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Full Length Research Paper

A high yield synthesis of phenytoin and related compounds using microwave activation

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A reaction system is described to synthesize phenytoin, a major antiepileptic drug, and structurally related compounds using a two-step approach. The first step involves the treatment of a benzil derivative by thiourea in dimethylsulfoxide (DMSO) in aqueous KOH under microwave activation. The resulting 2-thiohydantoin was then oxidized to the corresponding hydantoin using perhydrol in dimethylformamide (DMF) in acetic acid. Both steps proceeded in high yield. For example, with this method, phenytoin was obtained in 80% yield while by the conventional Biltz's method, the yield rarely exceeded 50%. The first step can be advantageously performed using microwave activation. Our process is based on a mechanistic approach supported by theoretical PM3 calculations.

Key words: Phenytoin, antiepileptic drug, 2-thiohydantoin, Biltz's method.

INTRODUCTION

More than 60 years have elapsed since Merrit and Putnam (1937) demonstrated that 5, 5-diphenyl-2, 4-imidazolidinedione (phenytoin) was effective against electrically induced seizures in cat. This remarkable discovery ushered in a new era in the treatment of major epileptic seizures (Krall et al., 1978) and still nowadays phenytoin is considered as a drug of choice in the treatment of generalised tonic-clonic seizures (the so-called grand mal epilepsy) and focal motor seizures (Bac et al., 1998). In addition to its well-known antiepileptic properties, several reports indicate that phenytoin is also endowed with neuroprotective and cardiopropective properties (Taylor and Taylor, 1996; Reagan et al., 1999).

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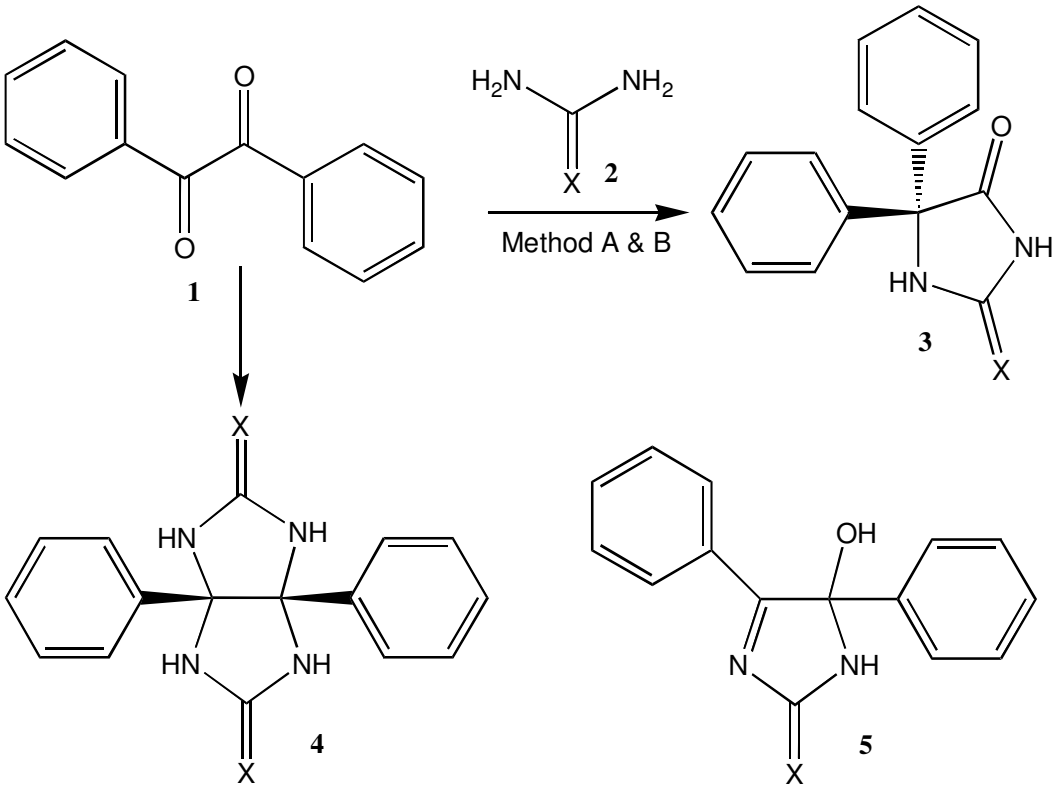
Abbreviations: DMSO, Dimethylsulfoxide; **DMF,** dimethylformamide; **IR,** infra red; **MS,** mass spectra; **TLC,** thin layer chromatography; **HPLC,** high-performance liquid chromatography.

Phenytoin has been employed as a template for the design of combinatorial chemistry libraries (El-Sherbenyet al., 2000). Recently, the hydantoin ring was employed for the synthesis of serotoninergic ligands (Maloney et al., 1999). In recent years, our group initiated a medicinal chemistry program targeting CB1/CB2 receptor ligands and using phenytoin as lead compound (Kanyonyo et al., 1999).

Contrarily to what is generally accepted, phenytoin was first synthesized by Michael (1887) but its structure was correctly assigned by Biltz (1908) some twenty years later. The preparation of phenytoin however using the base-catalyzed condensation of benzil (1) (Scheme 1) with urea (2, X = O) (Scheme 1) is commonly referred to as the Biltz synthesis of phenytoin (Hayward, 1983). After half a century of silence, the reaction was reinvestigated by Dumavant et al. (1956) who demonstrated that this transformation proceeds via the benzilic rearrangement of 4,5-diphenyl-4,5-dihydroxy-2-imidazolidonone, an intermediate which according to them would explain the concomitant production in nearly equivalent amount of 3 (Scheme 1) and the twin adduct 3a,7a-diphenylglycolureide 4 (Scheme 1) in the reaction products. These authors



Scheme 1. Method A. Biltz's approach to the synthesis of phenytoin. (Method A : X = O, KOH, EtOH, reflux 3-4 h; yield: ~50 % or microwave) and alternative improved method [Method B: (a) 2 (X = S)], aqueous KOH, DMSO, microwave, yield 92%; (b) H_2O_2, DMF, CH_3COOH, rt, 24 h, yield: 87%).

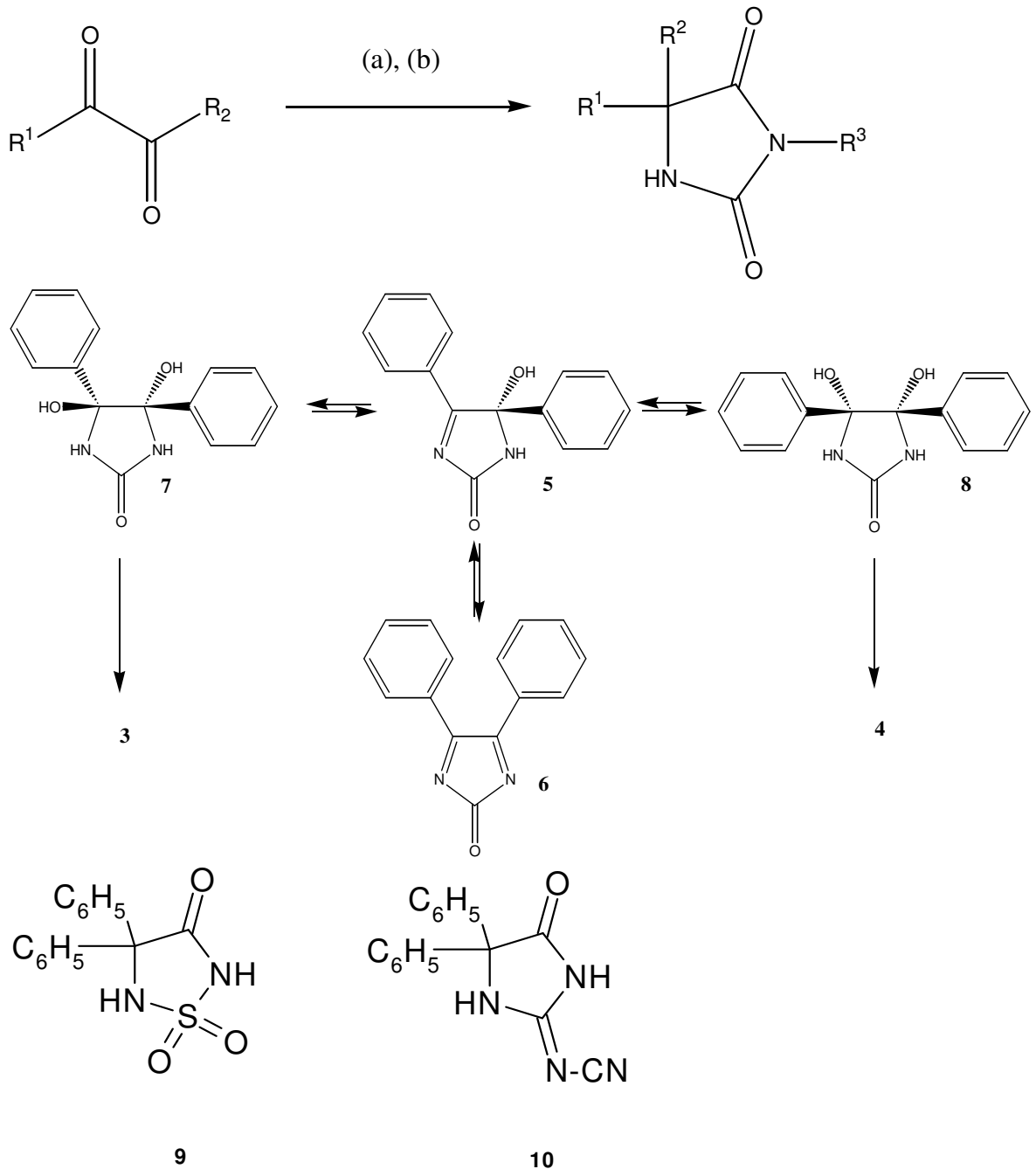
studied in detail the relative proportion of 1/2 in order to minimize the occurrence of 4 (Scheme 1). The optimal ratio reported by these authors has been employed in this study.

The Biltz synthesis was subsequently revisited in 1968 by Dietz and Mayer (1968) who described the structure-reactivity relationship of this reaction, emphasizing the passivating effect of electron-donating substituents on the phenyl groups of benzil. 4-Hydroxybenzil, for example, was reported not to react under Biltz's standard reaction conditions (Method A). The mechanism proposed by Dunnavant and James (1956) was revised by Butler and Leicht (1977) who postulated on the basis of kinetic and UV spectroscopic studies, the existence of 5 (Scheme1). In 1984, we were able to show that when the reaction was run in two-phase conditions using PEG 600 as phase transfer catalyst and an aqueous KOH/*n*-butanol solvent reaction system (Poupaert et al., 1984), the side-product 4 (Scheme1) could be dramatically diminished and consequently the yield of 1 (Scheme1) substantially increased (87-93%). In 1989, we demonstrated the existence of two diastereoisomeric forms of 3 (that is, 3a/3b) in the reaction medium by trapping these intermediate species as cyclic boronate esters, the structure of which was substantiated by ^{13}C- and ^{11}B-NMR and HPLC studies (Mergen et al., 1989). The glycolureide 4 (Scheme 1) was found to be produced as a single diastereoisomer and tentatively assigned the cis configuration on the basis of ^{13}C- and ^{15}N-NMR studies (Mergen et al., 1989).

In view of the considerable interest in medicinal chemistry for the hydantoin scaffold, we became interested in developing an efficient synthesis of heterocycles structurally related to 3 (Scheme 1) that could be easily automated. In this connection, this paper reports several improvements of the Biltz reaction (Methods A and B, Scheme 1) allowing a rapid synthesizing of phenytoin and structurally related derivatives in high yield. Our process is based both on experimental and mechanistic approaches supported by theoretical PM3 calculations using COSMO solvation parameters (here, water).

MATERIALS AND METHODS

Melting points (uncorrected) were determined in open capillary tubes using a Büchi SMP 20 melting point apparatus. Infrared (IR) spectra were recorded using a dispersion of the product in potassium bromide disks by means of a Perkin-Elmer Model 297 spectrometer. Proton and Carbon-13 Nuclear Magnetic Resonance (^1H- and ^{13}C-NMR) spectra were recorded using either a WP 80 SY or AC 300 P Bruker spectrometers. The NMR spectra were



Scheme 1. Method B. (a) H_2NC (=S) NH2, aqueous KOH, DMSO, microwave irradiation; (b) H_2O_2, DMF, CH_3COOH, rt, 24 h; (c) overall yield (%) from the corresponding benzil for the two-step procedure involving procedures (a) and (b) of M.

recorded at ambient temperature using tetramethylsilane (TMS) as internal reference (δ scale).

Mass spectra (MS) were recorded at the "Centre Universitaire de Mesure et d'Analyse" of the University of Lille II, Lille, France. Elemental analyses were obtained from the "Service Central d'Analyses du C. N. R. S." at Solaise Vernaison, France. All compounds reported here had IR, ^{1}H- and ^{13}C-NMR, MS, and elemental analysis data consistent with their structure. The experimental figures were found within 0.4% of the calculated values. Thin layer chromatography analyses were performed on Merck TLC plates (silica gel, 60 F 254, E. Merck, Darmstadt, ref. 5735). All the compounds reported here were found chromatographically homogenous in two standard solvents, that is, acetone/toluene/cyclohexane (5:2:3, v/v/v) and methanol/chloroform equilibrated with ammonia (1:9, v/v). High-performance liquid chromatography conditions (HPLC) were: C-18, methanol: water (75:25, v/v), 1.5 ml/min. The compounds reported here were homogenous under these HPLC conditions. All reagents were

purchased from Aldrich. Dimethylsulfoxide (DMSO) and dimethylformamide (DMF) were of the Gold Label grade. AM1 and PM3 calculations were run using the CS MOPAC package as implemented in Chem3D (CambridgeSoft Corporation, Cambridge, MA, USA).

5,5-Diphenylhydantoin (3) (microwave activation)

In 250 mL, Erlenmeyer flak was placed under stirring 100 mL of distilled water and 10.14 g (178 mmol) of potassium hydroxide; an exothermal reaction resulted. When a clear solution was obtained, a solution of 19.97 g of benzil (95 mmol) and 9.97 g of urea (166 mmol) in 40 mL of DMSO was added portion wise over 2 min. Efficient stirring was ensured throughout the operation to obtain a homogeneous paste. The reaction flask was then placed in a microwave oven and heated initially for 1.5 min at 1100 watt power. At times 6, 9, 12, 15, 18, 21, 24, and 30 min, a 30 sec pulse of 1100 watt were applied. The reaction mixture was then set aside for 10 min and then quenched with 250 mL of ice water. After 15 min stirring, the suspension was filtered to remove any floculent precipitate and the filtrate was acidified with glacial acetic acid till pH 4. An abundant white precipitate was formed. It was collected by suction on a Büchner funnel, washed twice with 100 mL of cold distilled water, dried and recrystallized from 380 mL of redistilled 95% ethanol to yield 18.3 g of 3. Mp 297-298°C, ^{13}C-NMR [(02 M, DMSO-d_6) 174.80 (C2), 156.05 (C4), 139.84 (ipso aromatic C), 128.35 (meta aromatic C), 127.93 (para aromatic C), 126.57 (ortho aromatic C), 70.30 (C5). This material was identical (mixed mp, TLC) to a commercial sample purchased from Aldrich.

5, 5-Diphenyl-2-thiohydantoin [3 (X = S)] (thermal activation)

To a solution of 2.1 g of benzil (10 mmol) and 1.14 g of thiourea (15 mmol) in 10 ml of DMSO was added in one portion and under stirring 1.71 g of potassium hydroxide (30 mmol), dissolved in 5 ml of distilled water. The reaction was stirred and heated in an oil bath thermostatized at 125°C for 1 h. The dark red reaction mixture was poured onto ice (~500 g) and acidified with concentrated HCl. The resulting precipitate was collected on a filter, dried and recrystallized from ethanol. Mp 238-240°C yield was 2.46 g (92%). This material was identical (mixed mp, TLC) to a commercial sample purchased from Aldrich.

Microwave activation

A reaction mixture composed of a solution of 2.1 g of benzil (10 mmol) and 1.14 g of thiourea (15 mmol) in 10 ml of DMSO and 1.71 g of potassium hydroxide (30 mmol) in 5 ml of distilled water was irradiated by 10 pulses for 30 s (power set at 750 W), each pulse being spaced out by 150 s to allow thermal equilibration. The reaction mixture initially blue turned to dark red. After precipitation by addition of 250 ml of ice water and acidification with concentrated HCl, isolation proceeded as described earlier. Yield was 2.41 g (90%). This material was identical (mp, TLC) to a commercial sample purchased from Aldrich.

5,5-diphenylhydantoin [phenytoin, 3 (X = O)]

To a solution of 2.68 g of 3 (X = S) in 10 ml of DMF were added in one portion, 1 ml of glacial acetic acid and 1 ml of perhydrol. The reaction mixture was stirred for 24 h at room temperature and then poured onto ice (~500 g). The resulting precipitate was collected on a filter, dried and recrystallized from ethanol. Yield was 2.19 g (87%). This material was identical (mp, TLC) to a commercial sample purchased from Aldrich.

(3a,7a)-Diphenyltetrahydroimidazo[4,5-d]imidazole-2,5-dione (4, X=O)

Condensation in basic medium

A solution of 19.97 g of benzil (95 mmol), 9.97 g of urea (166 mmol), and 10.14 g of potassium hydroxide (178 mmol) in 1000 ml of 95% ethanol was stirred at room temperature for a week. A thin white precipitate was slowly developed and collected on a Büchner filter, washed twice with 50 ml of 0.1 N sodium hydroxide (to remove any 3 present) and once with 100 ml of distilled water, dried and finally recrystallized from DMF: ethanol to give 6.3 g of 4. Yield: 22 %. Mp> 320°C ^{13}C-NMR (DMSO-d6, 50°C) 160.57 (C=O), 138.24 (ipso), 127.65, 127.20, 126.99, 126.87 (aromatic C), 81.77 (3a, 7a).

Condensation in acidic medium

A suspension of 19.97 g of benzil (95 mmol), 9.97 g of urea (166 mmol), and 200 ml of 96% formic acid was stirred and refluxed for 24 h. After cooling in an ice box, a precipitate was collected and copiously washed first with water and then ethanol, dried and recrystallized from DMF: ethanol to give the same product as above in 68% yield.

4,4-Diphenyl-1,2,5-thiazolidin-3-one-1,1-dioxide (9, thermal activation)

A solution of sodium ethoxide prepared by reacting 1 g of sodium in 100 mL of absolute ethanol was combined with a solution of 4.20 g (20 mmol) of benzil and 2.40 g (24 mmol) of sulfamide in 100 ml of absolute ethanol. Initially, a volume of 120 ml of ethanol was distilled, and the reaction mixture was then stirred and heated at reflux for 24 h after which time the solvent was removed *in vacuo*. The residue was redissolved in water (25 mL). Some insoluble material filtered off. The yellowish solution was extracted with ether (3 x 25 mL) and acidified with 10% aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water, dried and recrystallized from *n*-hexane-chloroform to give a white crystalline material (45% yield), mp 232-234°C ^{13}C-NMR (acetone-d_6) 75.81 (4), 128.16 (o), 128.81 (p), 129.01 (m), 139.67 (i) and 170.72 (3); Analysis ($C_{14}H_{12}O_3N_2S$) C, H, N.

Microwave activation

A reaction mixture composed of a solution of 4.2 g of benzil (20 mmol) and 2.40 g (24 mmol) of sulfamide in 25 ml of DMSO and 3.42 g of potassium hydroxide (60 mmol) in 10 ml of distilled water was irradiated by 30 pulses of 30 s (power set at 1200 W), each pulse being spaced out by 180 s to allow thermal equilibration. After precipitation by addition of 250 ml of ice water and acidification with concentrated HCl, isolation proceeded as described earlier; yield was 52%. This material was identical (mp, TLC) to the material obtained above.

4-Oxo-5,5-diphenyl-(3H)-1-imidazolyin-2-ylcyanamide (10)

A solution of 2.1 g of benzil (10 mmol) and 1.60 g of N-cyanoguanidine (20 mmol) in 20 ml of DMSO was mixed with 1.71 g of potassium hydroxide (30 mmol) in 5 ml of distilled water and the

Table 1. Solvent effect (% yield) in the Biltz synthesis of phenytoin (1).

Solvent	Microwave	Thermal
DMSO	79.7 [a]	36.5
DMSO:H2O[b]	76.4	62.1
Sulfolane	77.8	56.9
Sulfolane:H2O[b]	71.0	57.7
DMF	55.6	36.2
DMF:H2O[b]	15.7	03.9
Dioxane	45.7	25.0
Dioxane:H2O[b]	80.1	58.3
Ethanol:H20[c]	nd [d]	53.5

a, Experiments done in triplicate; b, 40:100, v/v ; c, 95:5, v/v ; d, nd = not determined.

mixture was irradiated by 20 pulses for 30 s (power set at 750 W), each pulse being spaced out by 150 s to allow thermal equilibration. After precipitation by addition of 250 ml of ice water and acidification with concentrated HCl, isolation proceeded as described earlier. Mp 260-262°C (from acetone: water) yield = 2.34 g (82%). IR (KBr) 3180, 3030, 2205 (CN), 1765 (C=O), 1665 (C=N). ^{1}H-NMR (DMSO-d_6) 7.38 (m, 10 H, aromatic), 9.90 and 11.30 (broad signals, 2 H, exchange with D_2O). ^{13}C-NMR (DMSO-d_6) 174.60 (C4), 160.67 (C=N), 138.92 (ipso), 126.99, 128.68, 128.77 (aromatic C-H), 115.27 (cyano) and 72.30 (C5).

(R, S)-5-(4-hydroxyphenyl)-5-phenylhydantoin (14)

A solution of 9.60 g of 4-methoxybenzil (50 mmol) and 11.4 g of thiourea (150 mmol) in 100 ml of DMSO at 50°C was added under stirring dropwise a hot freshly prepared solution of 17.1 g of potassium hydroxide (300 mmol) in 35 ml of distilled water. The resulting brown slurry was irradiated by 50 pulses of 30 s (power set at 1200 W), each pulse being spaced out by 180 s to allow thermal equilibration. After cooling, the reaction mixture was poured onto 500 g of ice water and stirred for 30 min. A thin colloid precipitated was collected on a filter. The filtrate was extracted with three times 50 ml of ethyl acetate to discharge a slight yellow color. It was then acidified to produce an abundant white precipitate which was collected on a filter and dried. This precipitate consisting of (R,S)-5-(4-methoxyphenyl)-5-phenyl-2-thiohydantoin [TLC, mp 172-173.5°C, MS 298(M+)] was dissolved in 50 ml of DMF and 10 ml of glacial acetic acid and treated dropwise with 10 ml of perhydrol. The mixture was stirred for 48 h at room temperature, a white precipitate slowly developing. The suspension was poured onto ice (500 g) and the copious precipitate consisting of (R, S)-5-(4-methoxyphenyl)-5-phenylhydantoin (TLC, mp 212-214°C, comparison with an authentic sample) was filtered off. This material was dissolved in 75 ml of hot glacial acetic acid and treated dropwise with 75 ml of 48% hydrobromic acid. The red solution was stirred, refluxed for 3 h, cooled, diluted with ice (250 g) and partially concentrated *in vacuo* to produce a white precipitate which was filtered, dried, and recrystallized from dioxane: water yielding 8.5 g (64%) of the title compound (mp 304-306°C). This material was identical to an authentic commercial sample (TLC, HPLC, mixed mp).

RESULTS AND DISCUSSION

Solvent effect and microwave activation (Scheme 1, Method A). A crucial point in the Biltz synthesis of phenytoin is the concomitant formation of 3 and 4 (Scheme 1, Method A).

In homogeneous reaction conditions, when absolute ethanol is employed as solvent, the yield of 3 is <50%. In ethanol/water mixtures, the yield of analytically pure 3 (X=O) never exceeds 55%. In our hands, the yield of analytically pure 4 (X=O) can be as high as 22%. A change in the strength of the base does not modify significantly the 3:4 ratios but rather affects the kinetics of the reaction. Conclusively, while the Biltz reaction has been explored on the point of view of the stoechiometry (Dunnavant and James, 1956) and the type of base (Poupaert et al., 1984), to the best of our knowledge, surprisingly the role of the solvent has never been explored in depth before.

Dipolar solvents are essential in microwave heating, and it is often necessary to adapt solvent systems to accommodate this requirement. In substituting solvent systems for microwave applications, high boiling point solvents are often used. In this connection, we first examined solvents such as DMSO and DMF. This was motivated in part by an earlier observation, when the reaction was carried out in DMSO: water, the yield of 3 could be raised up to 62%. When we performed the reaction with the same composition of the reaction mixture using microwave heating, the yield was somewhat improved (76.5%) with the additional bonus that the reaction went to completion in 40 min instead of 2 h under classical thermal conditions. When the reaction was performed in pure DMSO under microwaves, the yield of 1 was slightly increased (79.6%). Sulfolane and dioxane behaved rather similarly (Table 1), but DMF gave much lower yields. This fact can probably be ascribed to the extensive hydrolysis of DMF under such highly basic and temperature conditions, which rapidly depletes the potassium hydroxide concentration.

In solvents that did not contain water, it was noted that in the early stage of the reaction, a deep blue color developed. To our knowledge, this has never been reported and commented on. Looking backward to the literature, it was difficult to assign such a color to a known intermediate in this reaction as they do not possess a chromophore in the visible. One possibility however was to postulate the presence of the highly conjugated 4, 5-diphenyl-2-imidazolone (6) (Scheme 1), a structural analogue of 2,3,4,5-tetraphenyl-2,4-cyclopentanedione, a compound characterized by a deep violet color in solution.

Synthesis of phenytoin derivatives via 2-thiohydantoins: A two-step procedure (Scheme 1, Method B)

In our efforts to improve and extend the scope of Biltz's approach to phenytoin synthesis, a first clue came from the fact that water addition in the reaction medium improved the yield of 3 along with a corresponding

Table 2. Synthesis of phenytoin derivatives by the two-step procedure.

Cpd #	R1	R2	R3	Yield (c)	References
11	4-F-C6H4	C6H5	H	72	Nelson et al. (1979)
12	4-Br-C6H4	C6H5	H	78	Dumont et al. (1981)
13	4-CH3O-C6H4	C6H5	H	76	Henze and Isbell (1954)
14	4-HO-C6H4	C6H5	H	64	Poupaert et al. (1975)
15	C6H5	C6H5	CH3	80	Broan et al. (1989)
16	C6H5	C6H5	C2H5	82	Dilli and Pillai (1980)
17	C6H5	C6H5	n-C4H9	76	Poupaert et al. (1985)
18	4-F-C6H4	C6H5	CH3	75	Poupaert et al. (1985)
19	4-CH3O-C6H4	C6H5	CH3	78	Poupaert et al. (1985)

decrease of the production of 4. On the other hand, upon reading the “ancient “literature”, we noted that reaction of benzil with thiourea in ethanolic KOH did not produce any 4.

Along the line, after various trials, a satisfactory reaction system was finally found. It involved the use of DMSO: aqueous KOH as base catalyst and benzil(1)/thiourea (2, X = S) as reaction partners (Scheme 1). In view of the aforementioned results for phenytoin, DMSO was chosen as reaction solvent partner because of its high solvent power, high boiling point, and good capacity to absorb microwave radiation. The 2-thiohydantoin derivative (3, X = S) was obtained in high yield (92%) and the thioglycolureide (4, X = S) was virtually absent from the reaction mixture. After precipitation from the reaction mixture, the crude could be oxidized to phenytoin (3, X = O) by hydrogen peroxide in DMF/acetic acid at room temperature, again with a good yield (87%). Overall yield of phenytoin was quite satisfactory [80% from benzile (1)]. Incremental practical improvement of this reaction was made possible by running the first step of this reaction sequence under microwave activation. The major interest of microwave activation resided in our hands in a faster reaction time as further exemplified by the synthesis of 4,4-diphenyl-1, 2,5-thiazolidin-3-one-1,1-dioxide (9) (Table 2) (Lee et al., 1990). While by thermal activation, refluxing for 24 h was necessary to have complete conversion of the benzil in the presence of the poorly nucleophilic sulfamide ($H_2NSO_2NH_2$). With microwave activation, a 1.75 h period was sufficient. In the same way, using N-cyanoguanidine, we obtained the corresponding phenytoin bioisoster (9) (Table 2) in good yield (82%). Additional examples of the two-step procedure are listed in Table 2.

Proposal of mechanism for the Biltz synthesis of phenytoin. Reasons for the absence of thioglycolureide (4, X = S) in this reaction have remained somewhat elusive in the literature (Braon et al., 1991). We therefore tried to find an explanation in the mechanism of the reaction. On the basis of UV spectroscopic evidence (Butler et al., 1977), compound 5 (Scheme 1) has been postulated as an intermediate in the Biltz reaction. Evidence for the existence of cis and trans-diol (7 and 8) (Table 2) as intermediates in the Biltz reaction was gained by isolation of these compounds[26] and the corresponding boronate esters of these diastereoisomeric species (Mergen et al., 1989).

It is consequently conceivable that there is a thermodynamic equilibrium between 7 and 8 which operates via dehydration-hydration reactions with 5 as intermediate. This point has been discussed in the literature (Schwenker et al., 1992). As a cis-arrangement of the phenyl groups was assigned to 4 (X = O), it is likely therefore that 8 reacts with a second molecule of urea to generate 4 (X = O) while 7 undergoes a base-catalyzed benzilic rearrangement to produce 3 (X = O). If 7 and 8 are of similar energy content, it is then reasonable to expect that they will accumulate in relatively similar proportion in the reaction medium and consequently both 3 and 4 will be produced with nearly equal yields.

In order to assess the energy content of the various reacting species, semi-empirical quantum mechanics calculations were therefore undertaken using the PM3 method and COSMO water solvation parameters as implemented in MOPAC 97, the latest version supported by Fujitsu Corporation. The COSMO method is useful for determining the stability of various species in a solvent. The solvent chosen here is water with a dielectric constant of 78.4. The results are presented in the Table 3.

While the reaction coordinate for the sulfur compounds appears to be grossly situated at ±60 kcal/mol higher than the oxygen compounds, the difference as reflected by the $\Delta\Delta H_f$ figure remains relatively constant for all compounds, except for the thioglycolureide situated in energy at much higher level. This significant difference may probably account for the difficulty of synthesizing this compound. Using high excess of thiourea and running the Biltz reaction in absolute ethanol in presence of sodium ethoxide as base catalyst (conditions known to favour the glycolureide production), we were unable to obtain 4 (X= S) with a yield better than 3.2% yield. Incidentally, PM3 calculations were also in full agreement with the cis-configuration of the glycolureide, the trans species being highly strained and of much higher energy

Table 3. Formation energy (ΔH_f) and corresponding difference $\Delta\Delta H_{f(S-0)}$ calculated both for the oxygen and sulfur series.

#Compound	ΔHf (X = O)	ΔHf (X = S)	ΔΔHf (S-0)
3	-36.856	+23.192	60,048
4	-39.062	+80.149	119,211
5	-20.794	+39.518	60,312
6	+55.288	+127.238	71.950
7	-89.075	-33.500	55,575
8	-90.049	-32.975	57,074

ΔΔHf (S-0) = ΔHf (X = S) - ΔHf (X = O).

Table 4. % Yields for substituted (thio) phenytoin (DPH) and (thio) glycolureide (DPG) derivatives and corresponding calculated $\Delta\Delta H_f$.

X	Y	Z	%DPH/DPG	ΔΔHf (DPH)	ΔΔHf (DPG)
H	H	O	47/53	52.2	51.0
H	H	S	100/0	55.7	113.1
4-Br	H	O	77/06	54.7	49.5
4-Br	H	S	95/00	58.8	114.4
4-OCH3	H	O	44/35	54.1	50.6
4-OCH3	H	S	72/nd	56.8	113.1
3-OCH3	H	O	33/48	53.8	51.0
3-OCH3	H	S	70/21	57.0	114.1
4-OCH3	4-OCH3	O	49/42	53.8	51.4
4-OCH3	4-OCH3	S	80/12	56.8	113.0
3-OCH3	3-OCH3	O	42/46	54.6	50.0
3-OCH3	3-OCH3	S	90/nd	57.4	114.0
2-OCH3	2-OCH3	O	18/nd	52.0	53.5
2-OCH3	2-OCH3	S	92/00	57.6	114.9

$\Delta\Delta H_f$ (DPH), ΔH_f (trans-diol) – ΔH_f(DPH); $\Delta\Delta H_f$ (DPH), ΔH_f (cis-diol) – ΔH_f(DPG).

than the cis ((ΔH_f +1.578 and +128.349 for the oxygen and sulfur derivatives, respectively). Although less realistic because they do not take into account solvation, AM1 calculations (not reported here) lent to conclusions in the same trend as to those obtained by the PM3 method, for all compounds reported in the Table 4.

To validate the above calculation approach, we computed the $\Delta\Delta H_f$ of several substituted phenytoin (DPH) and glycolureide (DPG) derivatives (both in the oxygen and sulfur series) and compared the obtained figures with the corresponding yields as reported by Dietz and Mayer (1968).

As shown in Table 4, in the oxigene series, the $\Delta\Delta H_f$ values were relatively similar (in the range of +50-60 kcal/mol) and both DPH and DPG derivatives were in all cases produced in sensibly similar proportions. For the sulfur terms, while the $\Delta\Delta H_f$ (DPH) figures were relatively equal to those obtained in the oxigene series, the $\Delta\Delta H_f$ (DPG) was always consistently much higher (~+115 kcal/mol), a value reflecting the highly endothermal character of the process involved in the formation of the DPG thioderivatives. As the corresponding activation energies are likely to be in the same rank order, the high values encountered for $\Delta\Delta H_f$ (DPG) may explain the low yields or even absence of DPG derivatives formed in the sulfur series.

Conclusion

While the Biltz synthesis is an “old” reaction that has been many times revisited, the present work shows that it is often worthwhile reinvestigating so-called “old reactions” that can be revitalized to provide interesting pharmacological probes for the medicinal chemists. In a further effort to find an alternative to two-step reaction procedure presented earlier (Table 1), we extended these calculations to a series of phenytoin analogs in which the carbonyl in position 2 was substituted by a function easily hydrolyzable to the original carbonyl group (C=N-R where R = H, CN or Tos). From these calculations, 10 (R = CN)

(Table 2) emerged as a potential candidate where the $\Delta\Delta H_f$ (DPH) value was normal (+56.0 kcal/mol) but the $\Delta\Delta H_f$ (DPG) value was found rather high (+146.4 kcal/mol). In our hands, 10 were obtained in quite decent yield (82%) and could be hydrolyzed to 3 in mild conditions, even in refluxing phosphate buffer. These promising results, although not superior to the method reported earlier, indicate that additional work should be devoted to explore this approach.

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