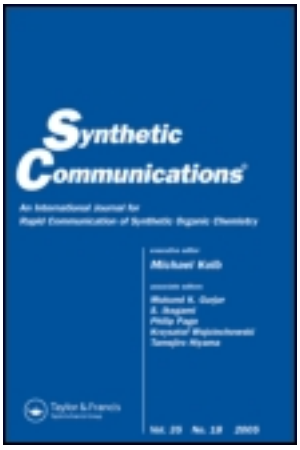

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Novel Synthesis of Fosphenytoin: Anti-Convulsant Prodrug

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Abstract: A simple, new synthesis of fosphenytoin sodium **1**, a prodrug, via imidate ester and employing mild reaction conditions is described.

Keywords: Anti-convulsant, hemiaminol, imidate ester

INTRODUCTION

Fosphenytoin sodium **1** as shown in Fig. 1 is a well-known anti-convulsant agent for the treatment of epileptic disorder, which is available in the market as Cerebyx®.[1] The mode of action of fosphenytoin involves the modulation of sodium channels of neurons that effectively prevents the convulsion.

In particular, the action potential across the neurons is accomplished through the sodium channels, and each sodium channel exists in three states: (a) resting state where the sodium ions are not allowed to enter into the cell, (b) active state where the enhanced influx of sodium ions are prevalent, and (c) inactive state where the sodium ions are not allowed at all. Fosphenytoin, a prodrug that provides phenytoin *in vivo* com blocks movements of ions through the sodium channels during propagation of the action potential and therefore blocks or limits the development of maximal convulsions.

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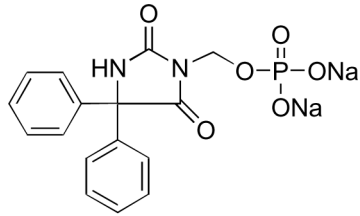

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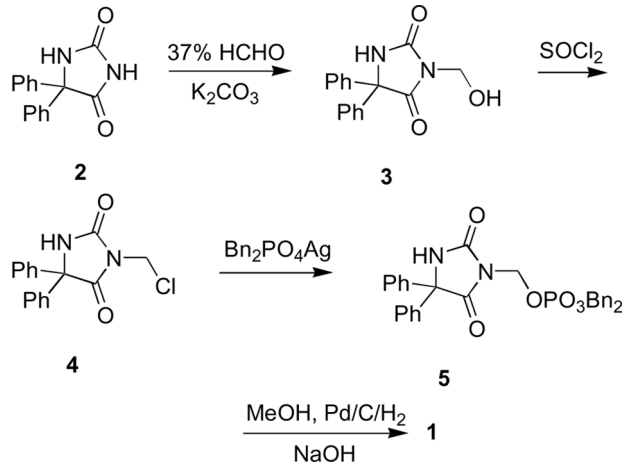
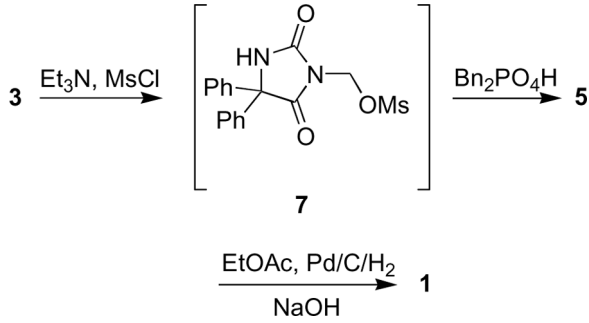
Figure 1. API's structural framework.

The reported synthetic method[2] for fosphenytoin sodium **1** prodrug involves four steps as shown in Scheme 1. Synthesis of **1** commences with the nucleophilic addition of phenytoin **2** to formaldehyde to give **3**, which upon chlorination using thionylchloride provided intermediate **4**. Phosphorylation of intermediate **4** using silver dibenzyl phosphate yielded the corresponding ester product **5**, which on hydrogenolysis and subsequent treatment with sodium hydroxide provided fosphenytoin sodium **1**. This process has certain disadvantages: (a) aforementioned process requires silver dibenzyl phosphate, and this reagent is expensive and light sensitive, (b) it is not efficient, as unwanted by-product silver chloride gets generated, which requires strict process control for silver metal estimation in the final API, and (c) usage of hazardous chemicals such as thionyl chloride and a range of solvents makes this method not environmentally friendly and less attractive for industrial scale-up.



2 **3** **4** **5** **1**

Scheme 1. Precedented approach.

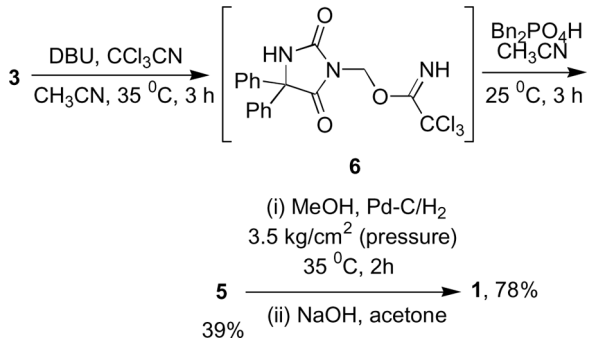


Scheme 2. Alternative synthesis: using -OMs as a leaving group.

A recent patent described a short and good-yielding method utilizing mesylester of hydroxymethyl phenytoin as key synthetic transformation[3] as shown in Scheme 2. The sulfonate derivative **7** was more reactive than the halide (e.g., **4**) that made the process efficient.

RESULTS AND DISCUSSION

In recent years trichloroacetamidate is widely used in organic transformations that avoid the heavy-metal salts as promoters[4], We took advantage of this fact and designed our synthetic route, which proved to be non-infringing and cost-effective; this article explores quantification of a base followed by imidate ester formation and the effect of solvents that afforded **1** in high yield. Herein, we report an economic and efficient novel synthesis of **1** in good yield with optimal purity employing mild reaction conditions, with relatively less consumption of reagents and energy.



Scheme 3. Novel synthetic approach.

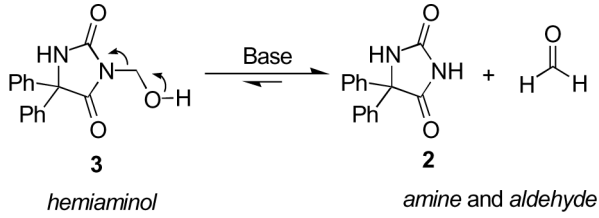


Figure 2. De-formylation: formation of major by-product **2**.

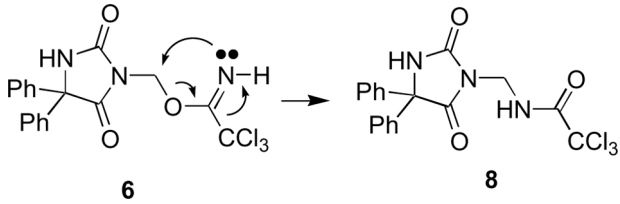
As presented the novel synthesis of **1** in Scheme 3, we were able to synthesize advanced intermediate **5** only in two steps. Preparation of the formylated intermediate **3** was accomplished by following the known protocol as presented in Scheme 1 (first step). Base-mediated formation of imidate ester **6** that involves in situ nucleophilic substitution with dibenzylphosphate afforded **5** in moderate yield. Finally, the synthesis of **1** was accomplished by hydrogenolysis and subsequent sodium salt formation.

Imidation of **3** with trichloroacetonitrile in the presence of different inorganic bases (e.g., potassium carbonate, sodium carbonate, and sodium bicarbonate) with solvents such as tetrahydrofuran, dichloromethane, acetone, ethylacetate, toluene, and heptane at different reaction conditions gave be, poor yield because of the formation of **2** and **3** as shown in Fig. 2. The emergence of **2** can be envisioned as an onset of base-catalyzed hemiaminol to amine and aldehyde equilibrium shift. However, we found in our optimization efforts that the DBU-catalyzed transformation afforded imidate ester **6** in good yield and purity (entry 3, Table 1). The employed sterically hindered base (DBU) was

Table 1. Screening of bases: formation of **6** in the presence of 1.2 equiv. of trichloroacetonitrile

		HPLC yield (%)		
Entry	Base (equiv.)	**2**	**3**	**6**
1	Potassium carbonate (0.32)	5.8	8.4	47.2
2	Potassium carbonate (0.5)[a]	65.5	25.0	—
3	1,8-Diazabicyclo[5.4.0]undec-7-ene (0.025)	1.04	0.4	79.9
4	DABCO (0.75)	15.7	27.5	30.2
5	Sodium hydride (2.8)	0.19	5.9	—
6	DMAP (0.5)	6.72	8.2	34.3

[a]Treatment of **3** with K_2CO_3 in the absence of CCl_3CN.



6 8

Figure 3. Rearrangement leading to amide **8**.

found to be easier to handle and commercially available. For large-scale preparation, the use of 0.3 equiv. of DBU appeared to be sufficient for the optimum imidation of **3** that afforded **6** in ~80% yield (HPLC).

In control experiments under these conditions, the reaction without usage of trichloroacetonitrile predominantly produced **2** (entry 2, Table 1).

We also observed the formation of intermediate **8** as result of intermolecular rearrangement of **6**,[5] as shown in Fig. 3, in the presence of more than 0.05 eq. of DBU. Its quantification is summarized in Table 2.

The solvents were screened to find a common solvent to efficiently effect the transformations of **3** to **6** and then to **5**. The results are summarized in Table 3. Although the transformations were smooth in most of the solvents employed, the best results were obtained with the acetonitrile (entry 2, Table 3).

We realized later that the acetonitrile and carried-over impurities, if any, were not compatible with the further debenzylation step. Therefore, we preferred to isolate **5** by employing various solvent combinations. Among the tested solvent combinations, isopropanal/*n*-heptane in a 2:3 ratio was found to be the best choice for isolation of **5** in good yield and purity.

Table 2. Impact of quantity of DBU on the formation of **8**

Entry	DBU: number of equivalence	HPLC yield (%)			
		2	**3**	**6**	**8**
1	0.025	1.04	0.4	79.9	2.7
2	0.05	4.6	2.7	60.3	4.65
3	0.075	1.45	2.26	66.3	6.4
4	0.1	1.35	0.44	65.4	9.1
5	1.0	14.9	1.39	4.23	33.6

Table 3. Solvent screening for the synthesis of **5**

Entry	Solvent	**3** to **5** overall yield (%)
1	Acetone	31.0
2	Acetonitrile	39.4
3	Dichloromethane	35.4
4	Ethyl acetate	23.0
5	Tetrahydrofuran	27.7
6	*N,N*-Dimethylformamide	5.2
7	Toluene	6.2

CONCLUSION

In conclusion, we accomplished a novel synthesis of **1** with consistency and significant reduction in energy consumption (most of the transformations were carried out at ambient conditions; no cryogenics or higher temperatures were involved) at an industrial scale.

EXPERIMENTAL

All commercially available reagents and solvents were used as received. The ^{1}H NMR spectra were measured on a Varian Gemini 200- or 400-MHz FT NMR spectrometer; the chemical shifts are reported in δ parts per million (ppm) relative to TMS. The Fourier transform-infrared (FT-IR) spectra were recorded in the solid state as KBr dispersion using a Perkin-Elimer 1650 FT-IR spectrometer. The mass spectrum (70 eV) was recorded on a HP-5989a liquid chromatography-mass spectroscopy (LC-MS) spectrometer.

3-Hydroxymethyl-5,5-diphenyl-imidazolidine-2,4-dione (3)

Potassium carbonate (0.64 kg, 4.64 mmol) and 37% aqueous formaldehyde (14.7 kg, 180.55 mmol) were added to a suspension of phenytoin (13.0 kg, 51.58 mmol) in water (390 L, 1547.6 mmol). After stirring for 3 h at 25°C, the resulting suspension was filtered, washed with water (78 L), and dried at 50°C for 5 h to afford 13.82 kg of hydroxymehtyl-phenytoin as a white crystalline solid in 95% yield and 96% purity (HPLC).

Phosphoric Acid Dibenzyl Ester 2,5-Dioxo-4,4-diphenyl-imidazolidin-1-ylmethyl Ester (5)

Trichloroacetonitrile (9.1 kg, 63.82 mmol) was added to a suspension of hydroxymethylphenytoin (12.0 kg, 42.55 mmol) in acetonitrile (108 L, 2117.47 mmol). After stirring for 20 min at 25°C, a solution of 1,8-diazobicyclo[5,4,0]undec-7-ene (DBU) (0.16 kg, 10.63 mmol) in acetonitrile (12.0 L, 234 mmol) was added to the resulting suspension slowly over 10 min to afford a clear solution that was additionally stirred for 3 h at 25°C. After completion of the reaction to form **6** (measured by thin-layer chromatography, TLC) a solution of dibenzylphosphate (9.47 kg, 34.0 mmol) in acetonitrile (120 L, 2352.9 mmol) was added slowly over 25 min at 25°C and stirred for 3 h. After completion of the reaction to form **5** (TLC), the solvent was distilled off completely, and ethylacetate (36 L, 562.5 mol) and water (120 L) were added to the resulting residue and stirred for 15 min. The organic layer was treated with water (2×120 L), evaporated under vacuum, and treated with a 3:2 ratio of ispropanol–heptane (48 L) to afford 9.1 kg of **5** as a white crystalline solid in 39.4% yield and 96% purity (HPLC).

Imidate 6: ^{1}H NMR (400 MHz, DMSO-d6): δ 9.8(s, 1H), δ 7.1–7.4 (m, 10H), δ 5.2 (s, 2H); MS (ES) calcd. for $C_{18}H_{14}C_{l3}N_3O_3$ (M^+) 426.68; found 424.90, 448.00 ($M^+ + Na$).

2,4-Imidazolidinedione-5,5-diphenyl-3-[(phosphonooxy) methyl], Disodium (1)

To a solution of **5** (9.4 kg, 17.31 mmol) in methanol (156 L), 5% palladium was added on activated carbon (0.94 kg). After stirring for 2 h at 25°C under hydrogen pressure of 3.0–3.5 kg/cm^2, the reaction progress was monitored by TLC. Upon completion the catalyst was filtered off, the solvent was removed under vaccum and residue was dissolved in acetone (128 L, 2206 mmol). Sodium hydroxide solution (1.37 kg, 0.03 mmol) was added to afford **1** as a crystalline solid (5.46 kg) in 78% yield and 99.5% purity (high-pressure liquid chromatography [HPLC]).

Rearranged Amide Derivative (8)

To a suspension of hydroxymethylphenytoin (20 g, 42.55 mmol) in dichloromethane (202 mL), trichloroacetonitrile (15.3 g, 0.10 mmol) was added. After stirring for 20 min at 25°C, a suspension of DBU (10.7 g, 0.07 mmol) in dichloromethane (10 mL, 0.12 mmol) was added slowly over 10 min. After stirring for 30 min at 25°C (completion of reaction;

TLC), the solvent was removed under vacuum, and the residue was dissolved in toluene. Compound **8** was isolated as a solid (21.0 g) in 70% yield and 95.4% purity (HPLC). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.2 (s, 1H), δ 7.2–7.4 (m, 10H), δ 5.0 (s, 2H); MS (ES) calcd. for $C_{18}H_{14}Cl_3N_3O_3$ (M^+) 426.68; found 424.90.

Spectroscopic data of the known compounds (**3**, **5**, and **1**) are in agreement with the reported values.

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