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Highly efficient and rapid synthesis of diverse hydantoin derivatives using nano-ordered ZnO catalyst under mechanochemical ball milling

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Abstract

A mild and efficient one-pot three-component and environmentally benign approach for the synthesis of a wide range of hydantoin annulated derivatives has been described. A multi-component reaction between a carbonyl compounds (ketone or aldehyde), potassium cyanide and ammonium carbonate (as cyanating agent and amine source, respectively leads to the formation of hydantoins. The proposed optimized reaction conditions, *i.e.* solvent-free conditions under ambient temperature in the presence of low amount of ZnOnano-catalyst, were very efficient resulting in the formation of the desired products with good to excellent yields. Furthermore, the presented methodology is in accord with green chemistry principles.

Keywords: Bucherer-Bergs; hydantoinderivatives; multicomponent reactions (MCRs); green chemistry.

Introduction

Amides and some of their derivatives are very interesting functional moieties present in a wide variety of biologically and chemically significant molecules. Hydantoins, imidazolidine-2,4-diones, 2,4-diketotetrahydroimidazo, was discovered by Adolph von Baeyer in 1861 by hydrogenolysis of allantoin [1]. Hydantoin is one of the five-membered cyclic amide including a useful reactive urea moiety. These compounds have occupied an important place in drug research because of their various biological and pharmacological activities such as anti-ulcer[2], anti-tumor[3], antiviral[4], antiandrogen[5], antimicrobial[6], antihypertensive[7], anti-diabetic[8], anti-arrhythmic[9], anticonvulsant[10], antiandrogenic[11] and the human immunodeficiency virus (HIV) [12] activities.

A number of substituted hydantoin derivatives have been therapeutically useful, *e.g.* of phenytoin as antiepileptic, azimilide as an antiarrhythmic, of nitrofurantoin as an antibacterial substance or of dantrium as a sceletal muscle relaxant; furthermore, hydantoins have also been developed as new drugs in the treatment of other diseases, for example, nilutamide, orally active antiandrogen in the therapy of metastatic prostate cancer (Figure1) [12].

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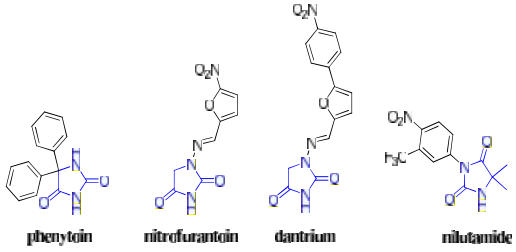


Figure 1. Therapeutically used Hydantoins

Furthermore, compounds containing hydantoin scaffold which have been found in many natural compounds show different biological activities. For example, many alkaloids extracted from sponges or corals contain a hydantoin moiety (Figure 2) [12].

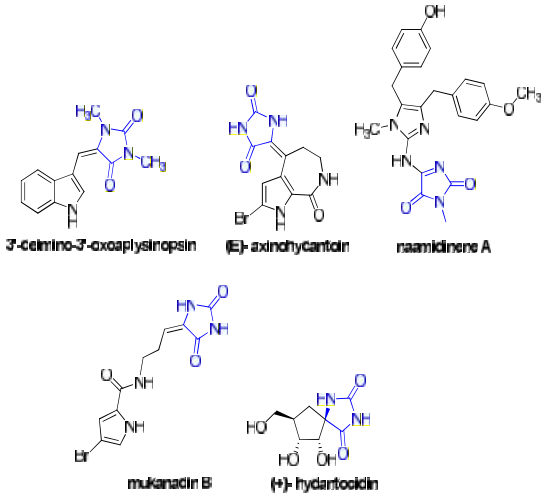


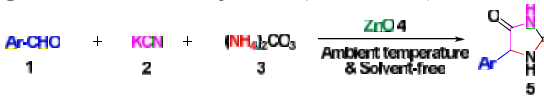
Figure 2. Naturally important molecules containing a hydantoin moiety

Over the last few decades, there has been considerable interest in the synthesis and characterization of the various useful synthetic hydantoin derivatives, owing to their potential useful biological activities. Among various methods reported in the literature for the preparation of hydantoin, Bucherer-Bergs multicomponent reaction is one of the most important strategies starting from carbonylcompounds(aldehydesorketones) orcyanohydrins with ammonium carbonate and potassium cyanide. Herein, the development of new catalytic multicomponent reactions (MCRs) can lead to new efficient and green synthetic strategies for the synthesis of hydantoin derivatives [13]. MCRs methodologies compared to multi-step reactions would justify a central place in the toolbox of sustainable synthetic methodologies due to creation of several new bonds in a one-pot reaction, low number of reaction and purification steps, high convergence& selectivity, atom economy, mild conditions and efficiency [14].

A literature survey reveals that several catalytic systems for MCR synthesis of hydantoin derivatives have been reported including different Lewis or Bronsted acids, homogeneous or heterogeneous catalysts and solvents. However, many proposed methods for the synthesis of these compounds suffered from several drawbacks such as multi-step conditions, the use of volatile solvents, high catalyst loading or catalysts containing transition metals, very expensive reagents, drastic reaction conditions, low yields and tedious work-up and high reaction time [15]. Therefore, obviation of these limitations is necessary to develop a simple and clean procedures and utilizing eco-friendly green catalyst[16]. In this regard, application of solvent-free mechanochemicalball milling technique and nano-catalyst are attractive candidates in academic and industrial research groups.

Herein, we report a quantitative, convenient, cost-effective and eco-friendly ball-milling methodology for the synthesis of diverse hydantoin derivatives in the presence of ZnO

nanocatalyst based on MCR strategy in good to excellent yields (Scheme 1).



Scheme 1. One-pot three-component reaction of different aldehydes, potassium cyanide and ammonium carbonate catalyzed by ZnO

Experimental

General

All commercially available starting materials and solvents were obtained from Merck (Germany) and Fluka (Switzerland) in high purity and were used without further purification, except for benzaldehyde which was used as a fresh distilled sample. The ball mill was a Retsch MM 400 swing mill with its 3Ddriving of the balls. A 10 mL stainless steel double-walled beaker was applied, and the milling frequency was at 28 Hz at the ambient temperatures. The methods used to monitor the reactions are analytical thin layer chromatography (TLC). Melting points were determined in open capillaries using an electrothermal 9100 apparatus and were uncorrected. IR spectra were measured on a Jasco 6300 FTIR spectrometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded onBruker DRX-400 spectrometers with DMSO-d^6 as solvent.

General procedure for the preparation of ZnOnano-catalysts

ZnO nanoparticles were synthesized according to the literature[17]. Zinc sulphateheptahydrate and sodium hydroxide were used as precursors of surfactant Free Synthesis of ZnO. Briefly, 0.1 M $ZnSO_4.7H_2O$ and 0.4 M NaOH deionized water solutions were mixed in the glass flask. Afterward, the resulting solution was stirred for 15 min and exposed to irradiate at microwave oven for 1 min. After completion of the reaction, the white product obtained was filtered and consecutively washed with distilled water (5-50 mL) and ethanol (3-10 mL) and was dried in an oven (60 °C, 2 h).

General procedure for the preparation of 5,5-disubstituted hydantoins (5a–j) usingZnO nanoparticles

Aldehyde or ketone (**1a**, 1mmol), potassium cyanide (**2**,**1.** 3 mmol), ammonium carbonate (**3**, 3 mmol), ZnOnanocatalysts (7.5 mg) was poured in the clean and dry 25 mL stainless steel double-walled ball mill beaker equipped. The milling was performed at ambient temperatures at a speed of 25 Hz for the times given in Tables 2. The reaction progress was followed by TLC (petroleum ether:ethyl acetate, 1.2:1 v/v), after every 10 min milling cycles. After completion, the mixture was poured in water and neutralized with dilute hydrochloric acid, the ZnO heterogeneous catalyst and solid products removed by filtration. Solid mixture was dissolved in EtoAc and filtered to remove the catalyst. The organic solvent of the filtrate was evaporated under reduced pressure to obtain essentially crude products. Products were further purified by crystallization from water ethanol mixture.

Characterization data of some of the compounds

X-ray diffraction of ZnO

Figure 3a shows the X-ray diffractograms of the calcined samples of ZnO nanoparticles. According to the X-ray diffractogram shown in Figure 3a, the synthesized ZnO nanoparticles are compatible with the literatures.The employed work-up procedure was an efficient way for the purification of the nanoparticles and according to this

pattern impurities have been completely removed.

SEM and TEM experiments of ZnO nanoparticles

The morphology and particle size of the ZnO nanopowder was revealed by SEM and TEM analysis. As shown in Figure 4a, no anisotropic growth was observed and all the ZnO nanoparticles had an irregular spherical shape. Also, the TEM image shows spherical morphology and a narrow distribution of sizes between60–80 average diameters.

Additional the XRD and SEM analysis (Figure 3b, 4b) for the nanoparticles after catalyst–recycle process showed that there is not any Specific change in the size and morphology of the ZnO nanoparticles after recycling of catalyst from reaction mixture. Just, it was also found that the nanoparticles aggrovate.

Nanoparticles agglomerate by adhesion of particles to each other under ball milling conditions in the reaction process (Figure 4b). In other words, the ZnO nanoparticles after reaction process shows spherical morphology and a narrow distribution of sizes about 50–80 average diameters.

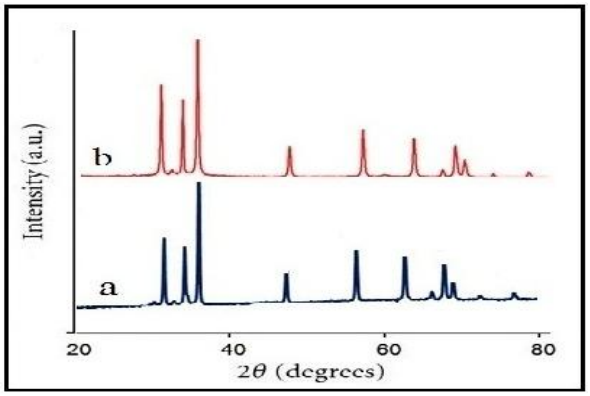


Figure 3. The X-ray diffractograms of the calcined samples of ZnO nanoparticles: a) before reaction; b) after catalyst–recycle process

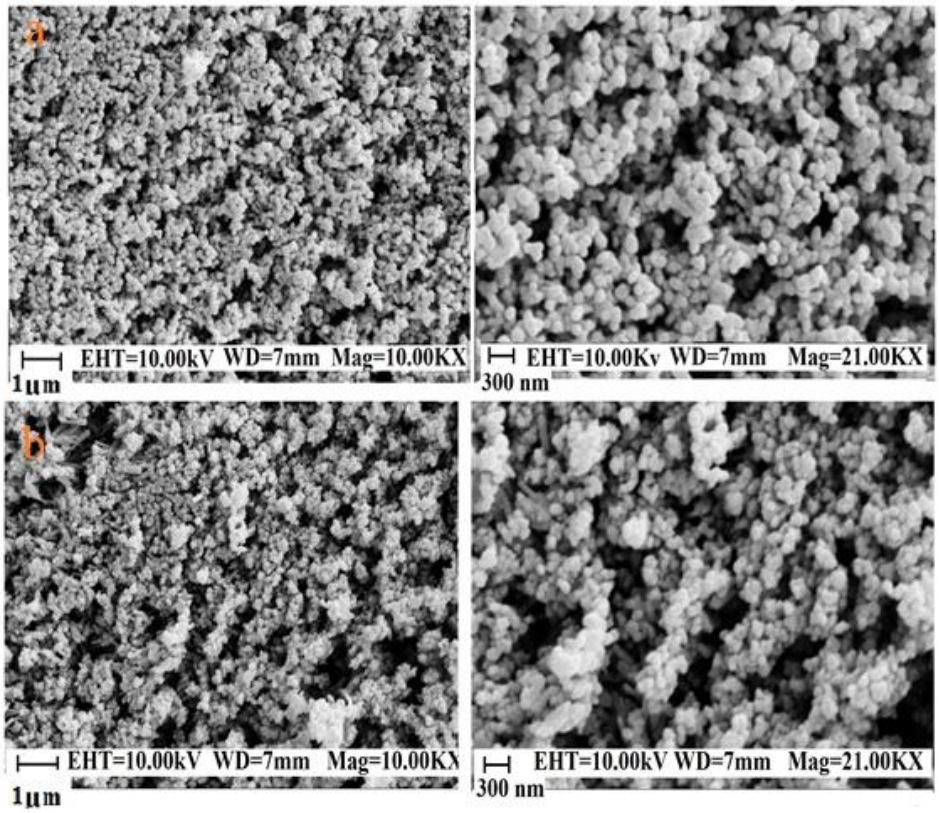


Figure 4. SEM of the ZnOnanopowder: a) before reaction; b) after catalyst–recycle process

Spectral data of products

5-Phenyl imidazolidine-2,4-dione ($C_9H_8N_2O_2$, 5c)

White powder crystals; 170 °C m.p; ^{1}H NMR (DMSO-d6, 400 MHz) d: 10.82 (s, 1H, N_3–H), 8.51(s, 1H, N_1–H), 7.21 (t, 1H), 7.39 (d, 2H), 7.51 (t, Hz, 2H) and 5.10 (s, 1H); IR (KBr cm^{-1}) ῡ: 3500 (N–H, s), 3290 (N–H, s), 3140 (=C–H), 3011 (=C–H), 1732 (C=O), 1720 (C=O), 1445 (C=C) and 1424 (N–H, b).

5-Methyl-5-phenyl-imidazolidine-2,4-dione ($C_{10}H_{10}N_2O_2$, 5i)

White powder; 190 °C m.p; ^{1}H NMR (DMSO-d6, 400 MHz) d: 10.65(s, 1H, N_3-H), 8.70 (s, 1H, N_1- H), 7.50–7.44 (d, 2H), 7.38–7.34 (t, 2H), 7.32-7.30 (t, 1H) and 1.64 (s, 3H); IR (KBr cm^{-1}) ῡ: 3279 (N-H, s), 3222 (N-H, s), 3055 (=C–H, m), 2982 (C–H, m), 1732 (C=O, s), 1721 (C=O, s) and 780 (=C–H, b).

Results and discussion

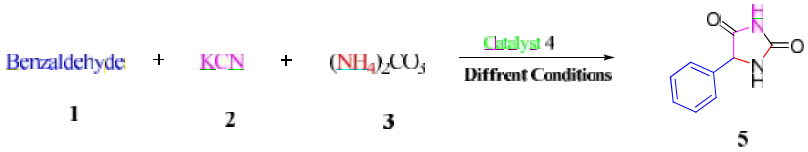
In order to obtain the best reaction conditions, the reaction between benzaldehyde (**1a**), potassium cyanide (**2**) and ammonium carbonate (**3**) (molar ratio: 1:1.3:3)was chosen as a model reaction and the effect of different factors on the yield of the desired 5-(phenyl)imidazolidine-2,4-dione (**5c**) was studied. The obtained results are summarized in Table 1.

As shown in Table 1, preliminary optimization experiments indicated that only a trace amount of the desired 5-(phenyl)imidazolidine-2,4-dione (**5c**) was formed in various solvents such as H_2O, CH_2Cl_2, CH_3CN, EtOH and EtOH/H_2O, even under reflux conditions (Entries 1–4). However, the use of solvent-free ball milling condition at ambient temperature improves the yield of the desired

product **5c** slightly (Entry 5). Therefore, the above experimental results showed that the mechanochemical ball milling can be approximately a useful techniquefor the synthesis of Hydantoin derivatives.

In the next step, in order to further improve the yield of the reaction, we investigated the model reaction in mechanochemical ball milling conditions in the presence of ZnO, magnetic Fe_3O_4[18],$CuFe_2O_4$[19] nanoparticles and silica sulfuric acid as catalyst at ambient temperature (entries 6-9). It was found that the higher yield of hydantoin was obtained in the presence of 20mg of ZnO nanoparticles as heterogeneous catalyst. In the next step, amount of catalyst was optimized (Entries 10-13). So, that the best result was obtained with 7.5mg of catalyst. ZnO nanopowder because of more surface atom sparticipating at their action, is more better than ZnO bulk (Entry14).

Table 1. Optimization of the reaction conditions[a]

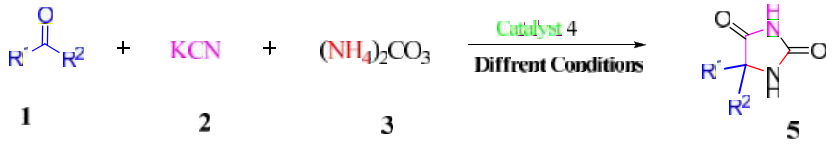


Entry	Catalyst (mg)	Conditions	Temp. (°C)	Time	Yield[b] (%)
1	-	H_2O	Reflux	Even to 24 h	Trace
2	-	EtOH	Reflux	Even to 24h	Trace
3	-	MeCN	Reflux	Even to 24h	Trace
4	-	H_2O/EtOH (1:1)	Reflux	Even to 24h	Trace
5	-	Ball milling	Ambient	60 min	20
6	ZnO (4a, 20)	Ball milling	Ambient	30min	98
7	Fe_3O_4 (4b, 20)[C]	Ball milling	Ambient	30min	40
8	$CuFe_2O_4$ (4c, 20)[d]	Ball milling	Ambient	30min	50
9	Silica Sulfuric Acid (SSA) (4d, 20)	Ball milling	Ambient	30min	65
10	ZnO (4a, 15)	Ball milling	Ambient	30min	98
11	ZnO (4a,10)	Ball milling	Ambient	30min	98
12	ZnO (4a,7.5)	Ball milling	Ambient	30min	98
13	ZnO (4a,5)	Ball milling	Ambient	30min	83
14	ZnO (4d, bulk, 10)	Ball milling	Ambient	30min	40

[a]Reaction conditions: Benzaldehyde (1a, 1mmol), potassium cyanide (2,1.3 mmol), ammonium carbonate (3,3 mmol), solvent (2 mL), and required ammount of the catalysts. [b]The yields refer to the isolated product 5a.[c]Fe_3O_4 nanoparticles were prepared using chemical co-precipitation according to the literatures[18]. The obtained nanocatalyst size was estimated around 18 nm by TEM. [d]The copper ferrite nanoparticles were prepared by co-precipitation according to the literatures[19]. That broadening of the peak at 2θ = 35.31 and the Scherrer equation present a particle size of 35 nm for copper ferrite nanoparticles.

In order to investigate the scope of the reaction, the optimized condition was employed for different carbonyl compounds. The results have been summarized in Table 2. It was found that, the carbonyl compounds containing an electron withdrawing group (ERG) on the aromatic ring are more reactive than carbonyl compounds containing electron donating groups (Table 2, Entries 1, 2 and 4).

Table 2. Synthesis of 5,5-disubstituted hydantoin derivatives **5a-j** catalyzed by ZnO nanoparticles under solvent-free conditions at ambient[a]

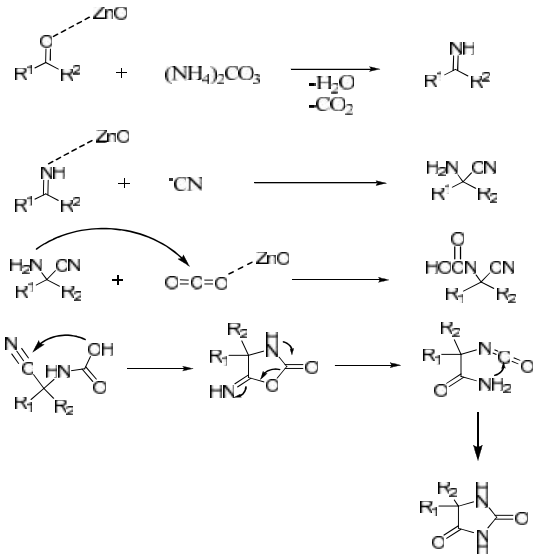


1 2 3 5

Entry	R^1	R^2	Product	Time (min)	Yield	MPrep/MPlit (°C)
1	4-ClC_6H_4	H	**5a**	25	97	300-302/ 290[20]
2	2-ClC_6H_4	H	**5b**	30	90	170-171/176[21]
3	C_6H_5	H	**5c**	30	98	170/164-165 [15b]
4	4-MeC_6H_4	H	**5d**	40	92	185-187/182.5[21]
5	4-$MeOC_6H_4$	H	**5e**	40	90	189-191/193-197[22]
6	2-$MeOC_6H_4$	H	**5f**	50	90	190-191/185-186[21]
7	4-ClC_6H_4	CH_3	**5g**	30	97	265-267/263-263[23]
8	4-MeC_6H_4	CH_3	**5h**	60	94	200-201/203.5[21]
9	C_6H_5	**CH_3**	**5i**	50	92	190-192/196-198[15a]
10	C_6H_5	**C_6H_4**	**5j**	50	90	295-297/296-298[22]

[a]Reaction conditions: Aldehyde or ketone (1a, 1mmol), potassium cyanide (2, 1.3 mmol), ammonium carbonate (3, 3 mmol), ZnOnanocatalyst (7.5 mg)

A plausible mechanism for the synthesis of hydantoin 5 outlined in Scheme 2 that as can be seen, the ZnOnano-catalyst could effectively increase the reactivity of the carbonyl functional group.



Scheme 2. Possible mechanism for the preparation of hydantoin derivatives

Conclusion

In conclusion, this work offers an efficient, simple and solvent-free three-component method for the synthesis of 5,5-disubstituted hydantoin derivatives in the presence of ZnOnano catalyst. Short reaction times, good to excellent yields and simple work-up are the main advantages of this reaction.

Acknowledgements

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