

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

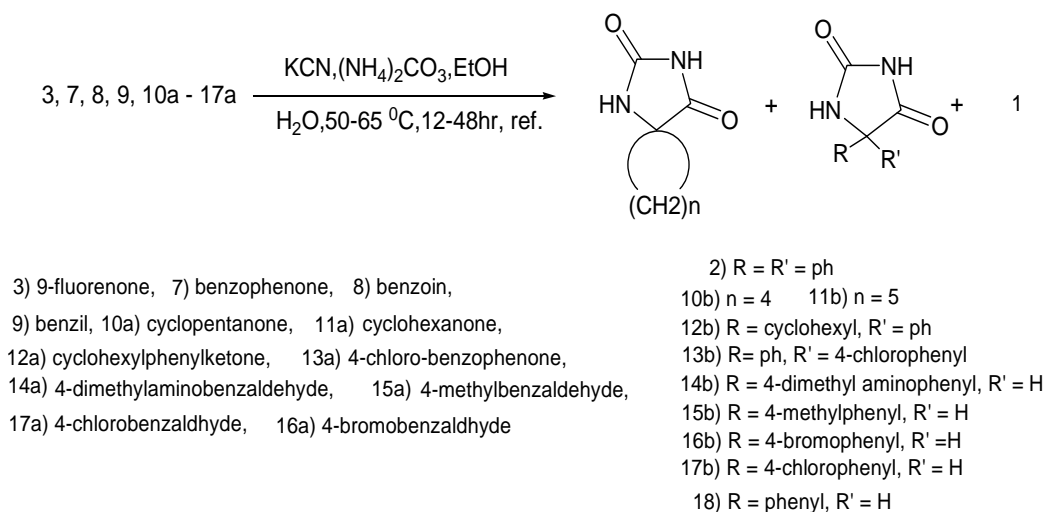
Re-examination of the facile one-pot synthesis of hydantoins is considered. An efficient method was utilized for the synthesis of hydantoins starting with ketones (**3**), (**7**), (**10a**)-(14a), benzoin (**8**), benzil (**9**), phenanthrene-9,10-dione (**4**) and aldehydes (**15a**)-(17a). Two main and convenient procedures using either i) KCN and (NH₄)₂ CO₃ or ii) urea and NaOH, EtOH were examined.

Keywords: Spirohydantoin, 5-substituted hydantoins, unsymmetrical hydantoin, phenanthren-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 antidepressant¹¹ antiviral activities^{12,13} as well as inhibited binding of HIV to lymphocytes¹⁴ 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 phenanthren-9,10-dione.



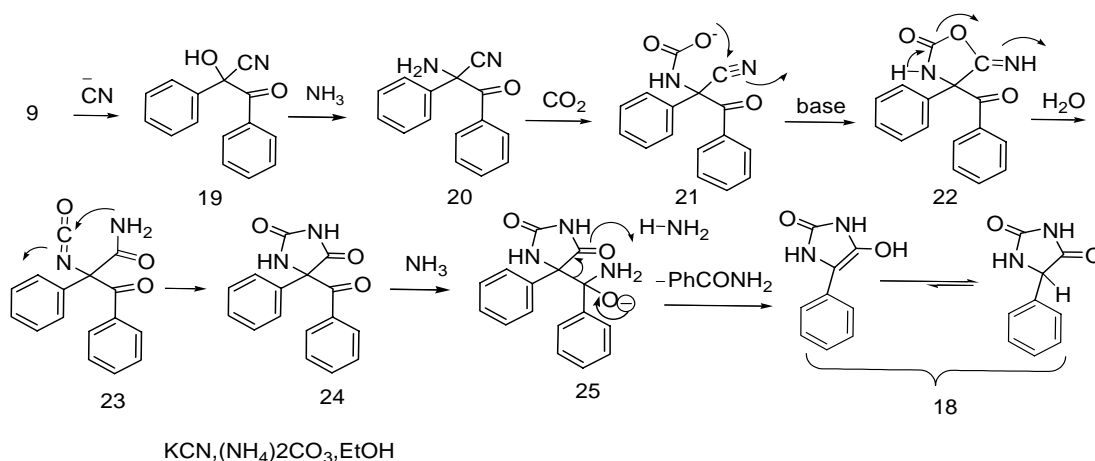
Scheme 2

Currently, there are no published data available on synthesis of unsymmetrically substituted hydantoin e.g., (**12b**) and (**13b**) (Scheme 2). The application of reaction condition (i) as described in Scheme 1 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 (Table 1). Using these conditions a variety of hydantoin substituted at C-5 were synthesized from ketones (**3**), (**7**), (**10a**)-(14a), benzoin (**8**), benzil (**9**), and aldehydes (**15a**)-(17a) (Table 1 and Scheme 2).

Table 1. Reaction Time and Yields of Formation of Hydantoin

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 NH₃ 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 hydantoin (**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 CDCl₃, CD₃COCD₃ or DMSD-d₆ 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) (NH₄)₂CO₃ were added to the solution of 50 mL of 50% EtOH. The reaction mixture was stirred and heated to reflux at 50-65 °C, 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 °C lit 324-325 °C dec.²⁵ (96 % EtOH); ¹H NMR (Acetone-d₆) δ: 10.1 (s, 1H, N₃-H), 7.54 (s, 1H, N₁-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); ¹³C NMR (DMSO- d₆) δ: 174.16 (C₂=O), 157.66 (C₄=O), 142.94 (C_{Ar}), 140.68 (C_{Ar}), 129.83 (C_{Ar}), 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 (C₂=O_{sym}), 1720 (C₄=O_{asym}), 1700 (C₄=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 C₁₅H₁₀N₂O₂, 250.0742 ; Found 250.0746.

1,3-Diazaspiro [4.4]nonane-2,4-dione (10b). White needles; m.p. 208 °C (96 % EtOH); ¹H NMR (Acetone-d₆) δ: 9.43 (s, 1H, NH), 7.22 (s, 1H, NH), 2.06 (p, J = 2.15 Hz, 4H, 2 x CH₂), 1.82 (t, J = 1.86 Hz, 4H, 2 x CH₂); ¹³C NMR (DMSO-d₆) δ: 176.50 (C₂=O), 157.44 (C₄=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 (C₂=O_{sym}), 1735 (C₄=O_{asym}), 1410 (CH₂); MS ; 155 (3), 154 (55), 127 (100), 112 (26), 89 (19), 83 (22), 54 (30); (EI): Exact mass: (M⁺) : calcd for C₇H₁₀N₂O₂, 154.0742; Found 154.0746.

1,3-Diazaspiro [4.5]decane-2,4-dione (11b). White needles; m.p. 220 °C (96 % EtOH); ¹H 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); ¹³C-NMR (Acetone-d₆) δ: 179.61 (C₂=O), 157.51 (C₄=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 (C₂=O_{sym}), 1720 (C₄=O_{asym}), 1460 (CH₂); 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 C₈H₁₂N₂O₂,168.0899 ; Found 168.0896.

Phenytain (2). White needles; m.p. 292 °C (lit.286-295 °C)¹⁹ (96 % EtOH); ¹H NMR (DMSO-d₆) δ: 10.7 (s, 1H, N-H), 8.9 (s, 1H, N-H), 7.2 (m, 10H, ArH); ¹³C NMR (DMSO-d₆) δ: 1707 (C₄=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 (C₂=O_{sym}), 1730 (C₄=O_{asym}), 1710 (C₄=O_{asym}), 1400, 760, 740; MS: (EI): exact mass: calcd for C₁₅H₁₂N₂O₂, 252.0899; Found 252.0896.

5-Cyclohexyl-5-phenylimidazolidine-2,4-dione (12b). White needles; m.p. 230 °C (96 % EtOH); ¹H NMR (DMSO-d₆) δ: 10.71 (s, 1H, N₃-H), 8.69 (s, 1H, N₁-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, CH₂), 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, CH₂, CH), 0.93 (m, J = 12.18 Hz, 1H, ArH); ¹³C (Acetone-d₆) δ, 173.87 (C₂=O), 157.27 (C₄=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 (C₂=O_{sym}), 1700 (C₄=O_{asym}); MS: (M⁺): (EI): exact mass: calcd for C₁₅H₁₈N₂O₂, 258.1308 ; found 258.1368.

5-(4-Chlorophenyl)-5-phenylimidazolidine-2,4-dione (13b). White needles; m.p. 240 °C dec. (96 % EtOH); ^1H NMR (DMSO) δ : 11.06 (s, 1H, N₃-H), 9.30 (s, 1H, N₁-H), [7.47 (d, J = 7.09 Hz, 2H, ArH), 7.38 (m, J = 7.2 Hz, 2H, ArH), 7.29 (t, J = 7.56 Hz, 1H, ArH), 7.32 (d, J = 7.16 Hz) 4H, ArH]; ^{13}C (DMSO-d₆): δ : 174.53 (C₂=O), 155.88 (C₄=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 (C₂=O_{sym}), 1715 (C₄=O_{asym}), 1485 (C-H bend); MS; (EI): exact mass: calcd for C₁₅H₁₁ClN₂O₂, 286.0509; Found 286.0512.

5-(4-(Dimethylamino)phenyl)imidazolidine-2,4-dione (14b). Pale yellow crystals; m.p. >300 °C (96 % EtOH); ^1H NMR (DMSO): Free base (DMSO-d₆): 10.57 (s, 1H, N₃-H), 8.73 (s, 1H, N₁-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 (C₂=O), 164.65 (C=N), 158.66, (C₄=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 (C₂=O_{sym}), 1720 (C₄=O_{asym}), 1705 (C₄=O_{asym}), 1660 (C=C); MS; (EI): 220 (27), 205 (100), 127 (86), 89 (18), 57 (11); (EI): (M⁺): Exact mass: calcd for C₁₁H₁₃N₃O₂, 219.1008; Found 219.1012.

5-p-Tolylimidazolidine-2,4-dione (15b). White needles; m.p. 220 °C dec (96 % EtOH); ^1H NMR Salt (DMSO-d₆) δ : 10.61 (s, 1H, N₃-H), 7.97 (s, 1H, N₁-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, CH₃); ^{13}C NMR (DMSO-d₆): δ : 173.71 (C₂=O), 157.62, (C₄=O), 136.43 (C_{Ar}), 129.35 (C_{Ar}), 128.69 (C_{Ar}), 127.95 (C_{Ar}), 62.88 (C_{Spiro}), 20.95 (CH₃); 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 C₁₀H₁₀N₂O₂; Exact Mass: 190.0742; Found 190.0741.

5-(4-Bromophenyl)imidazolidine-2,4-dione (16b). White crystals; m.p. >300 °C (96 % EtOH); ^1H NMR Free base (DMSO-d₆): 10.62 (s, 1H, N₃-H), 7.97 (s, 1H, N₁-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-d₆): 10.61 (s, 1H, N₃-H), 7.97 (s, 1H, N₁-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 (C₂=O_{sym}), 1660 (C₄=O_{asym}), 1590 (C=C), 1460 (CH₂), 800 (C-Br); Salt: 3300 (N-H), 3200 (N-H), 1720 (sym C=O), 1690 (asym C=O), 1595 (asym C=O), 1480 (CH₂), 810 (C-Br); ^{13}C NMR (DMSO-d₆): δ : 174.21 (C₂=O), 156.62, (C₄=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 C₉H₇BrN₂O₂, 253.9691; Found 253.9689.

5-(4-Chlorophenyl)imidazolidine-2,4-dione (17b). White powdery crystals; >290 °C (96 % EtOH); ^1H NMR Salt (DMSO-d₆): 10.83 (s, 1H, N₃-H), 8.42 (s, 1H, N₁-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-d₆) δ : 174.29 (C₂=O), 156.64, (C₄=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 (C₂=O_{sym}), 1720 (C₄=O_{asym}), 1490 (CH₂), 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 C₉H₇ClN₂O₂; 210.0196; Found 210.0193.

5-Phenylimidazolidine-2,4-dione (18). Very pale brown powdery crystals; m.p. 163°C (96 % EtOH); ¹H NMR (DMSO-d₆) δ: 10.78 (s, 1H, N₃-H), 8.39 (s, 1H, N₁-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); ¹³C (Acetone-d₆), 173.77 (C₄=O), 157.67 (C₂=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 (C₂=O_{asym}), 1710 (C₄=O_{sym}), 1450 (m), 1420 (s); MS: 177 (1), 176 (10), 127 (100), 104 (15), 89 (16), 51 (5); (EI): Exact mass: calcd for C₉H₈N₂O₂; 176.0586; Found 176.0584.

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