One-Pot Synthesis of Phenytoin Analogs in Solvent free Conditions Via the Use of Pestle/ Mortar

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Abstract

phenytoine derivatives were synthesized , via the pinacol condensation with the reaction of 1,3- diphenyl- propane- 1,3- dione (benzyl) analogs with urea or thiourea in presence of slica gel and solid KOH as Solid phase catalyst in the mortar / pestle at room temperatures. The reaction was completed at short reaction times (approximately 15min) and pure products were obtained with high yields (81-94%).

Key words: Phenytoin, Green Chemistry, Solvent free, Synthesis, Grinding

Introduction

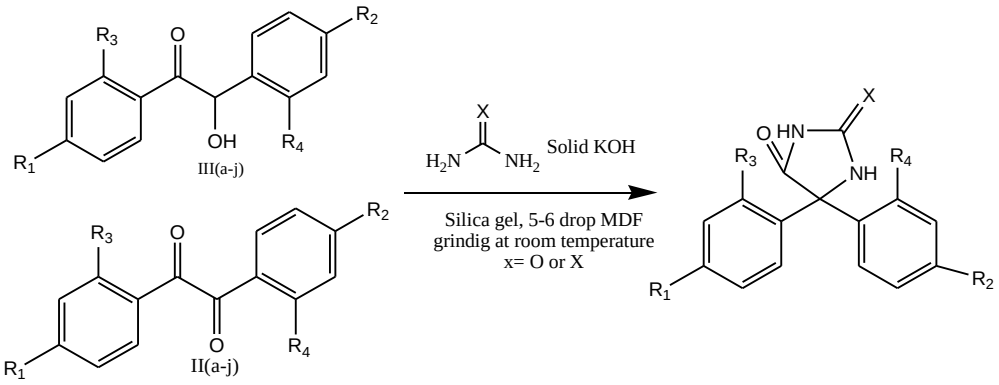
Due to the growing green chemistry concern and influence of organic solvents on environment as well as on human body, design of process that eliminate usage of conventional organic solvents attracted the attention of synthetic organic chemists. Although a number of modern solvent such as ionic liquid and water have been extensively studied recently, but not usage of solvent at all is definitely best option [1].

Solid state organic synthesis, is an active area in recent research because of the good dispersion of active reagent, immobilized on the porous solid support, enhanced selectivity and reactivity, easier work up, facilitated scale up, cleaner , faster, higher yielding reactions, reducing risk of polluting and explosions [2-7]. Heterocyclic compounds are an important units in variety of pharmacologically active substances and treatment diseas[8]. In the other hand, synthesis of biologically active moiety with high percentage yield as well as purity is one of the object of green chemistry, especially in CNS acting drugs, this goal could be achieved by omitting interfering solvents [9].

In this view, we investigated, the 5,5-diphenyl-2,4-imidazolidinedione (phenytoin) nucleus, a common 5- membered ring, containing a reactive cyclic urea core.

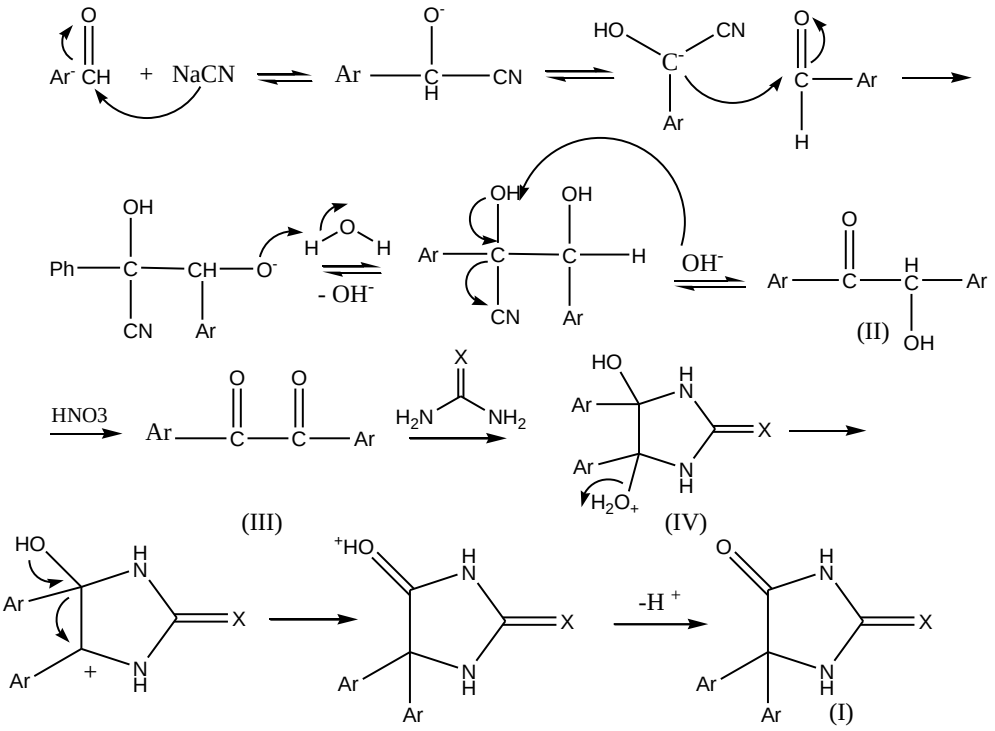
It used in wide range of biological activity such as anti arrhytmics [10], anticonvalsunt[11] and antitumor[12] agents. Among this, it is commonly used as antiepileptic drugs. It is used to treatment of tonic- clonic seizures and focal motor seizures [13], by reducing electrical conductance among brain cells, by stabilizing the inactive voltage gated sodium channels . Several, procedures for the synthesis of new hydantoin- like compounds were described previously[14-16].

Due to follow our attention to solid state organic reactions, we report a novel synthesis of phenytoin analogs from the easily accessible starting materials under solvent free conditions using solid KOH and silica gel and 5-6 drop of DMF as catalyst, by grinding in a mortar afforded the corresponding (1a).



Mechanism of phenytoin synthesis:

This reaction followed by benzoin condensation, self-condensation of aromatic aldehyde in presence of NaCN , corresponding α- hydroxyl ketone (III) obtained. then, in presence of concentrated nitric acid, oxidated to corresponding diketone (II) that due to intraction with urea, hetrocyclic structure (4,5- dihydroxy – 2- imidazolone as intermediate) informed(IV) and undergo pinacol rearrangment at acidic conditions and corresponding 5,5- diphenyl- imidazolidine- 2,4- dione was obtained.



EXPERIMENTAL

All chemicals were purchased from Sigma-Aldrich and were used without any purification. Melting points are determined on Buchi 530. IR spectra were recorded on Perkin-Elmer FTIR-1710 spectrophotometer usig KBR. The temperature of the reaction mixture was measured through a non- contact infrared thermometer (AZ, Mini Gun type, Model 8868).

Preparation of 3- hydroxyl – 1,3- diphenyl propane 1- ompoone analogs (IIIa)

General procedure

A round bottom flask, was charged with 50 ml ethanol 96%, 30 ml (3.9 g, 25mmol) of benzaldehyde, a solution of 2.5 g (38.3 mmol) sodium cyanide in 45 ml of distilled water was added, reaction mixture was stirred for 1 hour, under reflux conditions. The process of reaction was monitored by TLC. After complication of reaction, cooled the reaction mixture to room temperature and then in an ice bath, solid precipitate was obtained and Collected over in an Buchner funnel, It washed with distilled water (3-4 times) to remove excess sodium cyanide, and recrystalized from ethanol 96%. Pour product obtained as white crystals (26g, 86%).

m.p = ˚C Publisehed Data []: mp= ˚C

Preparation of 1,3- diphenyl- propane- 1,3- dione analogs (IIa)

General procedure

Round- bottom flask equeiped with 20.2g (96.2 mmol) of benzyl (IIIa) and 100 ml concentrated nitric acid, 10g (125mmol) sodium cyanide as catalyst and heated at the reflux conditions, for 90 min with stirring and gas trap, bring the solution to a gentle boil and monitoring the reaction mixture with TLC. Formation of NO_2 gas indicates oxidation of compound (IIa) when gas extracted completely, The solution was cooled and precipitate was filtered off, recrystallized with 96% ethanol. Yield 72.9g (72%), pale Yellow crystal, mp= 103 ˚C, previous report: mp= 102-104 ˚C

Preparation of 5,5- diphenyl imidazolidine 2,4- dione (Ia)

Classical method

A round bottom flask, was charged with 20.2 g (96.2 mmol) of benzyl, a 12.69 g (167mmol) of urea in 40 ml of DMSO, 25ml of 1.2 aqueous KOH mixture were added under reflux conditions for 2 hours. The process of reaction was monitored by TLC. After complication of reaction, cooled the reaction mixture to room temperature and then in an ice bath, solid precipitate was filtrated and the filtrate was acidified with HCl, the resulting precipitate was collected , dried and recrystalized from ethanol 96%. Pour product was obtained as white crystals (yield, 63%), m.p.= 295-296 ˚C

Solvent free Conditions:

A mixture of 20.2g (96.2 mmol) of benzyl (IIa), 12.69g (167 mmol) urea, 11/2g (200 mmol) Solid KOH, 50g Silica gel, 30 drop MDF, was ground by pestle and mortar at room temperature for the period indicated in (Table 1). After completion of reaction as indicated by TLC [eluent:CCl_4 / ether: 1:2]. The reaction mixture was worked- up in Dichloromethan.

Yield 83 g (83%), white crystal, mp=288- 295 ˚C .

5,5- di(4- Chloro phenyl)- imidazolidine- 2,4- dione (Ib)

As described for (Ia), 23.7g of 1,3- bis (4- Chloro- phenyl) propane- 1,3- dione (IIb) and 12.69g (167mmol) urea

5,5- di(4- Bromo phenyl)- imidazolidine- 2,4- dione (Ic)

As described for (Ia), 28.2g of 1,3- bis (4- Bromo- phenyl) propane- 1,3- dione (IIc) and 12.69g (167 mmol) of urea .

5,5- di(4- Cyano phenyl)- imidazolidine- 2,4- dione (Id)

As described for (Ia), 23.2g of 1,3- bis (4- Cyano- phenyl) propane- 1,3- dione (IId) and 12.69 g (167 mmol) of urea

5,5- di(2- Cl phenyl)- imidazolidine- 2,4- dione (Ie)

As described for (Ia), 23.7g of 1,3- bis (2- Cl- phenyl) propane- 1,3- dione (IIe) and 12.69g (167 mmol) of urea

5,5- diphenyl- 2- thioxo- imidazolidin- 4- one (If)

The synthesis was performed as for (Ia) under solvent free conditions but using thiourea,

5,5- di (4- Chloro phenyl)- 2- thioxo- imidazolidin- 4- one (Ig)

As described for (If), 23.7g of 1,3- bis (4- Chloro- phenyl) propane- 1,3- dione (IIg) and 14.3g (165 mmol) of thio urea

5,5- di (4- Bromo- phenyl)- 2- thioxo- imidazolidin- 4- one (Ih)

As described for (If), 28.2 g of 1,3- bis (4- Bromo- phenyl) propane- 1,3- dione (IIh) and 14.3 (165 mmol) of thio urea .

5,5- di (4- Cyano- phenyl)- 2- thioxo- imidazolidin- 4- one (Ii)

As described for (If), 23.2 g of 1,3- bis (4- Cyano- phenyl) propane- 1,3- dione (IIi) and 14.3 (165 mmol) of thio urea .

5,5- di (2- Chloro- phenyl)- 2- thioxo- imidazolidin- 4- one (Ij)

As described for (If), 23.7 g of 1,3- bis (2- Chloro- phenyl) propane- 1,3- dione (IIj) and 14.3g (165 mmol) of thio urea .

Mechanism of phenytoin synthesis:

This reaction followed by benzoin condensation, self-condensation of aromatic aldehyde in presence of NaCN , corresponding α- hydroxyl ketone (III) obtained. then, in presence of concentrated nitric acid, oxidated to corresponding diketone (II) that due to intraction with

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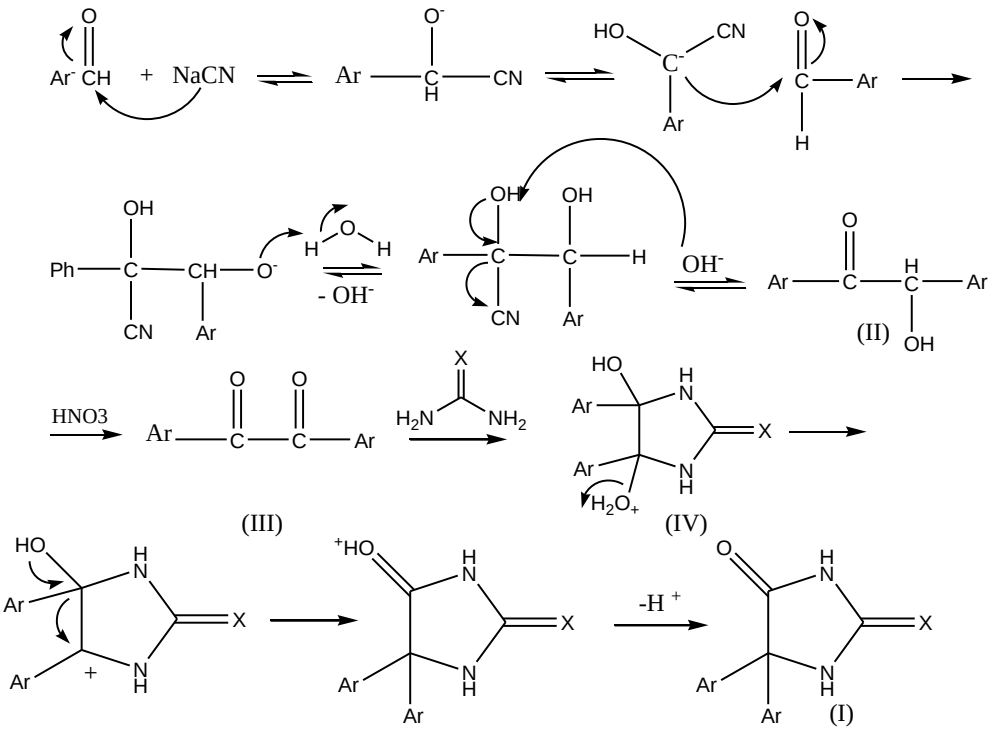

Table 1 : the time and yield of synthesized phenytoin

Comp	Ar	X	m. p. °C	Thermal		Pestel/ Mortar		Color
				Time (h)	Yield (%)	Time (min)	Yield (%)	
Ia	C6H5	O		2	63%	15	83%	White
Ib	P-Cl-C6H5	O		2	58%	15	81%	
Ic	P-Br-C6H5	O		2	65%	15	89%	
Id	P-CN-C6H5	O		2	68%	15	89%	
Ie	O-Cl-C6H5	O		2	54%	15	84%	
If	C6H5	S		2	55%	15	84%	White
Ig	P-Cl-C6H5	S		2	62%	15	90%	
Ih	P-Br-C6H5	S		2	69%	15	89%	
Ii	P-CN-C6H5	S		2	67%	15	90%	
Ij	O-Cl-C6H5	S		2	60%	15	86%	

Conclusion

We report a novel synthesis of phenytoin analogs by grinding the reaction mixture under solid phase conditions that involving, KOH, Silica gel without any solvent, so, it involves easy work up, Other advantages of this method are less reaction time, high yield reaction is carried out at room temperature and mild reaction conditions that make this procedure very useful and environment friendly.

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