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# Synthesis of 3-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione and 1,3-dipentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione

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**Abstract**

A novel *N3*-alkylation of 5-(4-chlorobenzylidene)imidazolidine-2,4-dione with 1-chloropentane in the presence of a base potassium carbonate was carried out in *N,N*-dimethyl formamide at 70 °C and 100 °C for 24 hours. At 70 °C, two products were obtained as 3-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **5** and the unexpected 1,3-dipentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **6** with the respective yields of 11% and 12%. Meanwhile, a two-fold increase of the synthetic yield of **5** (22%) was obtained when the reaction was undertaken at higher temperature (100 °C). Both products were characterized through several spectroscopic methods and reported as novel compounds.

Keywords: Hydantoin; Knoevenagel Condensation; Amide Alkylation; Heterocyclic Synthesis.

## 1. Introduction

Hydantoin **1** or imidazolidine-2,4-dione has been extensively studied for years. As a scaffold compound, hydantoin could be derived to create large libraries with varied novel synthetic methods [1]. In medicinal chemistry, its analogues exhibit biological and pharmaceutical properties [2-9]. Our previous work showed that 5-benzylidenehydantoins generate antimicrobial activities against *Candida albicans*, *Malassezia furfur*, *Escherichia coli* and *Staphylococcus aureus* [10]. 5-Benzalhydantoins with *n*-butyl at *N-3* position showed their high activity and specificity towards particular microorganism [10].

In this paper, it was decided to synthesize 3-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione in order to add the libraries of the N-3 alkylated benzalhydantoin. The targeted compound could be obtained with two distinct strategies. Firstly, a direct alkylation of hydantoin can be performed using base catalyst then followed by Knoevenagel condensation with benzaldehyde. Unfortunately, the yields are low due to unexpected intermediate racemic alcohol [11]. Secondly, this study can be accomplished using a two-component process namely "benzalhydantoin alkylation". It is possible that *N*-3-alkyl-substituted benzalhydantoins might be more efficiently obtained through 3-alkylation of the preformed benzalhydantoins.

## 2. Experimental

### 2.1 General

All chemicals solvents were purchased from Sigma-Aldrich Chemical Company. All solvents employed were of analytical grade and used without further purification. Thin-layer chromatography was conducted in silica gel $GF_{254}$. The melting points were obtained using a Mettler Toledo digital melting point apparatus and are uncorrected. Infra-red spectra were obtained on Perkin Elmer FTIR with potassium bromide (KBr) pellets. Exact masses were obtained using high resolution mass spectrometer (Waters Xevo QTOF HR-MS Lockspray). $^{1}H$ and $^{13}C$ NMR spectra were recorded on Agilent 500 MHz and 125 MHz spectrometers respectively in DMSO-$d_6$ and $CDCl_3$ were internally referenced relative to the solvent nuclei.

### 2.2 Synthesis of 5-(4-chloro-benzylidene)imidazolidine-2,4-dione

Hydantoin **1** (1.00 g, 10 mmol), ammonium acetate (0.85 g, 11 mmol), 5 mL of acetic acid glacial and the mixture were stirred. Then, 5 mL 4-chlorobenzaldehyde **2** (1.55 g, 11 mmol) was added

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at r.t and the mixture warmed to reflux for 7 hours at 115-116 °C. After reaction was completed, saturated sodium bicarbonate solution was added to the mixture. Precipitate was filtrated with vacuum and washed with cold water and ethanol. Compound was purified by recrystallization from ethanol to give 5-(4-chlorobenzylidene)imidazolidine-2,4-dione **3** as colorless needles 1,34 gram (60%); Mp. 292-294 °C (Lit. 294-296 °C); UV (MeOH) $\lambda_{max}$ (logε) 319 (4.28) nm; IR (KBr)$\nu_{max}$ 3227 (N-H), 1795 (C=O), 1733 (C=O), 1660(C=C) $cm^{-1}$; $^{1}$H NMR (500MHz, DMSO-$d_6$) **δ** ppm: 6.40 (s, 1H, H7'), 7.43 (d, 1H, *J* = 7.4 Hz, H2'), 7.45 (d, 1H, H6'), 7.62 (d, 1H, *J* = 7.7 Hz, H3'), 7.64 (d, 1H, H5'), 10.59 (s, 1H, N-1H), 11.28 (s, 1H, N-3H); $^{13}$C-NMR (DMSO-$d_6$, 125 MHz) **δ** ppm: 165.0 (C, C4), 156.0 (C, C2), 132.0 (C, C4'), 131.9 (C, C1'), 131.0 (CH, C2' and C6'), 128.0 (C, C5), 128.7 (CH, C3' and C5'), 107.0 (CH, C7'); HR-ESI-TOFMS: *m/z* 223.0047($M^+[^{35}Cl]$,100%), 225.0085($M^+[^{37}Cl]$,40%) calculated for $C_{10}H_7N_2O_2Cl$.

2.3 Synthesis of 3N-pentyl-5-(4-chloro-benzylidene)imidazolidine-2,4-dione **5** and 1N,3N-dipentyl-5-(4'-chlorobenzylidene)imidazolidine-2,4-dione **6**

5-(4'-chlorobenzylidene)imidazolidine-2,4-dione **3** (0.73 g, 3.3 mmol), 1-chloropentane **4** (0.80 mL, 6.6 mmol) and potassium carbonate (1.87 g, 13.5 mmol) were mixed together with *N*,*N*-dimethyl formamide 30 mL in round bottom flask 50 mL. Reaction temperature was adjusted to desired level (room temperature, 70 °C or 100 °C), then stirred for 24 hours. Reaction mixtures was monitored by TLC and stopped. Then, it was filtrated. Filtrate was poured into water. The volume of water is set at ten times the volume of filtrate. Mixture were extracted repeatedly with ethyl acetate and washed with saturated brine solution. After washing completed, ethyl acetate extract was dried with sodium sulfate anhydrous and evaporated with rotary evaporator at 40 °C. Obtained crude products (0.35 g) was then purified by column chromatography silica gel 60 (70-230 and 230-400 mesh) with isocratic elution (hexane-ethyl acetate 9:1 (*v*/*v*)) to give novel compounds of 3*N*-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **5** and unexpected product 1*N*,3*N*-dipentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **6.**

3*N*-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **5**: colorless needles at 70 °C: 113 mg (11 %) at 100 °C: 226 mg (22%) Rf 0.2 (hexane/ethyl acetate, 9:1 (v/v)); Mp. 202,5-203,5 °C; UV (EtOH) $\lambda_{max}$ (logε) 237 (3.80), 321 (4.15) nm; IR spectrum $\nu_{max}$ (KBr): 3294 (stretch N-H), 2954 (stretch C-H), 1771 (stretch C=O), 1761 (stretch C=O), 1653 (stretch C=C) $cm^{-1}$; $^{1}$H NMR (500 MHz, DMSO-$d_6$) **δ** ppm: 10.83 (1H, s, N1-H), 7.65-7.67 (d, 2H, *J* = 8.6 Hz, H3' and H5'), 7.45-7.47 (d, 2H, *J* = 8.55 Hz, H2' and H6'), 6.52 (s, 1H, H7'), 3.46 (t, 2H, *J* = 7.13 Hz, H8'), 1.26-1.33 (m, 2H, H9'), 1.19-1.33 (m, 4H, H10' and H11'), 0.86 (t, 3H, *J* = 7.15 Hz, H12'); $^{13}$C NMR (125 MHz, DMSO-$d_6$) **δ** ppm: 164.0 (C, C4), 155.2 (C, C2), 133.0 (C, C4'), 131.8 (C, C1'), 131.1 (CH, C5' and C3'), 128.7 (CH, C6' and C2'), 127.0 (C, C5), 107.9 (CH, C7'), 37.9 (CH2, C8'), 28.3 (CH2, C9'), 27.2 (CH2, C10'), 21.6 (CH2, C11'), 13.8 (CH3, C12'); HR-TOF-MS *m/z* 293.1068 ($M^+[^{35}Cl]$) 295.1098 ($M^+[^{37}Cl]$) (calcd. for $C_{15}H_{18}O_2N_2Cl$, 293.7729).

1*N*,3*N*-dipentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **6**: bright yellow viscous oil 149 mg (12%) Rf 0.4 (hexane/ethyl acetate, 9:1 (v/v)); UV (hexane) $\lambda_{max}$ (log ε) 228 (3.93), 306 (3.96) nm; IR spectrum $\nu_{max}$ (KBr): 2957 (stretch C-H), 1769 (stretch C=O), 1720 (stretch C=O), 1662 (stretch C=C) $cm^{-1}$; $^{1}$H NMR (500 MHz, $CDCl_3$) **δ** ppm: 7.37 (d, 2H, *J* = 8.3 Hz, H3' and H5'), 7.23 (d, 2H, *J* = 8.5 Hz, H2' and H6'), 6.84 (s, 1H, H7'), 3.60 (t, 2H, *J* = 7.3 Hz, H8'), 3.51 (t, 2H, *J* = 7.5 Hz, H13'), 1.67 (m, 2H, H9'), 1.33 (m, 4H, H10' and H14'), 1.11 (m, 2H, H11'), 1.04 (m, 2H, H15'), 0.90 (t, 3H, *J* = 7.1 Hz, H12'), 0.86 (m, 2H, H16'), 0.73 (t, 3H, *J*= 7.3 Hz, H17'). $^{13}$C NMR (125 MHz, $CDCl_3$) **δ** ppm: 163.8 (C4), 155.5 (C2), 134.3 (C4'), 131.7 (C1'), 130.4 (C5' and C3'), 128.8 (C6' and C2'), 128.4 (C5), 110.3 (C7'), 41.6 (CH2, C8'), 39.2 (CH2, C13'), 28.8 (CH2, C9'), 28.2 (CH2, C14'), 27.8 (CH2, C10'), 27.1 (CH2, C15'), 22.2 (CH2, C11'), 21.95 (CH2, C16'), 13.9 (CH3, C12'), 13.7 (CH3, C17'); HR-TOF-MS m/z 363.1844 ($M^+[^{35}Cl]$) 365.1896 ($M^+[^{37}Cl]$) (calcd. for $C_{20}H_{27}N_2O_2Cl$ 362.8994).

## 3. Result and Discussion

The first step of synthesis was the reaction between hydantoin **1** and 4-chlorobenzaldehyde **2** (Scheme 1). This Knoevenagel type condensation was proceeded with ammonium acetate as catalyst with acetic acid glacial as solvent in reflux system [12]. The course of reaction was monitored by TLC until all reactants were consumed. Previously, our group synthesized compound **3** with ethanolamine [13] and potassium acetate [14] and resulted 12% and 39%, respectively. Changing the condition to ammonium acetate has improved the yield to 60%. Geometric isomer that arises from compound **3** can be identified by $^{1}$H-NMR [15]. *E*- and *Z*-isomer shifted slightly different, particularly in its vinyl protons and aryl protons (H *ortho* and H *meta*). Vinyl proton of *E*-isomer is located around δH 6.28 - 6.37

while *Z*-isomer is more deshielded and located around δH 6.40 - 6.62. In benzene area, H *ortho* of *E*-isomer is more deshielded (δH 7.90 - 7.98) than the corresponding one in *Z*-isomer (δH 7.34 - 7.64) [8]. Vinyl proton of compound **3** showed two singlet signal at δH 6.40 and 6.28 with integration ratio (*Z*/*E*) = 1.0 : 0.1. Meanwhile, H *ortho* of compound **3** showed doublet signal in δH 7.64 (*Z*-isomer) and δH 7.93 (*E*-isomer) with integration ratio (*Z*/*E*) = 2.2: 0.2 (see supplementary file). Hence, *Z*-isomer is the main product, resulted from this Knoevenagel-like condensation under current given reaction condition (see experimental data).

Route to the synthesis of 3*N*-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **5** was given in Scheme 1. 5-(4-chlorobenzylidene)imidazolidine-2,4-dione **3** was further reacted with alkylating agent 1-chloropentane **4**. Alkylation was proceeded with inorganic base $K_2CO_3$ that serves as a catalyst in DMF as aprotic solvent since the reaction was via a bimolecular nucleophilic substitution ($SN_2$). In this step, 1:2 mol ratio of **3** and **4** was used. Synthesis was performed under three varied temperatures: room temperature, 70 °C and 100 °C. Under room temperature, the desired compound **5** was not generated. When the synthesis was performed at elevated temperature (70 °C), two products (**5** and **6**) were generated with yields of 11% and 12%, respectively. At a higher temperature (100 °C), yield of compound **5** was slightly improved to 22%. Unfortunately, the yield of compound **6** at this temperature was yet to be determined since it was not purified (TLC comparison).

Compound **5** and **6** showed fairly similar $^1$H-NMR features in its aryl protons. Both compounds had para-substituted benzene where its double of doublets splitting pattern ($J_{ortho}$ = 8.3 - 8.6 Hz) were located at 7.45 - 7.46 ppm for compound **5** and 7.23 - 7.37 ppm for compound **6,** respectively. The distinguishing properties between them were the saturated hydrocarbon chemical area and the disappearance of hydrogen amide signals. The amount of hydrogens from 0.73 ppm to 3.60 ppm differ greatly between compound **5** and **6**. Monoalkylated compound **5** has 11 hydrogens spanning from 0.84 ppm to 3.55 ppm while the latter compound **6** has 22 hydrogens total in this area (see supplementary material S8-S9).

Literatures described that hydrogen amides peaks of non-alkylated benzylidene hydantoins are showed as two peaks (10.2–11.3 ppm) [8]. When N3 of hydantoin was methylated, N1 hydrogen would give a peak at chemical shift of 10.6–10.7 ppm [8]. Since compound **5** has a pentyl ($C_5H_{11}$) substituent at N3 (Figure.1), the hydrogen signal of N1 of compound **5** was singlet and had the same region as the reference, which was located at 10.82 ppm. Contrary to compound **6**, there was no spotted peak in this area, which indicates both nitrogens were pentylated.

Compound **5** and **6** have fifteen carbons and twenty carbons, respectively, that complement to their molecular formulas. Both compounds have identical pattern with slight differences in aromatic area and similar carbonyl chemical shifts. Their differences reside in their saturated hydrocarbon area. Compound **5** has five distinctive peaks; as its shifts were increased as the carbon position became closer to electronegative atom (*N3*-position, Fig. 1). While Compound **6** has five more signals addition to its spectra (13.9–41.5 ppm) in the same region. Hence, both carbon spectrums strongly confirmed that compound **5** is product of monoalkylation and compound **6** is product of dialkylation (see supplementary material S9-10).

## 4. Conclusion

The products were obtained in two different temperatures as 3-pentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **5** and unexpected 1,3-dipentyl-5-(4-chlorobenzylidene)imidazolidine-2,4-dione **6** with the yields of 11% and 12%, respectively. A two-fold increase of the synthetic yield of compound **5** (22%) is obtained when the reaction was undertaken at a higher temperature (100 °C).

## 5. Conflicts of interest

There are no conflicts to declare.

## 6. Acknowledgements

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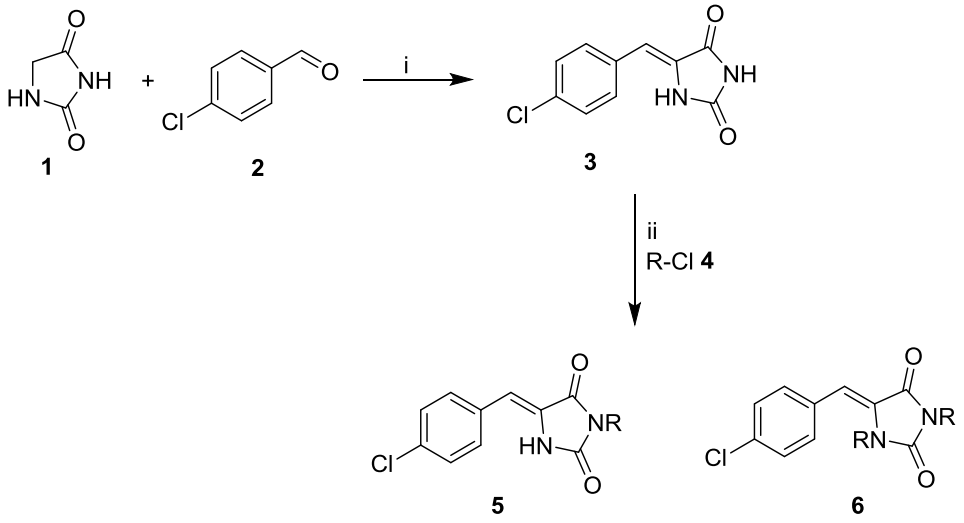


**Scheme 1.** Synthesis of condensation-alkylation of benzylidenehydantoins.

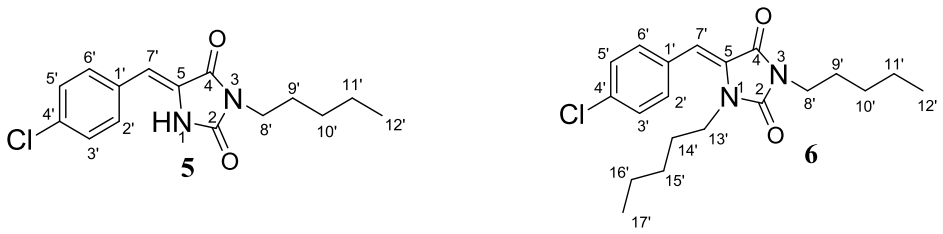


**Figure 1.** Numerical order of synthesized compound 5 and **6**.