# Evaluating the one-pot synthesis of hydantoins

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**Dedicated to Professor John L Belletire on the occasion of his 63rd birthday**

**Abstract**
Re-examination of the facile one-pot synthesis of hydantoins is considered. An efficient method was utilized for the synthesis of hydantoins starting with ketones (**3**), (**7**), (**10a**)-(**14a**), benzoin (**8**), benzil (**9**), phenanthrene-9,10-dione (**4)** and aldehydes (**15a**)-(**17a**). Two main and convenient procedures using either i) KCN and $(NH_4)_2$ $CO_3$ or ii) urea and NaOH, EtOH were examined.

**Keywords:** Spirohydantoin, 5-substituted hydantoins, unsymmetrical hydantoin, phenantheren-9,10-dione, 9H-fluoren-9-one

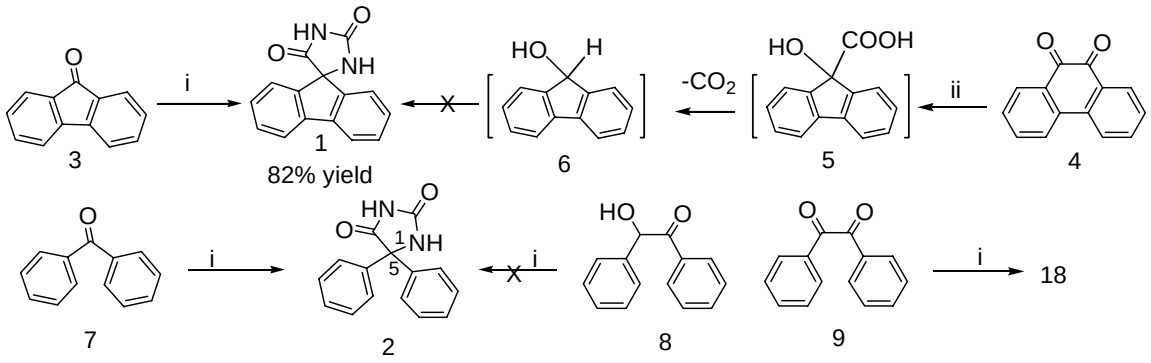
## Introduction

Hydantoin derivatives are synthetically valuable, e.g. as precursors to α-amino acid and pyruvic acid derivatives. [1-4] Hydantoins, originally observed as undesired by-products in the synthesis of peptides, [5-7] and they present a broad range of biological activity. [8-18] Hydantoins substituted at C-5 are important medicinal compounds. Epilepsy is a group of chronic neurological disorders whose symptoms result from a brain dysfunction or an abnormal discharge of cerebral neurons. Drug therapy is the major treatment for epilepsy, and among the major drugs used in its treatment are the hydantoins. The most familiar derivative, 5,5-diphenylhydantoin (phenytoin) (**2**) is extensively used as an anti-convulsant and cardiac antiarrhythmic [8c]. Recently antidepressant [11] antiviral activities [12,13] as well as inhibited binding of HIV to lymphocytes [14] were also reported for hydantoins.

A one-pot synthesis of phenytoin analogues was recently reported by our group. [19-21] Herein we detail a facile route for the syntheses of substituted hydantions such as (**1**), (**2**), (**10b**)-(**17b**) and **18** using ketones, aldehydes, diketones, α-hydroxyketones, and phenantheren-9,10-dione.

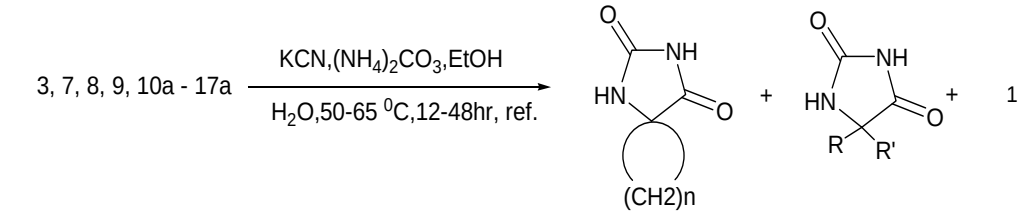
## Results and Discussion

Recently we became interested in the synthesis of novel hydantoins with varying substitution patterns on C-5, utilizing reaction of various aldehydes and ketones with either i) KCN and $(NH_4)_2$ $CO_3$ [22] and ii) urea and NaOH, EtOH. [23] We reported [19] the synthesis of a series of phenytoin analogs similar to (**2**) in 65-78% yields from the corresponding substituted benzils (**9**) and benzoins (**8**). For this current study our initial goal was the one pot preparation of a hydantoin derived from phenantheren-9,10-dione (**4**) in the presence of urea in alkali ethanol solution. Our expectation was that benzilic acid rearrangement and *in-situ* conversion to spirophenytoin (**1**) would occur (Scheme 1).




**Scheme 1**

However, the desired hydantoin (**1**) could not be prepared using this method even under a variety of conditions. These results suggest that the anticipated intermediate 9-hydroxy-9H-fluorene-9-carboxylic acid (**5**) was initially formed but subsequently underwent facile decarboxylation to provide 9-fluorenol (**6**) and a range of other byproducts (Scheme1). In other attempts the formation of target spirohydantoin (**1**) was accomplished by treatment of (**3**) with KCN and $(NH_4)_2$ $CO_3$. Attempts to obtain phenytoin (**2**) by applying the same reaction condition to (**7**) as shown in (Scheme 1) failed.




3) 9-fluorenone, 7) benzophenone, 8) benzoin,
9) benzil, 10a) cyclopentanone, 11a) cyclohexanone,
12a) cyclohexylphenylketone, 13a) 4-chloro-benzophenone,
14a) 4-dimethylaminobenzaldehyde, 15a) 4-methylbenzaldehyde,
17a) 4-chlorobenzaldhyde, 16a) 4-bromobenzaldhyde

2) R = R' = ph
10b) n = 4 11b) n = 5
12b) R = cyclohexyl, R' = ph
13b) R= ph, R' = 4-chlorophenyl
14b) R = 4-dimethyl aminophenyl, R' = H
15b) R = 4-methylphenyl, R' = H
16b) R = 4-bromophenyl, R' =H
17b) R = 4-chlorophenyl, R' = H
18) R = phenyl, R' = H

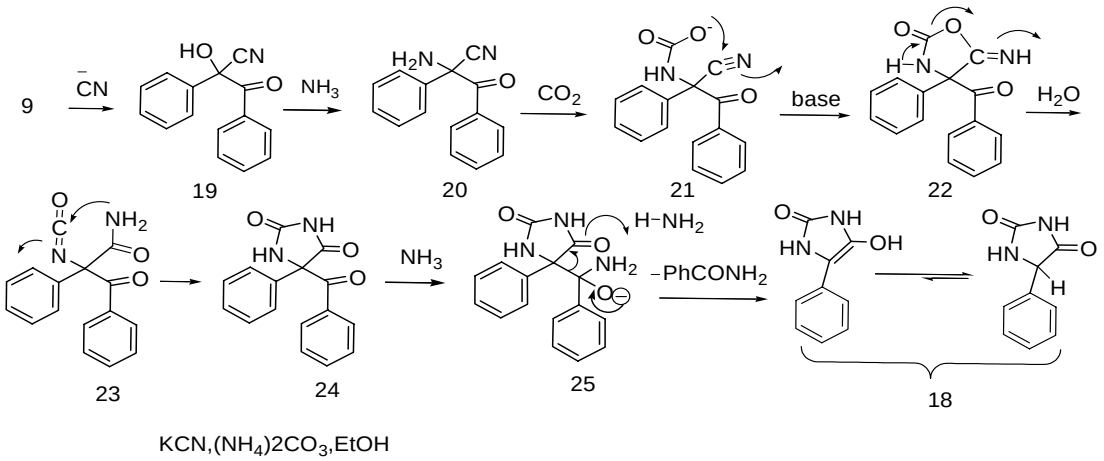
**Scheme 2**

Currently, there are no published data available on synthesis of unsymmetrically substituted hydantoins e.g., (**12b**) and (**13b**) (Scheme 2). The application of reaction condition (i) as described in Scheme1 to ketones (**12a**) and (**13a**) leads to the preparation of the unsymmetrical 5-cyclohexyl-5-phenylimidazolidine-2,4-dione (**12b**) and 5-(4-chlorophenyl)-5-phenylimidazolidine-2,4- dione (**13b**) in 77% and 2% yields, respectively (Table1).Using these conditions a variety of hydantoins substituted at C-5 were synthesized from ketones (**3**), (**7**), (**10a**)-(1**4a**), benzoin (**8**), benzil (**9**), and aldehydes (**15a**)-(**17a**) (Table1 and Scheme 2).

**Table1.** Reaction Time and Yields of Formation of Hydantoins

| Entry | Hydantoin Product | Time (h) | Yield % |
|---|---|---|---|
| **3** | **1** | 24 | 82 |
| **7** | **2** | 24 | trace |
| **8** | **18** | 48 | 100 |
| **9** | **18** | 12 | 53 |
| **10a** | **10b** | 12 | 57 |
| **11a** | **11b** | 12 | 54 |
| **12a** | **12b** | 24 | 77 |
| **13a** | **13b** | 12 | 2 |
| **14a** | **14b** | 48 | 20 |
| **15a** | **15b** | 36 | 92 |
| **16a** | **16b** | 24 | 58 |
| **17a** | **17b** | 24 | 53 |

Both benzil (**9**) and benzoin (**8**), lead to the formation of hydantoin (**18**) in 100% and 57% yields, respectively (Table 1). The formation of (**18**) from both (**8**) and (**9**) suggests that the reaction mechanism leading to (18) utilizing reagent (i) proceeds through similar pathways such as (**19**)-(**24**) as depicted in (Scheme 3).




**Scheme 3**

The ketohydantoin (**24**) reacts further (Scheme 3) with one molecule of $NH_3$ to give the unstable adduct (**25**). Further fragmentation of adduct (**25**) involves debenzoylation via coplanar geometry for maximum facilitation of the concerted movement of three electron pairs into hydantoins (**18**).

## Experimental Section

**General Procedures.** Melting points are uncorrected and determined by Mettler Fp5 melting point apparatus. IR spectra were obtained on a Shimadzu IR-470. Products were characterized by IR, NMR, GC-MS, TLC, and m.p.). All NMR data were recorded in $CDCl_3$, $CD_3COCD_3$ or DMSD-$d_6$ using a Bruker Avance 500-MHz spectrometer. Chemical shifts are reported in ppm (δ) using TMS as internal reference. Mass spectra were obtained from a GC-MS Agilent Technologies QP-5973N MSD instrument.

**Synthesis of (1) from 9- fluorenone (3): a typical procedure**

To a 100mL round bottom flask equipped with a reflux condenser 3g (17 mmol) (**3**), 2.16 g (33 mmol) KCN and 6.38 g (66 mmol) $(NH_4)_2CO_3$ were added to the solution of 50 mL of 50% EtOH. The reaction mixture was stirred and heated to reflux at 50-65 $^oC$, by an oil bath for 24h. The reaction mixture was then cooled to r.t. and filtered. The pH of the aqueous filtrate solution was adjusted to pH of 2-3 by carefully adding conc. HCl so as to facilitate further

recrystallization. The crude material was recrystallized from 96% EtOH, several times giving 3.4g (82 %) of analytically pure, white needle crystals of (**1**).

**Spiro[fluorene-9,4'-imidazolidine]-2',5'-dione (1).** White needles; m.p. >300 $^{o}$C lit 324-325 $^{o}$C dec.[25] (96 % EtOH) ; $^{1}$H NMR (Acetone-$d_6$) δ: 10.1 (s, 1H, $N_3$-H), 7.54 (s, 1H, $N_1$-H), 7.45 (dd, J = 0.9, 0.9 Hz, 2H, ArH), 7.49 (dd, J = 0.9, 0.9 Hz, 2H, ArH), 7.54 (s, 1H, ArH), 7.56 (d, J = 7.5, Hz, 2H, ArH), 7.86 (d, J = 7.5 Hz, 2H, ArH) ; $^{13}$C NMR (DMSO- $d_6$) δ: 174.16 ($C_2$=O), 157.66 ($C_4$=O), 142.94 ($C_{Ar}$), 140.68 ($C_{Ar}$), 129.83 (CAr), 128.35($C_{Ar}$), 123.5 ($C_{Ar}$), 120.73 ($C_{Ar}$), 72.44 ($C_{Spiro}$), IR (KBr, cm$^{-1}$): 3220 (N-H), 3150 (N-H), 3020 (C-H Ar), 1770 ($C_2$=$O_{sym}$), 1720 ($C_4$=$O_{asym}$), 1700 ($C_4$=$O_{asym}$), 1420 (C-H bend); MS: 251 (7), 250 (43), 179 (100), 178 (20), 180 (18), 221 (3), 151 (14), 76 (14); (EI): Exact mass: ($M^+$): calcd for $C_{15}H_{10}N_2O_2$, 250.0742 ; Found 250.0746.

**1,3-Diazaspiro [4.4]nonane-2,4-dione (10b).** White needles; m.p. 208 $^{o}$C (96 % EtOH); $^{1}$H NMR (Acetone-d6) δ: 9.43 (s, 1H, NH), 7.22 (s, 1H, NH), 2.06 (p, J = 2.15 Hz, 4H, 2 x $CH_2$), 1.82 (t, J = 1.86 Hz, 4H, 2 x $CH_2$); $^{13}$C NMR (DMSO-$d_6$) δ: 176.50 ($C_2$=O), 157.44 ($C_4$=O), 70.23 ($C_{Spiro}$), 34.84 ($C_{Ar}$), 22.31($C_{Ar}$); (IR (KBr, cm$^{-1}$): 3200 (N-H), 3050 (N-H), 2950 (C-H), 1775 ($C_2$=$O_{sym}$), 1735 ($C_4$=$O_{asym}$), 1410 ($CH_2$) ; MS ; 155 (3), 154 (55), 127 (100), 112 (26), 89 (19), 83 (22), 54 (30) ; (EI): Exact mass: ($M^+$) : calcd for $C_7H_{10}N_2O_2$, 154.0742; Found 154.0746.

**1,3-Diazaspiro [4.5]decane-2,4-dione (11b).** White needles; m.p. 220 °C (96 % EtOH); $^{1}$H NMR (Acetone-d6) δ: 9.35 (s, 1H, NH), 7.4 (s, 1H, NH), 2.06 (p, J = 2.09 Hz, 10H, 5 x CH2); $^{13}$C-NMR (Acetone-$d_6$) δ: 179.61 ($C_2$=O), 157.51 ($C_4$=O), 62.89 ($C_{Spiro}$), 39.76 ($C_{Ar}$), 25.33 ($C_{Ar}$), 21.71 ($C_{Ar}$); IR (KBr, cm$^{-1}$): 3200 (N-H), 3050 (N-H), 2925 (C-H), 1770 ($C_2$=$O_{sym}$), 1720 ($C_4$=$O_{asym}$), 1460 ($CH_2$) ; MS : 169 (9), 168 (91),139 (10), 113 (100), 127 (80), 96 (25), 89 (15), 82 (15), 69 (25), 54 (50); (EI): Exact mass: ($M^+$): calcd for $C_8H_{12}N_2O_2$,168.0899 ; Found 168.0896.

**Phenytoin (2).** White needles; m.p. 292 $^{o}$C (lit.286-295 $^{o}$C)[19] (96 % EtOH); $^{1}$H NMR (DMSO-$d_6$) δ: 10.7 (s, 1H, N-H), 8.9 (s, 1H, N-H), 7.2 (m, 10H, ArH); $^{13}$C NMR (DMSO-$d_6$) δ: 1707 ($C_4$=O),160 (C=O), 143.22 ($C_{Ar}$), 129.56 ($C_{Ar}$), 128.41($C_{Ar}$), 126.35($C_{Ar}$), 75.52 ($C_{Spiro}$); IR (KBr, cm-$^{1}$): 3270 (N-H), 3200 (N-H), 1770 ($C_2$=$O_{sym}$), 1730 ($C_4$=$O_{asym}$), 1710 ($C_4$=$O_{asym}$), 1400, 760, 740; MS: (EI): exact mass: calcd for $C_{15}H_{12}N_2O_2$, 252.0899; Found 252.0896.

**5-Cyclohexyl-5-phenylimidazolidine-2,4-dione (12b).** White needles; m.p. 230 $^{o}$C (96 % EtOH); $^{1}$H NMR (DMSO-$d_6$) δ: 10.71 (s, 1H, $N_3$-H), 8.69 (s, 1H, $N_1$-H), 7.5 (d, J = 7.86 Hz, 2H, ArH), 7.37 (t, J = 7.2 Hz, 2H, ArH), 7.29 (t, J = 7.56 Hz, 1H, ArH), 2.07 (t, J= 11.33 Hz, 1H, C-H), 1.71H (d, J = 12.3 Hz, 1H, C-H), 1.57 (d, J = 10.40 Hz, 2H, C-H), 1.51 (d, J = 11.57 Hz, 1H, $CH_2$), 1.22 (t, J = 12.29 Hz, 1H, C-H), 1.13 (t, J = 12.6 Hz, 1H, C-H), 1.04 (t, J = 11.23 Hz, 3H, $CH_2$, CH), 0.93 (m, J = 12.18 Hz, 1H, ArH); $^{13}$C (Acetone-$d_6$) δ, 173.87 ($C_2$=O), 157.27 ($C_4$=O), 136.49 (C-Ar), 129.09 (C-Ar), 128.77 (C-Ar), 127.11 (C-Ar), 63.25 ($C_{spir}$) 39.56 ($C_{cycl}$), 26,12 ($C_{cycl}$) 25.43 ($C_{cycl}$), 21.71 ($C_{cycl}$), IR (KBr, cm-$^{1}$): 3330 (N-H), 3200 (N-H), 3050 (Ar-H), 2900 (C-H), 2850 (C-H), 1765 ($C_2$=$O_{sym}$), 1700 ($C_4$=$O_{asym}$); MS: ($M^+$): (EI): exact mass: calcd for $C_{15}H_{18}N_2O_2$, 258.1308 ; found 258.1368.

**5-(4-Chlorophenyl)-5-phenylimidazolidine-2,4-dione (13b).** White needles; m.p. 240 $^{o}$C dec. (96 % EtOH); $^{1}$H NMR (DMSO) δ: 11.06 (s, 1H, $N_3$-H ), 9.30 (s, 1H, $N_1$-H), [7.47 (d, J = 7.09 Hz, 2H, ArH), 7.38 m, J = 7.2Hz, 2H, ArH), 7.29 (t, J = 7.56 Hz, 1H, ArH), 7.32 (d, J = 7.16 Hz) 4H, ArH)] ;$^{13}$C (DMSO-$d_6$): δ; 174.53 ($C_2$=O), 155.88 ($C_4$=O), 139.62 ($C_{Ar}$), 138.76 ($C_{Ar}$), 132.90 ($C_{Ar}$), 128.64 ($C_{Ar}$) , 128.54 ($C_{Ar}$), 128.51 ($C_{Ar}$), 126.5 ($C_{Ar}$) ,69.75 ($C_{Spiro}$); IR (KBr, cm-$^{1}$): 3200 (N-H), 3100 (N-H), 3050 (ArH), 1770 ($C_2$=$O_{sym}$), 1715 ($C_4$=$O_{asym}$), 1485 (C-H bend); MS; (EI): exact mass: calcd for $C_{15}H_{11}ClN_2O_2$, 286.0509; Found 286.0512.

**5-(4-(Dimethylamino)phenyl)imidazolidine-2,4-dione (14b).** Pale yellow crystals; m.p. >300 $^{o}$C (96 % EtOH); $^{1}$H NMR (DMSO): Free base (DMSO-$d_6$): 10.57 (s, 1H, $N_3$-H), 8.73(s, 1H, $N_1$-H), 7.37 (s, 2H, ArH). 6.60 (s, 1H, ArH) 6.59 (s, 1H, ArH), 2.88 (s, 6H, 2 x CH3); $^{13}$C NMR (DMSO): δ; 173.86 ($C_2$=O), 164.65 (C=N), 158.66, ($C_4$=O), 134.43 ($C_{Ar}$), 130.55 ($C_{Ar}$), 124.84 ($C_{Ar}$), 120.08 ($C_{Ar}$), 40.43 (CH3); IR (KBr, cm$^{-1}$): 3325 (N-H), 3200 (N-H), 3050 (ArH), 1770 ($C_2$=$O_{sym}$), 1720 ($C_4$=$O_{asym}$), 1705 ($C_4$=$O_{asym}$), 1660 (C=C); MS; (EI): 220 (27), 205 (100), 127 (86), 89 (18), 57 (11); (EI): ($M^+$): Exact mass: calcd for $C_{11}H_{13}N_3O_2$, 219.1008 ; Found 219.1012.

**5-p-Tolylimidazolidine-2,4-dione (15b).** White needles; m.p. 220 $^{o}$C dec (96 % EtOH); $^{1}$H NMR Salt (DMSO-$d_6$) δ: 10.61 (s, 1H, $N_3$-H), 7.97 (s, 1H, $N_1$-H), 7.57 (s, 1H, C-H), 7.78 (d, J = 8.25 Hz, 2H, ArH), 7.43 (d, J = 8.52 Hz, 2H, ArH), 2.36 (s, 3H, $CH_3$); $^{13}$C NMR (DMSO-$d_6$): δ: 173.71 ($C_2$=O), 157.62, ($C_4$=O), 136.43 ($C_{Ar}$), 129.35 ($C_{Ar}$), 128.69 ($C_{Ar}$), 127.95 ($C_{Ar}$), 62.88 ($C_{Spiro}$), 20.95 ($CH_3$); IR (KBr, cm-$^{1}$): 3390 (N-H), 3300 (N-H) 3200 (ArH), 2900 (C-H), 1690 (C=$O_{sym}$), 1670 (C=$O_{asym}$), 1600 (C=C), 1380 (CH3); MS: 192 (20), 191 (5) 190 (36), 132 (72), 129 (27), 127 (100), 115 (25), 105 (77), 91 (25); (EI): ($M^+$): Exact mass: calcd for $C_{10}H_{10}N_2O_2$; Exact Mass: 190.0742; Found 190.0741.

**5-(4-Bromophenyl)imidazolidine-2,4-dione (16b).** White crystals; m.p. >300 $^{o}$C (96 % EtOH); $^{1}$H NMR Free base (DMSO-$d_6$): 10.62 (s, 1H, $N_3$-H), 7.97 (s, 1H, $N_1$-H), 7.87 (d, J = 8.61 Hz, 2H, ArH). 7.70 (d, J = 8.62 Hz, 2H, ArH), 7.42 (s, 1H, C-H); Salt (DMSO-$d_6$): 10.61 (s, 1H, $N_3$-H), 7.97 (s, 1H, $N_1$-H), 7.78 (d, J = 8.25 Hz, 1H), 7.57 (s, 1H, ArH), 7.43 (d, J = 8.52 Hz, 2H, ArH), 5.4 (s, 1H, C-H); IR (KBr, cm-$^{1}$): Free base: 3350 (N-H), 3200(N-H), 2950 (C-H), 1700 ($C_2$=$O_{sym}$), 1660 ($C_4$=$O_{asym}$), 1590 (C=C), 1460 ($CH_2$ ), 800 (C-Br) ; Salt : 3300 (N-H), 3200 (N-H), 1720(sym C=O), 1690 (asym C=O), 1595 (asym C=O), 1480 ($CH_2$), 810 (C-Br); $^{13}$C NMR (DMSO-$d_6$): δ: 174.21 ($C_2$=O), 156.62, ($C_4$=O), 135.83 ($C_{Ar}$), 131.85 ($C_{Ar}$), 132.69 ($C_{Ar}$), 122.95 ($C_{Ar}$), 61.88 ($C_{Spiro}$), MS: 212 (20), 211 (6), 210 (63), 182 (9), 138 (100), 132 (45), 111 (17), 75 (18), 50 (9); (EI): ($M^+$): Exact mass: calcd for $C_9H_7BrN_2O_2$, 253.9691; Found 253.9689.

**5-(4-Chlorophenyl)imidazolidine-2,4-dione (17b).** White powdery crystals; >290 $^{o}$C (96 % EtOH); $^{1}$H NMR Salt (DMSO-$d_6$): 10.83 (s, 1H, $N_3$-H), 8.42 (s, 1H, $N_1$-H), 7.45 (d, J = 7 Hz, 2H, ArH), 7.35 (d, J = 7.07 Hz, 2H, ArH), 5.19 (s, 1H, C-H); $^{13}$C NMR (DMSO-$d_6$) δ: 174.29 ($C_2$=O), 156.64, ($C_4$=O), 134.93 ($C_{Ar}$), 128.81 ($C_{Ar}$), 129.39 ($C_{Ar}$), 133.35 ($C_{Ar}$), 61.94 ($C_{Spiro}$), IR (KBr, cm-$^{1}$): 3325 (N-H), 3200 (N-H), 3050 (ArH), 1770 ($C_2$=$O_{sym}$), 1720 ($C_4$=$O_{asym}$), 1490 ($CH_2$), 1420 (m), 1390 (m), 820 (C-Cl); MS: 212 (20), 210 (63), 211 (6), 182 (9), 138 (100), 132 (45), 111 (17), 75 (18); (EI): ($M^+$): Exact Mass: for $C_9H_7ClN_2O_2$ ; 210.0196; Found 210.0193.

**5-Phenylimidazolidine-2,4-dione (18).** Very pale brown powdery crystals; m.p. 163$^{o}$C (96 % EtOH); $^{1}$H NMR (DMSO-$d_6$) δ: 10.78 (s, 1H, $N_3$-H), 8.39 (s, 1H, $N_1$-H), [7.39(t, J = 6.59 Hz), 7.34 (d, J = 10.78 Hz), 7.32 (d, J = 7.51 Hz)] 5H, ArH), 5.15 (s, 1H, C-H); $^{13}$C (Acetone-$d_6$), 173.77 ($C_4$=O), 157.67 ($C_2$=O), 136.49 $C_{Ar}$, 129.09 $C_{Ar}$, 128.77 $C_{Ar}$, 127.11 $C_{Ar}$, 62.26 ($C_{spir}$); IR (KBr, cm-$^{1}$): 3500 (N-H), 3300 (N-H), 3150 (ArH), 3025 (ArH), 1745 (sym C=O), 1720 ($C_2$=$O_{asym}$), 1710 ($C_4$=$O_{sym}$), 1450 (m), 1420 (s); MS: 177 (1), 176 (10), 127 (100), 104 (15), 89 (16), 51 (5) ; (EI): Exact mass: calcd for $C_9H_8N_2O_2$; 176.0586; Found 176.0584.

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