Bucherer–Bergs Multicomponent Synthesis of Hydantoins

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The Bucherer–Bergs reaction is one of the most convenient general methods for the preparation of 5-substituted and 5,5-disubstituted hydantoins (imidazolidine-2,4-diones, 2,4-dioxoimidazolidines). Generally, in this multicomponent reaction, the aldehyde or ketone in aqueous ethanol is heated at 60–70° with potassium (or sodium) cyanide and ammonium carbonate to produce directly hydantoins 1.

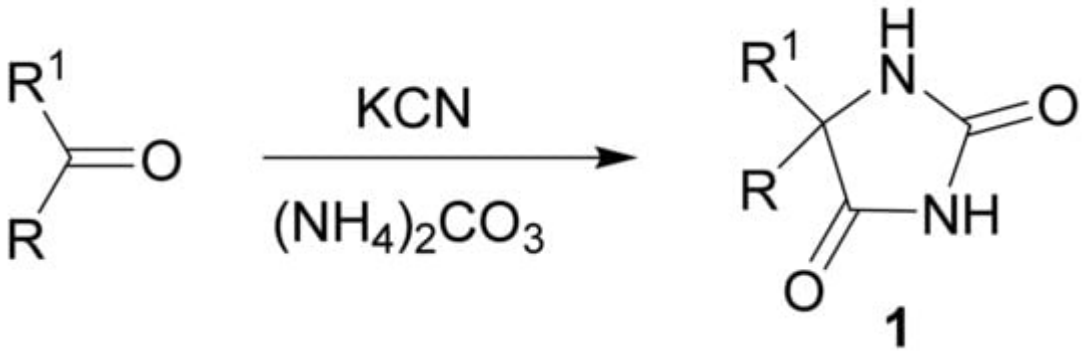
hydantoins aldehyde ketone multicomponent reaction Bucherer–Bergs reaction

1. Overview

Hydantoins and their hybrids with other molecules represent a very important group of heterocycles because they exhibit diverse biological and pharmacological activities in medicinal and agrochemical applications. They also serve as key precursors in the chemical or enzymatic synthesis of significant nonnatural α-amino acids and their conjugates with medical potential. This review provides a comprehensive treatment of the synthesis of hydantoins via the Bucherer–Bergs reaction including the Hoyer modification but limited to free carbonyl compounds or carbonyl compounds protected as acetals (ketals) and cyanohydrins used as starting reaction components. In this respect, the Bucherer–Bergs reaction provides an efficient and simple method in the synthesis of important natural products as well as for the preparation of new organic compounds applicable as potential therapeutics. The scope and limitations, as well as a comparison with some other methods for preparing hydantoins, are also discussed.

2. Bucherer–Bergs Reaction

The Bucherer–Bergs reaction is one of the most convenient general methods for the preparation of 5-substituted and 5,5-disubstituted hydantoins (imidazolidine-2,4-diones, 2,4-dioxoimidazolidines). Although the reaction was first discovered by Bergs [1] (but the first formation of 5,5-dimethylhydantoin from a mixture of acetone and hydrocyanic acid exposed to sunlight for a period of 5–7 months was observed by Ciamician and Silber in 1905 [2]), it is usually credited to Bucherer, who elaborated most of the experimental conditions and applications [3][4][5]. Generally, in this multicomponent reaction, the aldehyde or ketone in aqueous ethanol is heated at 60–70° with potassium (or sodium) cyanide and ammonium carbonate to produce directly hydantoins **1** (Scheme 1).



Scheme 1. General reaction scheme of the Bucherer–Bergs reaction. R and R^1 varied alkyl or aryl substituent.

This reaction works well for aliphatic and aromatic aldehydes or ketones and for cyclic ketones despite some reports concerning the failure of this reaction. For such difficult cases, the use of acetamide (formamide as well as dimethylformamide) as a solvent has been recommended [6][7]. It was found that ultrasonication could also accelerate hydantoin formation [8]. Alternatively, better yields of hydantoins offer the Hoyer modification [9]. In this case, the standard reaction mixture is heated in the atmosphere of CO_2 in a closed system at elevated pressure. Because of the wide applicability of the Bucherer–Bergs reaction, it has formerly been proposed as an analytical method for identifying ketones [10].

Hydantoins may be regarded as cyclodehydrated hydantoic acids (α-ureido acids), and this is reflected in their properties because both these compounds are readily interconvertible. Several natural or synthetic hydantoins themselves or their conjugates with other molecules exhibit diverse biological and pharmacological activities in medicinal, such as antimicrobial [11][12][13][14][15], antiviral [16][17][18], antitumor [19][20][21][22], antiarrhythmic [23][24][25][26], anticonvulsant [27][28][29][30][31][32][33][34], antihypertensive [35], antidiabetic [36][37][38][39], and agrochemical, such as herbicidal and fungicidal [40][41][42][43][44][45], applications. The studies on the biological activities of hydantoins has made great progress during the last three decades, and hydantoin derivatives have been therapeutically applied or are in the stage of investigation (**Figure 1**). For example, Phenytoin (Phenytek®, Dilantin®, Epanutin®, Diphenin®)—an antiepileptic drug—is still the drug of choice for the treatment of generalized tonic–clonic seizures (grand mal epilepsy) and focal motor seizures [29][46][47][48][49]; today, Phenytoin has found new applications because of the neuro- and cardioprotective properties [50][51]; Mephenytoin (Mesantoin®; it is no longer available in the US or the UK) and Fosphenytoin (Cerebyx®, Prodilantin®) are also effective anticonvulsants, the latter is used only in hospitals for the short-term (five days or less) treatment of epilepsy [52]; Nitrofurantoin (Furadantin®, Macrobid®, Macrodantin®) and Nifurtoinol (Urfadyn®)—produces antibacterial activity effective for the treatment of urinary tract infections [53][54][55]; Nilutamide—produces an antiandrogenic effect in the treatment of an advanced stage of the carcinoma of the prostate [19][20][22]; Sorbinil—an aldose reductase inhibitor that blocks the formation of sorbitol from excess glucose and thus may prevent many diabetic neuropathies [56][57][58]; Dantrolene (Dantrium®)—used to treat malignant hyperthermia, neuroleptic malignant syndrome, ecstasy intoxication, and muscle spasticity (stiffness and spasms) caused by conditions such as a spinal cord injury, stroke, cerebral palsy, or multiple sclerosis and is currently the only specific and effective treatment for malignant hyperthermia [59]; Azimilide—an investigational class III anti-arrhythmic drug that blocks fast and slow components of the delayed rectifier

cardiac potassium channels (until now, it has not been approved for use in any country but is currently in clinical trials in the United States) [60]. Iprodione (Rovral®, Kidan, Glycophene) is an example of a commercially used fungicide [61]. Because of their unique features, some glycofuranosylidene- and glycopyranosylidene-spiro-hydantoins have received wide attention. For example, (+)-hydantocidin (D-ribofuranosylidene-spiro-hydantoin) [62][63] possesses significant herbicidal and plant growth regulatory activities [41][64][65][66]; glucopyranosylidene-spiro-hydantoin [36][67][68] is among the most potent inhibitors of rabbit muscle glycogen phosphorylase known to date (*K*i = 3–4 μM).

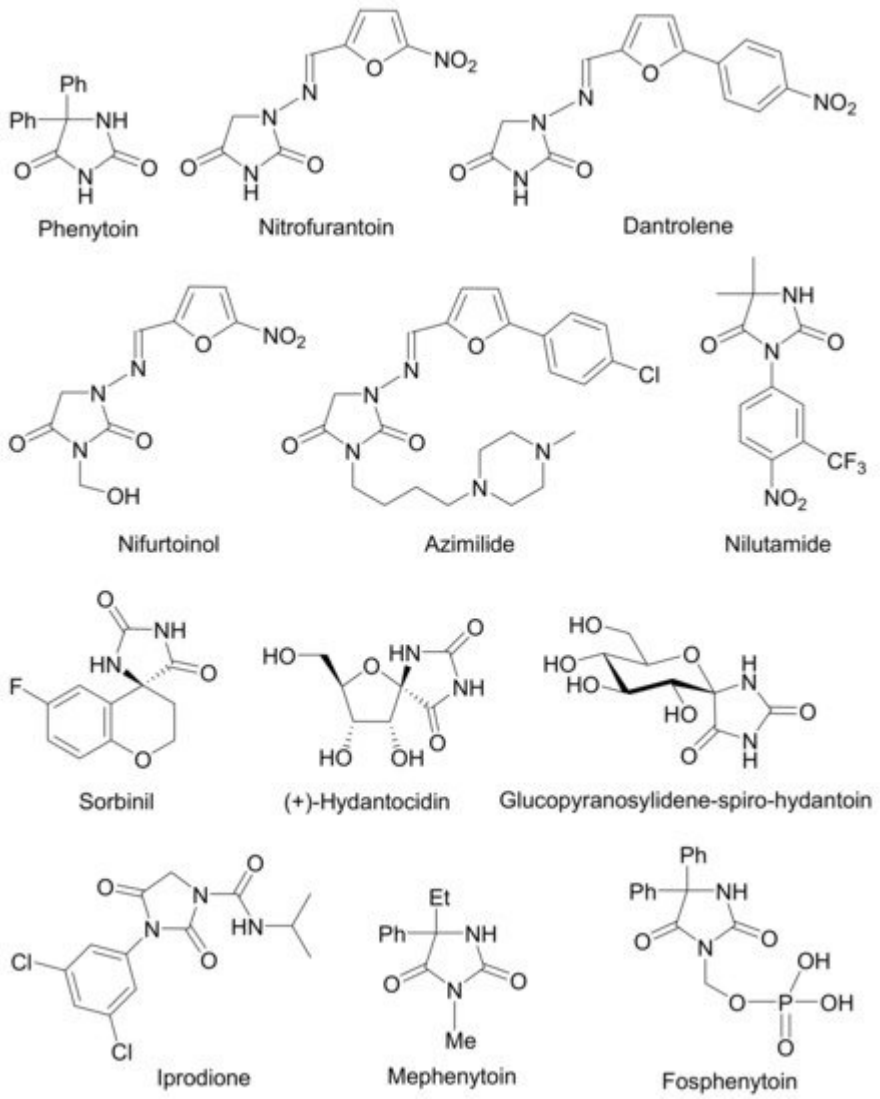


Figure 1. Therapeutically applied hydantoin derivatives.

Additionally, hydantoins also serve as key precursors in the chemical or enzymatic synthesis of significant nonnatural α-amino acids and their conjugates with medical potential. In this respect, the Bucherer–Bergs reaction provides an efficient method in the synthesis of important natural products as well as for the preparation of new organic compounds applicable as potential therapeutics.

Until now, five relevant reviews [69][70][71][72][73] and one book chapter [74] have appeared regarding the chemistry of hydantoins covering, inter alia, some aspects of the Bucherer–Bergs reaction. This review provides a comprehensive treatment of the synthesis of hydantoins via the Bucherer–Bergs reaction including the Hoyer modification but limited to free carbonyl compounds or carbonyl compounds protected as acetals (ketals) and cyanohydrins used as starting reaction components (i.e., the “classical” Bucherer–Bergs reaction starting from carbonyl compounds). The synthesis of hydantoins starting from corresponding amino nitriles (prepared from carbonyl compounds in a separate reaction step) or imines (prepared separately from carbonyl compounds or cyanides) were not included because, in this synthetic modification, only two reaction components are comprised, so these reactions are not multicomponent. Analogously, the other synthetic methods affording hydantoins were not reviewed in this review.

3. Conclusions

Although several synthetic methods for the preparation of hydantoins have been described so far, the Bucherer–Bergs reaction represents the simplest and very effective approach, in particular to 5-substituted and 5,5-disubstituted hydantoins (unsubstituted on N-1 and N-3). Therefore, this synthetic method is still current and often used for the synthesis of biologically and pharmacologically active compounds applicable in medicine, pharmacy, or agro-industry. In this respect, the presented review covered in depth the knowledge gained during the almost century-old history of hydantoin synthesis via the Bucherer–Bergs reaction.

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