Conventional and microwave-assisted synthesis of 1,5-diaryl-2-thiohydantoins

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A simple and efficient method for synthesis of new 1,5-diaryl-2-thiohydantoins using microwave radiation has been standardized. The compounds have been synthesized from phenylacetic acid by esterification, bromination, amination and cyclization using conventional as well microwave irradiation methods.

Keywords: Microwave irradiation, 1,5-diaryl-2-thiohydantoins

Thiohydantoins are the sulphur analogues of hydantoins with one or both carbonyl groups replaced by thiocarbonyl groups. Among the known thiohydantoins, 2-thiohydantoins are the most notably known due to their wide application as anticarcinogenic, antimutagenic, antithyroidal, antiviral, antitubercular, hypolipidemic, antimicrobial, antiulcer and antiinflammatory compounds.

The most antiinflammatory agents, including the recently approved drugs like celecoxib and refecoxib, belong to the diarylheterocycle class of compounds. These compounds have been investigated extensively as Cox-2 inhibitors. Prolonged use of these compounds gives rise to adverse reactions such as gastric irritation or ulceration and renal complication. Therefore, there is still a need of novel, selective, potent Cox-2 inhibitors with better pharmacologic profile than the current Cox-2 inhibitors. The proposed molecules, i.e., 1,5-diaryl-2-thiohydantoins, contain pyrazolindione moiety as a heterocyclic ring. Phenyl group attached at 1st and 5th positions and substitution at p-position of one of the aryl rings makes the molecules too large to fit into the Cox-1 active site but it can still fit into Cox-2 active site. Hence, it was decided to synthesise 1,5-diaryl-2-thiohydantoins in the hope of producing new antiinflammatory compounds.

Various synthetic methods have been developed to prepare 2-thiohydantoins. Some of the most commonly used methods are the treatment of α-amino acids with acetic anhydride followed by ammonium thiocyanate and the coupling reaction between α-amino acid derivatives and isothiocyanate. Other preparative methods for 2-thiohydantoins include reaction between thiourea and benzil and reaction between thiourea and haloacid. However, all these methods often suffer from one or more synthetic limitations for the large scale preparation of 2-thiohydantoin derivatives due to the use of expensive, moisture sensitive and highly toxic starting materials such as acetic anhydride, isothiocynate, thiourea and haloacid. The method of synthesis carried out by this group involved use of cheaper, nontoxic and easily available starting materials.

Microwave-assisted heating under controlled conditions is an invaluable technology for medicinal chemists and drug discovery application, because it often dramatically reduces reaction time, typically from days to hours or minutes or seconds. The short reaction time provided by microwave synthesis makes it ideal for reaction scouting and optimization of reaction conditions.

Traditionally, organic reactions make use of an external heat source and therefore, the heat transfer is by conduction. This is comparatively slower and an inefficient method for transferring energy into the system, because it depends on the thermal conductivity of various materials that must be penetrated. Hence, the temperature of the reaction vessel is higher than that of the reaction mixture. In contrast, microwave irradiation produces efficient internal heating by direct coupling of microwave energy with polar molecules that are present in the reaction mixture.

The present work describes a simple and rapid method of synthesis of 1,5-diaryl-2-thiohydantoins.

Results and Discussion

Conventional method for the synthesis of 1,5-diaryl-2-thiohydantoin derivatives was carried out in four steps, viz., esterification, bromination, amination and cyclization.

Esterification was carried out by refluxing phenylacetic acid with excess of methanol (AR grade) in the presence of concentrated H₂SO₄ or PTSA (p-toluenesulfonic acid) as a catalyst. Bromination of
an ester 1 was carried out by using NBS (N-bromosuccinimide) as a brominating agent and concentrated H$_2$SO$_4$ or p-toluenesulfonic acid as a catalyst. Amination of this brominated ester 2 was carried out by condensing it with an aromatic amine. Three different amines – aniline, p-anisidine and p-toluidine – were used. Cyclization of these aminated products 3a-c was carried out by using potassium thiocyanate and triethylamine to get the final products 4a-c.

The reactions involved in the synthesis of 1,5-diaryl-2-thiohydantoins are presented in **Scheme I**.

All the four steps were then carried out by microwave irradiation (MW) method. In the conventional method, the total reaction time (for all the four steps) for the synthesis of 1,5-diaryl-2-thiohydantoin derivatives was found to vary from 50 hr to 80 hr. When the same reactions were carried out by microwave irradiation, the total reaction time was found to be in the range of 7-7.5 hr and the yield of the products was found to increase by 1-23% as compared to that in the conventional method. The reaction time and the yield of products by conventional and microwave irradiation methods is listed in **Table I**. The antiinflammatory study of the final products 4a-c is in progress.

**Experimental Section**

The chemicals required for the synthesis of 1,5-diaryl-2-thiohydantoins were purchased from Merck Chemical Co, Spectrochem Laboratories and Rankem Laboratories.

Synthesis of 1,5-diaryl-2-thiohydantoins was carried out using conventional and microwave irradiation methods. For microwave irradiation method, the microwave synthesizer from CEM Corporation, USA, was used. In both the methods, the completion of a chemical reaction was monitored by thin layer chromatography using pre-coated silica gel G plate as a stationary phase and a suitable mobile phase. The final products were purified by recrystallization from aqueous ethanol. The melting points (m.p.) of the synthesized compounds were determined in open capillaries by Expo-hi-tech melting point apparatus and are uncorrected. The structures of all the synthesized compounds were characterized by recording their infra red (IR) spectra on Jasco-FTIR spectrophotometer-410. The structures of 1,5-diaryl-2-thiohydantoins 4a-c were confirmed by the nuclear magnetic resonance ($^1$H NMR) spectra on JNM-MY 60 FT-NMR spectrometer operating at 300 MHz using TMS as an internal standard. The mass spectra of the compounds 4a-c were recorded on API QSTAR Pulsar spectrometer using atmospheric pressure ionization source.

**Step 1: Esterification**: Synthesis of methyl-$\alpha$-phenyl acetate, 1

**Conventional method**: Phenylacetic acid (1.36 g, 10 mmol) and methanol (5 mL) were mixed together
in a 250 mL round bottom flask. Concentrated H$_2$SO$_4$ (0.5 -1 mL) or p-toluenesulfonic acid (PTSA) (1.9 g, 10 mmol) was used as a catalyst. The reaction mixture was refluxed for 3-5 hr. This mixture was then poured into about 100 mL of ice-cold water in a separating funnel. Upper layer of crude ester was extracted in ether. The ether layer was washed with 20 mL of saturated sodium bicarbonate solution, followed by about 100 mL of ice-cold water. The ether layer was then dried using 2-3 g of anhydrous sodium sulphate. Ether was recovered. The ester thus obtained was used immediately for the next step.

**Microwave method:** The mixture of phenylacetic acid (1.36 g, 10 mmol), methanol (5 mL) and conc. H$_2$SO$_4$ (0.5 -1 mL) or PTSA (p-toluenesulfonic acid) (1.9 g, 10 mmol) was irradiated with microwave radiation at 490 W till the reaction was complete. The reaction mixture was processed in the same way as that in the conventional method.

**Methyl-α–phenyl acetate, 1:** Yield: Conventional: 46%, MW: 60%. TLC: [Hexane: Ethyl acetate (4:1)], R$_f$: 0.90; b.p. 218-20°C; IR (KBr): 1159 (C-O str), 1496 (C=C str), 1739 cm$^{-1}$ (C=O str).

**Step 3: Amination:** Synthesis of methyl-α-(p-substituted phenylamino) - α-phenyl acetate, 3a-c

**Conventional method:** To a solution containing compound 2 (0.22 g, 1.0 mmol) in ethanol (5 mL) and DMF (2 mL), amines such as aniline (0.18 g, 2.0 mmol) or anisidine (0.24 g, 2.0 mmol) or p-toluidine (0.20 g, 2.0 mmol) were added at RT. The reaction mixture was stirred and refluxed for 7-32 hr and then heated to remove part of the ethanol. The reaction mixture was diluted by adding water (10 mL) to it. It was then extracted by using ethyl acetate and the organic layer was dried over anhydrous Na$_2$SO$_4$. The aminated product thus formed was used immediately for the next step.

**Microwave method:** For the synthesis of compounds 3a-c by MW irradiation method, the above reaction mixture was irradiated under microwaves at 490 W till the completion of the reaction and it was processed in the same manner as that in the conventional method.

<table>
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<tr>
<th>Compd</th>
<th>Catalyst used</th>
<th>Conventional method</th>
<th>Microwave method</th>
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<td>Reaction Time (hr)</td>
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<tr>
<td>4c</td>
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Table I — Reaction time and per cent yield of compounds 1-4c by conventional and microwave irradiation methods
Methyl-α-(phenylamino)-α-phenyl acetate, 3a: Yield: Conventional: 48%, MW: 50%, TLC: [Hexane: Ethyl acetate (3.5:1.5)], Rₜ: 0.35; m.p. 138-40°C; IR (KBr): 1262 (C-O str), 1514 (C=C str), 1604 (N-H ben), 1651 (C=O str), 3416 cm⁻¹ (N-H str).

Methyl-α-(p-methoxyphenylamino)-α-phenyl acetate, 3b: Yield: Conventional: 9%, MW: 10%, TLC: [Hexane: Ethyl acetate (3.5:1.5)], Rₜ: 0.35; m.p. 116-18°C; IR (KBr): 1284 (C-O str), 1514 (C=C str), 1606 (N-H ben), 1651 (C=O str), 3265 cm⁻¹ (N-H str).

Methyl-α-(p-methylphenylamino)-α-phenyl acetate, 3c: Yield: Conventional: 8%, MW: 21%, TLC: [Hexane: Ethyl acetate (3.5:1.5)], Rₜ: 0.35; m.p. 116-18°C; IR (KBr): 1284 (C-O str), 1514 (C=C str), 1604 (N-H ben), 1651 (C=O str), 3416 cm⁻¹ (N-H str).

Step 4: Cyclization: Synthesis of 1,5-diaryl-2-thiohydantoins, 4a-c

Conventional method: Compound 3a or 3b or 3c (4.98 mmol) was dissolved in ethanol (10 mL) by heating. Potassium thiocyanate (KNCS) (0.87 g, 8.95 mmol) in water (5 mL) and triethylamine (1.26 g, 9.04 mmol) were added to it and the mixture refluxed till the reaction was complete. The reaction mixture was then concentrated and made acidic. The resulting solid was washed with ice water and purified by recrystallization from aqueous ethanol.

Microwave method: The reaction mixture used in the conventional method was irradiated under microwaves at 490 W till the reaction was complete and it was processed in the same manner as that of the conventional method.

1, 5-Diphenyl-2-thiohydantoin, 4a

Yield: Conventional: 5%, MW: 7%, TLC: [Methanol: Dichloromethane (5:0.5)], Rₜ: 0.27; m.p. 140-42°C; IR (KBr): 1190 (C=S str), 1487 (C=C str), 1597 (N-H ben), 1664 (C=O str), 3288 cm⁻¹ (N-H str); ¹H NMR: δ 3.749 (s, 1H, C-H), 7.102 (s, 1H, N-H), 7.124-7.443 (m, 6 H, Ar-H), 7.430 (d, 2H, J = 6.2, Ar-H), 7.517 (d, 2H, J = 6.2, Ar-H); MS: m/z 269.33 (M+1).

1-(p-Methoxyphenyl)-5-phenyl-2-thiohydantoin, 4b: Yield: Conventional: sticky product, MW:10%, TLC: [Methanol: Dichloromethane (5:0.5)], Rₜ: 0.75; m.p. 108-10°C; IR (KBr): 1197 (C=S str), 1487 (C=C str), 1593 (N-H ben), 1701 (C=O str), 3400 cm⁻¹ (N-H str); ¹H NMR: δ 3.6 (s, 1H, C-H), 3.63 (s, 3H, OCH₃), 7.156-7.160 (m, 5H, Ar-H), 7.261 (s, 1H, N-H), 7.461 (d, 4H, Ar-H); MS: m/z 299.35 (M+1).

1-(p-Methylphenyl)-5-phenyl-2-thiohydantoin, 4c: Yield: Conventional: 18%, MW: 25%, TLC: [Methanol:Dichloromethane (5:0.5)], Rₜ: 0.3; m.p. 95-98°C; IR (KBr): 1197 (C=S str), 1514 (C=C str), 1595 (N-H ben), 1701 (C=O str), 3030 cm⁻¹ (N-H str); ¹H NMR: δ 2.286 (s, 3H, CH₃), 3.841 (s, 1H, C-H), 7.144-7.172 (m, 5H, Ar-H), 7.287 (s,1H, N-H), 7.460 (d, 4H, J = 6.3, Ar-H); MS: m/z 283.35 (M+1).

The anti-inflammatory study of compounds 4a, 4b and 4c is in process.

Conclusion

In conclusion, a simple and efficient method for the synthesis of 1,5-diaryl-2-thiohydantoins by microwave irradiation method has been developed. The products are obtained in much shorter time as compared to the conventional method with increase in yield from 1-23%. The quality of products is also found to be better as compared to the conventional method.

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References