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Synthesis of thiohydantoins under one-pot three-component solvent-free conditions

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Abstract A direct and efficient one-pot three-component synthesis protocol was developed for the synthesis of thiohydantoins from readily and widely available substrates (isothiocyanates, ethyl chloroacetate, and amines) employing solvent-free conditions.

Keywords Heterocycles; Multicomponent reactions; Solvent-free; Cyclizations; Isothiocyanates.

Introduction

Thiohydantoins are an important class of heterocyclic compounds in medicinal and agricultural chemistry because they display a fascinating array of biological properties [1]. For example, some thiohydantoins can be used as cardioprotective agents for the prevention of atherosclerosis in man [2]. *Lambert et al.* have proved the human CB1 and CB2 cannabinoid receptor affinity of the thiohydantoins [3]. In addition, several other compounds can act as gelatinase inhibitors, desmutagens and herbicides [4–6].

The classical method for the synthesis of thiohydantoins is the reaction of isothiocyanates with N-substituted α-amino acids or their esters [2, 7]. A variety of synthesis methods for the formation of thiohydantoins have been developed during past two decades [8]. For example, *Nielsen et al.* developed an efficient method for the synthesis of thiohydantoins by treatment of isothiocyanates with N-substituted α-amino acids under microwave-assisted conditions [9]; The *Ganesan* group reported a solution-phase synthesis of a combinatorial thiohydantoin ensemble by a one-pot three-component reaction of α-amino acid ester, aromatic aldehyde, and isothiocyanate in the presence of sodium triacetoxyborohydride (as reducing agent) [10]. *Kurth et al.* have established a viable route for the synthesis of novel isoxazole- and thiohydantoin-containing heterocycles *via* solid-phase method [11]; *Kidwai et al.* also reported the potassium carbonate supported solventless approach to this class of compounds *via* the cyclization of diarylthoiurea with chloroacetylchloride under microwave irradiation [12]. However, the present methods have some drawbacks, such as lack of versatility, use of expensive and corrosive reagents and solvents, long reaction times, and tedious work-up procedures. Therefore, the development of an efficient and versatile method for the preparation of thiohydantoins seems to be important. Nowadays carrying out organic reactions in the absence of solvents is one of the more important goals in clean synthesis. Herein we wish to disclose a more

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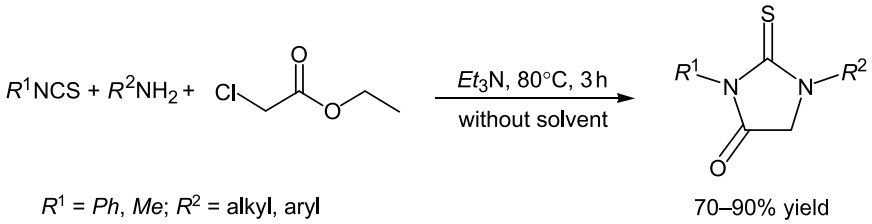

Scheme 1

practical and efficient alternative for the synthesis of thiohydantoins by a three-component condensation of isothiocyanates, ethyl chloroacetate, and amines at 80°C under solvent-free condition (Scheme 1).

Results and discussion

In the beginning, efforts were directed towards the evaluation of the solvent in the synthesis of thiohydantoins. According to literature, methylene chloride can be used as solvent for the reaction of isothiocyanate and α-amino acids esters [10]. Therefore, our initial experiments were carried out in methylene chloride. To have a control experiment in hand, the model reaction was accomplished using benzyl amine, isothiocyanates, and ethyl chloroacetate in boiling methylene chloride. Compound **3** was obtained in 80% yield after a 10 h reaction time. But this initial attempt was not very encouraging. The reaction time is too long and the yield is unsatisfactory. Therefore it was necessary to optimize the reaction conditions. To improve yields and purity, and to minimize chromatographic purifications, the effects of several parameters (without solvent or solvent, as *e.g.*, 1,2-dichloroethane or *THF*; reaction temperature and time, and the number of equivalents of triethylamine) were studied. The influences of solvents on the yield of the reaction are shown in Table 1. The best results were obtained when the reaction was conducted in the absence of solvent.

Table 1 Effect of solvent on the synthesis of **3**

Solvent	Reaction conditions		Yield[a]/%
	Temperature/°C	Time/h	
Methylene chloride	40	10	80
1,2-Dichloroethane	84	5	84
THF	68	10	87
Without solvent	80	3	90

[a] Yield of isolated product

Table 2 Yields for the synthesis of **3** under solvent-free condition in different temperatures

Reaction		
Temperature/°C	Time/h	Yield[a]/%
50	6	80
60	6	80
70	5	87
80	3	90
90	3	88
100	3	80

[a] Yield of isolated product

The yield was also significantly affected by the reaction temperature. The results are shown in Table 2. As can be seen from Tables 1 and 2, to reach comparable yields the solvent-free reactions needed much shorter reaction time than the solvent reactions, but required higher reaction temperature.

In addition, effects of molar ratio of triethylamine to isothiocyanate on this one pot reaction without solvent were investigated (Table 3). In the absence of this catalyst, the reaction did not proceed well even after prolonged reaction time under solventless condition. Triethylamine catalyzed the reaction very efficiently producing good yields of products in a much shorter time. It was found that the molar ratio between triethylamine and isothiocyanate could play important role in determining the yield. When the molar ratio is 1, the reaction can be carried out successfully, but triethylamine/isothiocyanate of 1.05–1.30 is a better ratio for preparing the thiohydantoins. Hence this ratio (1.05) was used in the next

Table 3 The influence of the amount of triethylamine on the reaction of synthesis of thiohydantoins

Triethylamine/isothiocyanate (mole ratio)	0	1	1.05	1.3	1.4	1.5	2
Yield[a]/%	<60	82	90	90	87	82	74

[a] Yield of isolated product

Table 4 Solvent-free three-component synthesis of thiohydantoins

Entry	R^1	R^2	Yield[a]/%	m.p./°C	Ref.
1	C_6H_5	C_6H_5	70	212	[13]
2	C_6H_5	4-CH_3–C_6H_4	72	170–171	this work
3	C_6H_5	$C_6H_4CH_2$	90	188.5–189.5	[14]
4	C_6H_5	C_4H_9	82	133–135	this work
5	C_6H_5	3-Cl–C_6H_4	70	157–158	this work
6	C_6H_5	4-F–C_6H_4	70	185–187	this work
7	C_6H_5	4-CH_3O–C_6H_4	73	190–192	this work
8	C_6H_5	Cyclic-C_6H_{11}	72	231–232	this work
9	CH_3	C_6H_5	76	113–113.5	[7a]
10	CH_3	4-CH_3–C_6H_4	78	135–137	this work
11	CH_3	$C_6H_4CH_2$	82	74	[15]
12	CH_3	C_4H_9	77	oil	this work

[a] Yield of isolated product

experiment. A further increase in the amount of triethylamine showed no substantial improvement in the yield, whereas the yield was reduced when the ratio reached to 2. The results showed that the optimum reaction conditions were triethylamine/isothiocyanate: 1.05–1.30 (molar ratio), the range of temperature from 70 to 90°C, and the reaction time from 2 to 3 h.

Under these optimized reaction condition, a range of structurally diverse amines and isothiocyanates were subjected under this protocol to produce the corresponding thiohydantoins (Table 4). Aliphatic amines produced good yields of thiohydantoins. Aromatic amines also worked well with this protocol, but the yield was less than that of aliphatic amines. The substituted aromatic amines having electron-donating group gave thiohydantoins in good yields. However, in the case of electron-withdrawing groups relatively low yield were obtained. In addition, we found that a strongly electron-withdrawing functionality such as CF_3 on the aromatic amines dramatically decreased the reactivity, cyclization (step 2) would become difficult, and no reaction was observed even after refluxing for a prolonged period (10 h).

Finally, this method requires no product purification and affords the desired product in good yields without the formation of unwanted side products. Therefore, only ionic impurities (*i.e.*, NH_4Cl) need to be washed with the mixture of ethyl acetate/petroleum ether (1/10) and water from the products. The purity of the products was, in most cases, in excess of 95% and no further purification was necessary.

In conclusion, we developed a novel and efficient one-pot three-component method for the synthesis of thiohydantoins under solvent-free conditions providing good isolated yields. The reasonable reaction times, solvent-free, high yields, simple work-up procedure, and a one-pot reaction without the necessity to isolate the products are main merits of this method.

Experimental

Melting points were recorded in open capillary using Büchi melting point B540 apparatus. Analytical thin-layer chromatography (TLC) was carried out on precoated plates (silica gel 60 F254), and spots were visualized with UV light. All chemicals used were reagent grade procured commercially and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker AM-400 (400 MHz) spectrometer with $CDCl_3$ as the solvent using *TMS* as internal standard. High-resolution mass spectra were recorded under electron impact conditions using a MicroMass GCT CA 055 instrument. Infrared spectra were recorded with a Nicolet Magna-IR 550 spectrometer. All known compounds proved to be identical (m.p., IR, ^1H NMR, and MS) with those described in the references.

General procedure for the one-pot synthesis of thiohydantoins
Ethyl chloroacetate (1.84 g, 15 mmol) was added dropwise to a mixture of 15 mmol amine, 3.54 g triethyl amine (15.8 mmol). After about 0.5 h of stirring at room temperature, the mixture was gently heated to 80°C for 0.5 h, and then 15 mmol isothiocyanate was added at 80°C over a period of 2–3 h. After the completion of reaction monitored by TLC, it was cooled to room temperature and washed with the mixture of ethyl acetate/petroleum ether (1/10) and water. The product was collected by filtration. Some of the solid product can be further purified by recrystallization from ethanol.

1-(4-Methylphenyl)-3-phenyl-2-thiohydantoin
(**2**, $C_{16}H_{14}N_2OS$)
Pale yellow solid; IR (KBr): $\bar{\nu}_{max} = 3055$, 1753, 1507, 1456, 1306, 1273, 1172, 754, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57–7.30$ (m, 9H), 4.60 (s, 2H), 2.42 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 182.31$, 169.31, 138.27, 135.50, 133.29, 130.08, 129.37, 129.24, 128.55, 125.44, 55.36, 21.21 ppm; HRMS: m/z $[M]^+$: Calcd for $C_{16}H_{14}N_2OS$: 282.0827; found: 282.0830.

1-(3-Chlorophenyl)-3-phenyl-2-thiohydantoin
(**5**, $C_{15}H_{11}ClN_2OS$)
White solid; IR (KBr): $\bar{\nu}_{max} = 3069$, 2953, 1716, 1646, 1585, 1486, 1375, 1275, 1154, 728 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.49–6.92$ (m, 9H), 4.01 (s, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 171.02$, 154.32, 147.73, 135.68, 134.81, 130.21, 129.26, 129.23, 128.47, 126.38, 124.82, 120.81, 32.86 ppm; HRMS: m/z $[M]^+$: Calcd for $C_{15}H_{11}ClN_2OS$: 302.0281; found : 302.0281.

1-(4-Fluorophenyl)-3-phenyl-2-thiohydantoin
(**6**, $C_{15}H_{11}FN_2OS$)
Pale yellow solid; IR (KBr): $\bar{\nu}_{max} = 3054$, 2941, 1758, 1514, 1455, 1400, 1309, 1264, 1170, 1092, 836, 760 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.57–7.18$ (m, 9H), 4.61 (s, 2H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 182.85$, 168.93, 133.17, 129.43, 129.26, 128.47, 127.66, 127.57, 116.57, 116.34, 55.27 ppm; HRMS: m/z $[M]^+$: Calcd for $C_{15}H_{11}FN_2OS$: 286.0576; found: 286.0576.

1-(4-Methoxyphenyl)-3-phenyl-2-thiohydantoin
(**7**, $C_{16}H_{14}N_2O_2S$)
Pale yellow solid; IR (KBr): $\bar{\nu}_{max} = 3054$, 2933, 2836, 1758, 1516, 1456, 1247, 1168, 1028, 833, 757 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.56–7.00$ (m, 9H), 4.59 (s, 2H), 3.86 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 182.61$, 169.28, 159.15, 133.31, 130.78, 129.33, 129.21, 128.51, 127.13, 114.69, 55.60, 55.54 ppm; HRMS: m/z $[M]^+$: Calcd for $C_{16}H_{14}N_2O_2S$: 298.0775 found: 298.0776.

1-Cyclohexyl-3-phenyl-2-thiohydantoin (**8**, $C_{15}H_{18}N_2OS$)
Pale yellow solid; IR (KBr): $\bar{\nu}_{max} = 3052$, 2942, 2855, 1762, 1588, 1474, 1297, 1248, 1233, 1170, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.52–7.34$ (m, 5H), 4.78–4.72 (m, 1H), 4.13 (s, 2H), 2.06–1.24 (m, 10H) ppm. ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 181.69$, 170.19, 133.16, 129.14, 129.07, 128.46, 55.48, 48.44, 30.05, 25.23 ppm. HRMS: m/z $[M]^+$: Calcd for $C_{15}H_{18}N_2OS$: 274.1140, found: 274.1140.

1-(4-Methylphenyl)-3-methyl-2-thiohydantoin
(**10**, $C_{11}H_{12}N_2OS$)
Pale yellow solid; IR (KBr): $\bar{\nu}_{max} = 3065$, 2958, 1740, 1513, 1453, 1336, 1278, 1116, 818, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40$ (d, $J = 8.10$ Hz, 2H), 7.27 (d, $J = 8.10$ Hz, 2H), 4.40 (s, 2H), 3.35 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): $\delta = 182.66$, 169.91, 138.04, 135.49, 129.99, 125.16, 54.88, 28.43, 21.14 ppm; HRMS: m/z $[M]^+$: Calcd for $C_{11}H_{12}N_2OS$: 220.0670, found: 220.0671.

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References

1. a) Nagpal KL, Williamsville NY (1984) US Patent 4473393, Chem Abstr 98:224844; b) Erve JCL, Amarnath V, Sills RC, Morgan DL, Valentine WM (1998) Chem Res Toxicol 11:1128; c) Teng X, Degterev A, Jagtap P, Xing X, Choi S, Denu R, Yuan J, Cuny GD (2005) Bioorg Med Chem Lett 15:5039; d) LeTiran A, Stables JP, Kohn H (2001) Bioorg Med Chem 9:2693
2. Elokdah H, Sulkowski TS, Abou-Gharbia M, Butera JA, Chai SY, McFarlane GR, McKean M, Babiak JL, Adelman SJ, Quinet EM (2004) J Med Chem 47:681
3. a) Muccioli GG, Wouters J, Scriba GKE, Poppitz W, Poupaert JH, Lambert DM (2005) J Med Chem 48:7486; b) Muccioli GG, Martin D, Scriba GKE, Poppitz W, Poupaert JH, Wouters J, Lambert DM (2005) J Med Chem 48:2509; c) Muccioli GG, Fazio N, Scriba GKE, Poppitz W, Cannata F, Poupaert JH (2006) J Med Chem 49:417
4. Zhang Y, Li D, Houtman JC, Witiak DT, Seltzer J, Bertics PJ, Lauhon CT (1999) Bioorg Med Chem Lett 9:2823
5. Takahashi A, Matsuoka H, Ozawa Y, Uda Y (1998) J Agric Food Chem 46:5037
6. Theodoridis G (1990) US Patent 4902338, Chem Abstr 113:24243
7. a) Dutcher JD, Johnson JR, Bruce WF (1945) J Am Chem Soc 67:1736; b) Öhberg L, Westman J (2001) Synlett 12:1893
8. a) Nizamuddin MG, Khan MH, Srivastava MK, Tiwari S (2000) Indian J Chem Sect B Org Chem Incl Med Chem 39B(11):853; b) Nefzi A, Giulianotti M, Truong L, Rattan S, Ostresh JM, Houghten RA (2002) J Comb Chem 4:175; c) Reyes S, Burgess K (2006) J Org Chem 71:2507; d) Sundaram GSM, Venkatesh C, Ila H, Junjappa H (2007) SynLett 2:251
9. Khodair AI, Nielsen J (2002) Heterocycles 57:1017
10. Sim MM, Ganesan A (1997) J Org Chem 62:3230
11. Park KH, Kurth MJ (1999) J Org Chem 64:9297
12. Kidwai M, Venkataramanan R, Dave B (2001) Green Chem 3:278
13. Wheeler HL, Brautlecht CA (1911) Am Chem J 45:446
14. Tomisek AJ (1949) J Am Chem Soc 71:1138
15. Farbenindustrie AG (1950) FR 956150