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SHORT COMMUNICATIONS

Preparation of Phenytoin Derivatives under Solvent-Free Conditions Using Microwave Irradiation*

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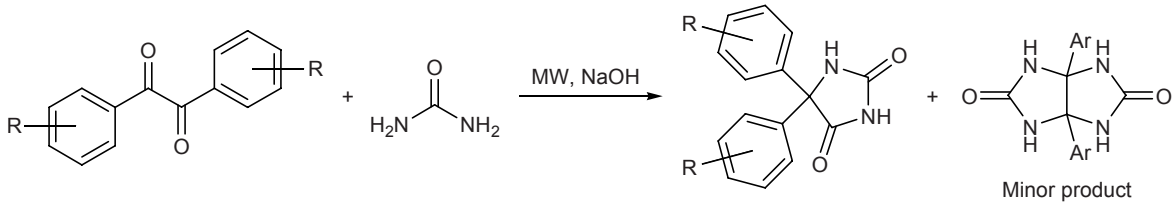
Phenytoin or 5,5-diphenylimidazolidine-2,4-dione is an anticonvulsant drug which can be useful in the treatment of epilepsy. The primary site of action appears to be the motor cortex, where spreading of the seizure activity is inhibited. Phenytoin is indicated for the control of grand mal and psychomotor seizures [1].

Several methods for the preparation of hydantoins have been reported, such as treatment of benzils with urea in ethanolic solution of potassium or sodium hydroxide [2–10]. These methods suffer from some drawbacks, including long reaction times, low yield, difficult operating conditions, and tedious work-up.

In the recent years, applications of microwave irradiation in a variety of organic reactions have rapidly increased due to short reaction time and operational simplicity [11–25]. Taking into account the importance of hydantoin and its derivatives for biological and medicinal chemistry, we decided to optimize methods of synthesis of these compounds. We now report a simple synthetic procedure for the preparation of phenytoin derivatives under microwave irradiation in the presence of sodium hydroxide. To choose the best base among various common bases, comparative study was performed using benzil and urea as representative starting materials (Table 1). Reactant mixtures were irradiated in a microwave oven at a power of 100 W in the presence of different bases. The results showed that sodium hydroxide without solid support ensured the best yield and the shortest reaction time, so that it was selected as base for subsequent experiments. The presence of a base was obligatory, otherwise no reaction occurred.

Initially, we synthesized some benzoin derivatives from the corresponding substituted benzaldehydes and converted them into benzil derivatives. A number of phenytoin derivatives were then prepared from substituted benzils and urea under microwave irradiation (100 W) in the presence of NaOH. All reactions were easily performed in a beaker, and their progress was monitored by thin-layer chromatography. The results are summarized in Table 2. The process was accompanied by formation of an insignificant amount of the corresponding 3a,6a-diarylglycoluril as by-product. The latter can readily be separated by treatment of the reaction mixture with water.

The structure of the products was confirmed by physical and spectral data. Their ^{1}H NMR spectra contained signals from the NH proton as one broadened and one sharp singlet in the region δ 9–12 ppm. In the IR spectra we observed absorption bands in the regions 1660–1740/1440 (C=O/C=C) and 3250–3450 cm^{-1} (NH).



R = H, 4-Cl, 4-Me, 2-O_2N, 4-O_2N, 2-Cl, 4-Br, 2-Me; Ar = RC_6H_4.

* The text was submitted by the authors in English.

Table 1. Preparation of phenytoin by reaction of benzil with urea in the presence of various bases

Base	Time, min	Yield, %
None	10	0
$NaHCO_3$	6	29
Na_2CO_3	2	37
$Mg(OCH_3)_2$	2	15
NaOH	1.5	99
$Ca(OH)_2$	5	23

Table 2. Preparation of phenytoins from benzil derivatives and urea under microwave irradiation

R	Time, s	Yield,[a] %	mp, °C
H	120	98 (1.6)	295–299
4-Cl	60	96 (3.2)	222–227
4-Me	90	97 (2.5)	295–299
2-O_2N	30	95 (4.2)	230–234
4-O_2N	15	98 (1.5)	238–240
2-Cl	60	93 (6)	127–132
4-Br	90	95 (4)	240–245
2-Me	180	95 (4)	286–290

[a] The yield of the corresponding 3a,6a-diarylglycoluril is given in parentheses.

To conclude, the proposed procedure for the preparation of phenytoin derivatives is advantageous due to its experimental simplicity, short reaction time, and excellent yields.

5,5-Diphenylimidazolidine-2,4-dione. A mixture of 0.5 g (2.3 mmol) of benzil and 0.5 g (11.9 mmol) of urea was placed into an open glass container, 0.5 g (12.5 mmol) of sodium hydroxide was added, and the mixture was irradiated in a microwave oven at a power of 100 W over a period of 1.5 min. The hot mixture was then poured into ice water, and the precipitate of 3a,6a-diphenylglycoluril was filtered off, dried for 2 days in a desiccator over calcium chloride, and recrystallized from glacial acetic acid. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate of 5,5-diphenylhydantoin was filtered off, dried as described above, and recrystallized from ethanol. White solid, mp 295–299°C. IR spectrum (KBr), ν, cm^{-1}: 3200–3280 s (NH); 1720 s, 1780 s (C=O); 1400 m, 1500 m (C–C_{arom}); 747 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.35 m (2H), 7.39 m (8H), 9.35 s (1H), 11.0 s (1H).

The other compounds were synthesized in a similar way from the corresponding substituted benzils. 3a,6a-Diarylglycolurils isolated as by-products were identified by comparing their physical constants and spectral parameters with those reported in [2, 15, 26].

5,5-Bis(4-chlorophenyl)imidazolidine-2,4-dione. Pale yellow solid, mp 217–222°C. IR spectrum (KBr), ν, cm^{-1}: 3000–3200 m (NH); 1690 s, 1740 s (C=O); 1440 m, 1500 m (C–C_{arom}); 770 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.40 m (8H), 9.10 s (1H), 10.90 s (1H).

5,5-Bis(4-methylphenyl)imidazolidine-2,4-dione. Pale yellow solid, mp 295–299°C. IR spectrum (KBr), ν, cm^{-1}: 3100–3300 br (NH); 1720 s, 1780 s (C=O); 1480 s, 1540 s (C–C_{arom}); 745 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 2.20 s (6H), 7.10 m (8H), 8.90 s (1H), 10.80 s (1H).

5,5-Bis(2-nitrophenyl)imidazolidine-2,4-dione. Brown solid, mp 230–234°C. IR spectrum (KBr), ν, cm^{-1}: 3000–3200 m (NH); 1650 s, 1700 s (C=O); 1470 m, 1500 m (C–C_{arom}); 1280 s, 1340 s (NO_2); 770 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.10–8.0 m (8H), 8.20 s (1H), 11.70 s (1H).

5,5-Bis(4-nitrophenyl)imidazolidine-2,4-dione. Pale yellow solid, mp 238–240°C. IR spectrum (KBr), ν, cm^{-1}: 3000–3200 m (NH); 1700 s (C=O); 1470 s, 1525 s (C–C_{arom}); 1290 s, 1360 s (NO_2); 725 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.20–8.10 m (8H), 8.30 s (1H), 11.90 s (1H).

5,5-Bis(2-chlorophenyl)imidazolidine-2,4-dione. Orange solid, mp 127–132°C. IR spectrum (KBr), ν, cm^{-1}: 3250–3450 m (NH); 1660 s, 1740 s (C=O); 1440 s, 1510 s (C–C_{arom}); 745 s (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.10–7.60 m (8H), 9.20 s (1H), 11.0 s (1H).

5,5-Bis(4-bromophenyl)imidazolidine-2,4-dione. Pale yellow solid, mp 240–245°C. IR spectrum (KBr), ν, cm^{-1}: 3100–3300 m (NH); 1700 s, 1750 s (C=O); 1450 m, 1510 m (C–C_{arom}); 780 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 7.60 m (8H), 9.30 s (1H), 11.10 s (1H).

5,5-Bis(2-methylphenyl)imidazolidine-2,4-dione. Brown solid, mp 286–290°C. IR spectrum (KBr), ν, cm^{-1}: 3100–3300 br (NH); 1720 s, 1780 s (C=O); 1470 s, 1540 s (C–C_{arom}); 725 m (δ=C–H). ^{1}H NMR spectrum, δ, ppm: 2.30 s (6H), 7.10–7.30 m (8H), 8.90 s (1H), 10.90 s (1H).

The IR spectra were recorded in KBr on Perkin–Elmer 781 and Impact 400 Nicolet FTIR spectrometers. The ^{1}H NMR spectra were measured from solutions in DMSO-d_6 on a Bruker DRX-400 instrument

using tetramethylsilane as internal reference. The melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. The progress of reactions and the purity of products were monitored by TLC on Polygram SILG/UV 254 silica gel plates (Merck).

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