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One-Pot Synthesis of Imidazolidine-2-Thiones, Hydantoins and Thiohydantoins under Solvent-Free and Grinding Conditions

Mohammad M. Ghanbari[1*], Javad Safari[2], Zahra Roohi[1]

[1]Young Researchers and Elite Club, Sarvestan Branch, Islamic Azad University, Sarvestan, Iran
[2]Department of Chemistry, Faculty of Science, University of Kashan, Kashan, Iran
Email: [*]m.mehdi.ghanbari@gmail.com

Received 15 July 2014; revised 4 September 2014; accepted 7 October 2014

Abstract

A convenient, environmentally friendly and mild green synthesis of imidazolidine-2-thiones, hydantoin and thiohydantoin derivatives was developed by the one-pot reaction of benzils, urea or thiourea derivatives, and strong base at with grinding. The key advantages are the short reaction times, excellent yields, simple workup, and easy purification in the solvent-free condition. The present method aimed to overcome the limitations and drawbacks of the reported methods such as hard work-up, low yield, hazardous solvent and long reaction time.

Keywords

Green Synthesis, Imidazolidine-2-Thiones, Hydantoin, Thiohydantoin, Grinding, Solvent-Free

Subject Areas: **Green Chemistry, Organic Chemistry**

1. Introduction

The imidazolidine-2,4-dione (hydantoin) and 2-thioxoimidazolidin-4-one (thiohydantoin) are a common 5-membered ring containing a reactive cyclic urea or thiourea core. They have a number of biological activities as antiarrhythmic, anti-inflammatory, antitumor, and antidiabetic properties, as well as the herbicidal and fungicidal activity [1]-[6]. In recent years, considerable efforts have been devoted to the development of novel and more efficient methods for the preparation of hydantoin and thiohydantoin derivatives. Besides conventional multi-

[*]Corresponding author.

How to cite this paper: Ghanbari, M.M., Safari, J. and Roohi, Z. (2014) One-Pot Synthesis of Imidazolidine-2-Thiones, Hydantoins and Thiohydantoins under Solvent-Free and Grinding Conditions. *Open Access Library Journal*, **1**: e705.
http://dx.doi.org/10.4236/oalib.1100705

step methods, one-pot, solid-phase and microwave-assisted approaches have been published [7]-[11]. As a part of our current studies on the development of new routes in heterocyclic synthesis [12]-[14], we now report here a novel and efficient method for the solid-phase synthesis of imidazolidine-2-thiones **3**, hydantoins and thiohydantoin **4**. **Scheme 1** illustrates the synthesis of imidazolidine-2-thiones **3**, hydantoins and thiohydantoins **4**. All these facts prompted me to find an ecofriendly new method and to employ grinding for the synthesis of the of imidazolidine-2-thiones a-c, hydantoins and thiohydantoins 4a-y in a solvent-free environment (**Table 1**).

2. Results and Discussion

The synthesis of a number of imidazolidine-2-thiones **3**, hydantoins and thiohydantoins **4** has been reported. The compounds of type **3** and **4** have been prepared by reacting benzils **1** with urea and thiourea derivatives **2** in the presence of strong base in solvent under reflux or solvent-free under microwave irradiation [7]-[14].

The reaction proceeded spontaneously under Solvent-Free and Grinding Conditions, and was completed within a few minutes. The ^{1}H and ^{13}C NMR spectra of the crude products clearly indicated the formation of **3** and **4**. The structures of compounds 4a-4y were deduced from their elemental analyses and their IR, ^{1}H NMR, and ^{13}CNMR spectra. The mass spectra of these compounds displayed molecular ion peaks at appropriate m/z values. Any product other than **3** and **4** could not be detected by NMR spectroscopy.

The structure **3** and **4** was assigned to the isolated products on the basis of their elemental analyses and IR, ^{1}H, and ^{13}C NMR and mass spectral data. Thus, the ^{1}H NMR spectrum of each of the isolated products **4** exhibited two NH proton signals at about 9.0 - 12.5 ppm. Further evidence was obtained from the ^{13}C NMR spectra, which displayed C=O and C=S carbon signals at about 160 - 185 ppm. The aryl residues gave rise to characteristic signals in the aromatic region of the spectrum.

A plausible mechanism for the formation of hydantoins and thiohydantoins 4a-4y has been reported in the literatures [10].

3. Conclusion

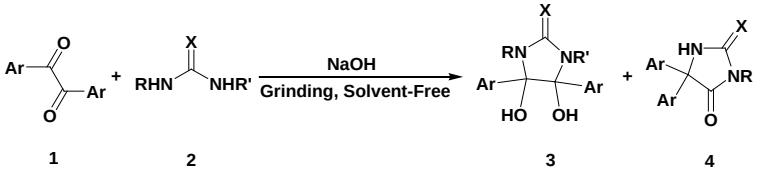
In conclusion, we have developed a simple, rapid, efficient and "green" synthesis of hydantoins and thiohydantoins in solvent-free conditions. Grinding has been applied to the reaction mixtures containing benzils and urea or thiourea derivatives, which allow me to achieve hydantoin and thiohydantoin derivatives in a good yield, low cost, simple workup, easy purification and short reaction time. This convenient procedure will allow a further increase of the diversity within the hydantoin and thiohydantoin family.

4. Experimental

Urea and thioureas **2** and sodium hydroxide were obtained from Fluka and were used without further purification. Benzils **1** was prepared by known methods [15]. Melting points (uncorrected) were measured on an Electrothermal 9100 apparatus. Elemental analyses for C, H, N and S were performed using a Heraeus CHN-O-Rapid analyzer. The experimental data were in good agreement with the calculated values. ^{1}H and ^{13}C NMR spectra ($CDCl_3$) were measured with a Bruker DRX-500 Avance spectrometer. IR spectra were recorded on a Shimadzu IR-460 spectrometer.

4.1. General Procedure for the Preparation of 4

A mixture of 1 mmol of **1** and 2 mmol of urea or thioureas were placed into a mortar, 0.080 g (2 mmol) of sodium hydroxide was added, and the mixture was thoroughly mixed in by grinding until the completion of reaction as indicated by thin-layer condensation (TLC). The hot mixture was then poured into ice water, and the pre-



Scheme 1. Synthesis of compounds 3.

Table 1. Synthesis of 3a-c and 4a-y by grinding.

Product	Ar	R	R'	X	Time/min	Yield[b] (%)	Mp (°C)	
							Found	Reported[a]
3a	C_6H_5	Me	Me	S	5	90	146 - 148	146 - 147
3b	4-MeC_6H_4	Me	Me	S	6	88	132 - 134	132 - 133
3c	C_6H_5	Et	Et	S	7	85	109 - 111	108 - 110
4a	C_6H_5	H	H	S	4	98	229 - 230	229 - 231
4b	4-FC_6H_4	H	H	S	3	96	305 - 306	304 - 306
4c	2-MeC_6H_4	H	H	S	6	95	130 - 131	130 - 132
4d	4-MeC_6H_4	H	H	S	5	97	95 - 97	94 - 96
4e	2-ClC_6H_4	H	H	S	7	93	134 - 135	135 - 137
4f	4-ClC_6H_4	H	H	S	5	96	233 - 235	234 - 236
4g	4-$MeOC_6H_4$	H	H	S	1	93	184 - 186	184 - 186
4h	2-$NO_2C_6H_4$	H	H	S	1.5	95	167 - 169	168 - 170
4i	4-$NO_2C_6H_4$	H	H	S	0.5	98	265 - 266	265 - 266
4j	4-BrC_6H_4	H	H	S	4	95	226 - 228	_____
4k	C_6H_5	Me	H	S	4.5	90	180 - 182	181 - 182
4l	4-ClC_6H_4	Me	H	S	5.5	88	182 - 184	183 - 184
4m	4-MeC_6H_4	Me	H	S	5.5	87	151 - 153	152 - 153
4n	C_6H_5	H	H	O	5	96	295 - 297	295 - 299
4o	2-MeC_6H_4	H	H	O	7	94	286 - 290	286 - 290
4p	3-MeC_6H_4	H	H	O	7	92	315 - 317	316 - 318
4q	4-MeC_6H_4	H	H	O	6	95	295 - 297	296 - 298
4r	2-ClC_6H_4	H	H	O	8	90	127 - 132	127 - 132
3s	4-ClC_6H_4	H	H	O	6	93	217 - 222	222 - 227
4t	2-$NO_2C_6H_4$	H	H	O	2	94	230 - 234	230 - 234
4u	3-$NO_2C_6H_4$	H	H	O	2	91	272 - 273	273 - 275
4v	4-$NO_2C_6H_4$	H	H	O	1	96	238 - 240	238 - 240
4w	4-FC_6H_4	H	H	O	4	91	305 - 306	304 - 306
3x	4-$MeOC_6H_4$	H	H	O	3	90	184 - 186	184 - 186
4y	4-BrC_6H_4	H	H	O	5	92	240 - 242	_____

[a]All the products were characterized on the basis of their IR, ^{1}H NMR and ^{13}C NMR spectral analysis and compared with the literature data [4]-[7].
[b]Isolated yields.

cipitate was filtered off. The filtrate was acidified with concentrated hydrochloric acid, and the precipitate of **4** was filtered off, dried for 2 days in a desiccator over calcium chloride, and recrystallized from ethanol.

4.2. 5,5-Bis(4-Bromophenyl)-2-Thioxoimidazolidin-4-One (3j)

Cream powder; mp: 226˚C - 228˚C; yield: 0.40 g (95%); IR (KBr) (ν_{max}/cm^{-1}): 3100 (NH), 1695 (C=O), 1524 (C=C). $C_{15}H_{10}N_2Br_2OS$ (426.13): C, 42.28; H, 2.37; N, 6.57; S, 7.52. Found: C, 42.10; H, 2.26; N, 6.60; S, 7.55. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 - 7.70 (8 H, m, CH), 11.40 (1 H, s, NH), 12.20 (1 H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 77.4 (C), 129.1 (4CH), 129.8 (4 CH), 131.4 (2 C), 138.2 (2 C), 162.5 (C=O), 180.7 (C=S).

4.3. 5,5-Bis(4-Bromophenyl)Imidazolidine-2,4-Dione (3y)

Cream powder; mp: 240˚C - 242˚C; yield: 0.38 g (92%); IR (KBr) (ν_{max}/cm^{-1}): 3200 (NH), 1725 (C=O), 1450 (C=C). Anal. Calcd (%) for $C_{15}H_{10}Br_2N_2O_2$ (410.06): C, 43.94; H, 2.46; N, 6.83. Found: C, 44.20; H, 2.36; N, 6.61. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.10 - 7.70 (8 H, m, CH), 9.30 (1 H, s, NH), 11.10 (1 H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 71.4 (C), 129.4 (4CH), 129.9 (4 CH), 131.7 (2 C), 138.5 (2 C), 162.8 (C=O), 173.1 (C=O).

Acknowledgements

We are grateful to the Young Researchers Club of Islamic Azad University Sarvestan Branch for the partial support to this work.

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