_{10}N_2O_2$ [M + H]$^+$ 191.0821; found 191.3321.

1-(2-Anthracenyl)hydantoin (4j): Greenish solid. M.p. 100 °C. IR (KBr): $\tilde{\nu}$ = 3161, 3047, 1764, 1716, 1626, 1450, 1395 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 4.62 (s, 2 H), 7.45–8.53 (m, 9 H), 11.30 (br. s, 1 H, NH) ppm. HRMS (ESI, MeOH): calcd. for $C_{17}H_{12}N_2O_2$ [M + H]$^+$ 277.0977; found 277.4276.

Methyl 1-Benzylhydantoate (5): White crystalline solid. M.p. 122–124 °C. IR (KBr): $\tilde{\nu}$ = 3460, 3203, 2960, 2925 1749, 1678, 1612, 1495, 1438, 1217 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 3.60 (s, 3 H), 3.89 (s, 2 H), 4.43 (s, 2 H), 6.10 (br. s, 2 H, NH) 7.22–7.34 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.28, 52.41, 52.56, 127.18, 128.11, 129.21, 136.56, 159.33, 170.83 ppm. HRMS (ESI, MeOH): calcd. for $C_{11}H_{14}N_2O_3$ 222.2405; found 245.3596 [M + Na]$^+$.

4,4′-Bis(*N*-1-hydantoin)diphenyl Ether (10): Creamy solid. M.p. >300 °C (dec.). IR (KBr): $\tilde{\nu}$ = 3169, 3061, 2944, 1762, 1721, 1508, 1446 cm^{-1}. ^1H NMR (400 MHz, [D_6]DMSO): δ = 4.43 (s, 4 H), 7.00–7.60 (m, 8 H) 11.13 (br. s, 1 H, NH) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 51.64, 119.33, 120.61, 134.20, 153.11, 155.28, 170.93 ppm. HRMS (ESI, MeOH): calcd. for $C_{18}H_{14}N_4O_5$ 367.1042 [M + H]$^+$; found 367.3242.

Supporting Information (see footnote on the first page of this article): ^1H and ^{13}C NMR spectra of products **3**–**5**, **9**, and **10**.

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[1] a) E. Ware, *Chem. Rev.* **1950**, *46*, 403; b) C. Avendano, G. G. Trigo, *Adv. Heterocycl. Chem.* **1985**, *38*, 177; c) M. Meusel, M. Gütschow, *Org. Prep. Proc. Int.* **2004**, *36*, 391; d) W. J. Brouillette, Y. P. Jestkov, M. L. Brown, M. S. Aktar, T. M. Delorey, G. B. Brown, *J. Med. Chem.* **1994**, *37*, 3289; e) R. M. Schelkun, P. W. Yuen, K. Serpa, L. T. Meltzer, L. D. Wise, *J. Med. Chem.* **2000**, *43*, 1892; f) H. U. Stilz, W. Guba, B. Jablonka, M. Just, O. Klinglcr, W. Konig, V. Wehner, G. Zoller, *J. Med. Chem.* **2001**, *44*, 1158.

[2] a) K. H. Hollenbeak, F. J. Schmitz, *Lloydia* **1977**, *40*, 479; b) R. F. Struck, M. C. Kirk, L. S. Rice, W. J. Suling, *J. Med. Chem.* **1986**, *29*, 1319.

[3] M. Matsukura, Y. Daiku, K. Ueda, S. Tanaka, T. Igarashi, N. Minami, *Chem. Pharm. Bull.* **1992**, *40*, 1823.

[4] A. Novelli, *Anales Farm. y Bioquim.* **1954**, *21*, 81; *Chem. Abstr.* **1956**, *50*, 4922d.

[5] a) H. Haruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima, T. Haneishi, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1637; b) S. Mirza, *Chem. Abstr.* **1992**, *117*, 8356; c) S. Mio, R. Ichinose, K. Goto, S. Sugai, S. Sato, *Tetrahedron* **1991**, *47*, 2111; d) S. Mio, M. Shiraishi, S. Sugai, H. Haruyama, S. Sato, *Tetrahedron* **1991**, *47*, 2121; e) S. Mio, Y. Kumagawa, S. Sugai, *Tetrahedron* **1991**, *47*, 2133; f) P. Chemla, *Tetrahedron Lett.* **1993**, *34*, 7391; g) P. M. Harrington, M. E. Jung, *Tetrahedron Lett.* **1994**, *35*, 5145; h) H. Sano, S. Sugai, *Tetrahedron* **1995**, *51*, 4635.

[6] a) C. J. F. Bichard, E. P. Mitchell, M. R. Wormald, K. A. Watson, L. N. Johnson, S. E. Zographos, D. D. Koutra, N. G. Oikonomakos, G. W. J. Fleet, *Tetrahedron Lett.* **1995**, *36*, 2145; b) T. W. Brandsletler, Y.-H. Kim, J. C. Son, H. M. Taylor, P. M. Q. Lilley, D. J. Watkin, L. N. Johnson, N. G. Oikonomakos, G. W. J. Fleet, *Tetrahedron Lett.* **1995**, *36*, 2149; c) T. W. Brandsteller, C. de la Fuente, Y.-B. Kim, L. N. Johnson, S. Crook, P. M. Q. Lilley, D. J. Watkin, K. E. Tsitsanou, S. E. Zographos, E. D. Chrysina, N. G. Oikonomakos, G. W. J. Fleet, *Tetrahedron* **1996**, *52*, 10721; d) M. Yamagishi, Y. Yamada, K. Ozaki, T. Date, K. Okamura, M. Suzuki, K. Matsumoto, *J. Org. Chem.* **1992**, *57*, 1568; e) V. Stella, *J. Adv. Drug Deliver. Rev.* **1996**, *19*, 311; f) B. C. Vanwagenen, R. Larsen, J. H. Cardellina, *J. Org. Chem.* **1993**, *58*, 335.

[7] a) K. Lavrador, D. Guillerm, G. Guillerm, *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1629; b) F. Tellier, F. Acher, I. Brabet, J.-P. Pin, R. Azerad, *Bioorg. Med. Chem.* **1998**, *6*, 195.

[8] a) J. A. Monn, M. J. Valli, S. M. Massey, R. A. Wright, C. R. Salhoff, B. G. Johnson, T. Howe, C. A. Alt, G. A. Rhodes, R. L. Robey, K. R. Griffey, J. P. Tizzano, M. J. Kallman, D. R. Helton, D. D. Schoepp, *J. Med. Chem.* **1997**, *40*, 528; b) J. A. Monn, M. J. Valli, S. M. Massey, M. M. Hansen, T. J. Kress, J. P. Wepsiec, A. R. Harkness, J. L. Grutsch, R. A. Wright, B. G. Johnson, S. Andis, L. A. Kingston, R. Tomlinson, R. Lewis, K. R. Griffey, J. P. Tizzano, D. D. Schoepp, *J. Med. Chem.* **1999**, *42*, 1027; c) F. Tellier, F. Acher, I. Brabet, J. P. Pin, R. Azerad, *Bioorg. Med. Chem.* **1998**, *6*, 195.

[9] a) Urech, *Justus Liebigs Ann. Chem.* **1873**, *165*, 99; b) W. T. Read, *J. Am. Chem. Soc.* **1922**, *44*, 1749.

[10] a) H. T. Bucherer, W. Steiner, *J. Prakt. Chem.* **1934**, *140*, 291; b) H. T. Bucherer, V. A. Lieb, *J. Prakt. Chem.* **1934**, *141*, 5.

[11] a) J. T. Edward, *Chem. Org. Sulfur Compd.* **1966**, *2*, 287; b) H. Fujiwara, A. K. Bose, J. M. V. Veen, *J. Chem. Soc. Perkin Trans. 2* **1979**, *5*, 653.

[12] a) E. Colacino, F. Lamaty, J. Martinez, I. Parrot, *Tetrahedron Lett.* **2007**, *48*, 5317; b) A. Ganesan, *Methods Enzymol.* **2003**, *369*, 415; c) J. Va′zquez, M. Royo, F. Albericio, *Lett. Org. Chem.* **2004**, *1*, 224; d) S. H. DeWitt, J. S. Kiely, C. J. Stankovic, M. C. Schroeder, D. M. R. Cody, M. R. Pavia, *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 6909; e) B. A. Dressman, L. A. Spangle, S. W. Kaldor, *Tetrahedron Lett.* **1996**, *37*, 937; f) X. Xiao, K. Ngu, C. Chao, D. Patel, *J. Org. Chem.* **1997**, *62*, 6968; g) A. Nefzi, J. M. Ostresh, M. Giulianotti, R. A. Houghten, *Tet-*

rahedron Lett. **1998**, *38*, 8199; h) P. Y. Chong, S. J. Janicki, P. A. Petillo, *J. Org. Chem.* **1998**, *63*, 8515.
[13] a) W. Zhang, Y. Lu, C. Hiu-Tung Chen, L. Zeng, D. B. Kassel, *J. Comb. Chem.* **2006**, *8*, 687; b) D. Zhang, X. Xing, G. D. Cuny, *J. Org. Chem.* **2006**, *71*, 1750; c) C. Montagne, M. Shipman, *Synlett* **2006**, 14; d) J. M. Ignacio, S. Macho, S. Marcaccini, R. Pepino, S. Manku, D. P. Curran, *J. Org. Chem.* **2005**, *70*, 4470; e) T. Torroba, *Synlett* **2005**, 20; f) M.-J. Lee, C.-M. Sun, *Tetrahedron Lett.* **2004**, *45*, 437; g) M. Meusel, A. Ambrozak, T. K. Hecker, M. Gutschow, *J. Org. Chem.* **2003**, *68*, 4684; h) N. Dieltiens, D. D. Claeys, V. V. Zhdankin, V. N. Nemykin, B. Allaert, F. Verpoort, C. V. Stevens, *Eur. J. Org. Chem.* **2006**, 2649; i) W. Zhang, Y. Lu, C. H.-T. Chen, D. P. Curran, S. Geib, *Eur. J. Org. Chem.* **2006**, 2055.
[14] O. O. Orazzi, R. A. Corral, *Experientia* **1965**, *21*, 508.
[15] A. Volonterio, C. Ramirez de Arellano, M. Zanda, *J. Org. Chem.* **2005**, *70*, 2161.
[16] a) V. Kumar, M. P. Kaushik, *Chem. Lett.* **2005**, *34*, 1230; b) V. Kumar, M. P. Kaushik, *Tetrahedron Lett.* **2005**, *46*, 8121; c) V. Kumar, M. P. Kaushik, *Chem. Lett.* **2006**, *35*, 312; d) V. Kumar, M. P. Kaushik, *Tetrahedron Lett.* **2006**, *47*, 1457; e) V. Kumar, M. P. Kaushik, *Synth. Commun.* **2006**, *36*, 2385; f) V. Kumar, M. P. Kaushik, *Synlett* **2007**, 2937; g) V. Kumar, M. P. Kaushik, *Bull. Chem. Soc. Jpn.* **2008**, *81*, 160.
[17] a) I. Th. Benders, P. H. Hackman, *Recl. Trav. Chim. Pays-Bas* **1972**, *91*, 343; b) O. Wallach, *Ber. Dtsch. Chem. Ges.* **1899**, *39*, 1872; c) W. L. Garbrecht, *J. Org. Chem.* **1953**, *18*, 1003; d) D. Bialey, C. G. deGrazia, H. E. Lape, R. Frering, D. Fort, T. Skulan, *J. Med. Chem.* **1973**, *16*, 151; e) A. E. Kretov, A. P. Momsenko, *Zh. Org. Khim.* **1964**, *1*, 1734; f) H. T. Nagasawa, C. H. Kwon, *US Patent* 4870056, **1989**.
[18] V. Kumar, *Synlett* **2005**, 1638.

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