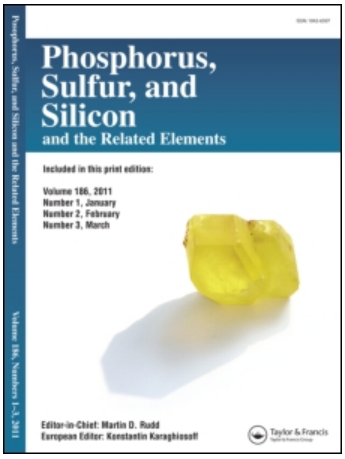

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Synthesis of New Thiohydantoin Derivatives Under Phase Transfer Catalysis

M. K. Abou El-Regal[a]; A. A. Abdalha[a]; M. A. El-Kassaby[a]; A. T. Ali[a]
[a] Chemistry Department, Ain Shams University, Abbassia, Cairo, Egypt

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M. K. Abou El-Regal
A. A. Abdalha
M. A. El-Kassaby
A. T. Ali
Chemistry Department, Ain Shams University, Abbassia, Cairo, Egypt

*A novel synthesis of thiohydantoin derivatives is achieved using phase transfer catalysis conditions via nucleophilic displacement of organohalogen compounds by 3-phenyl-2-thiohydantoin (**1**) and its arylidene derivative (**5**), yielding new thiohydantoin derivatives (**2–9**), which have pronounced biological activities and wide applications.*

Keywords Thiohydantoin; phase transfer catalysis; arylidene

INTRODUCTION

Phase Transfer Catalysis (PTC) is now a commercially mature discipline with over 600 applications covering a wide spectrum of industries, such as pharmaceuticals, agrochemicals, perfumes, flavors, dyes, specialty polymers, and pollution control.[1–4]

Moreover, the pronounced biological activities[5,6] and wide applications[7–12] of thiohydantoin derivatives stimulated the authors to synthesize new derivatives PTC alkylion[13–16] of some heterocyclic compounds were reported, which somewhat resembles our present investigation.

RESULTS AND DISCUSSION

In our present PTC investigation, we used solid-liquid phases;[17,18] the solid phase was anhydrous potassium carbonate, and the liquid phase was dioxane, while Tetrabutyl Ammonium Bromide (TBAB) was used as

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Address correspondence to A. A. Abdalha, Chemistry Department, Faculty of Science, Ain Shams University, Abbassia, Cairo, Egypt. E-mail: abdoelaal@yahoo.com

a catalyst[20] in the nucleophilic displacement of some halo-compounds by 3-phenyl-2-thiohydantoin (**1**) and its arylidene derivative (**5**). The one-pot reaction of (**1**) with monohalocompounds as ethyl bromide or benzyl chloride and carbondisulphide as a reactant and in presence of dioxane as a solvent under PTC conditions afforded thiohydantoin deravative (**2a**) and thiobenzylhydantoin derivative (**2b**), respectively. On the other hand, the PTC reaction of (**1**) with dihalo-compounds, namely ethylene dibromide or 1,3-dibromopropane in the presence of CS_2, yielded 1,3-dithiolidine derivative (**3a**) or 1,3-dithioxane derivative (**3b**), respectively. It was found that treatment of thiohydantoin derivative (**1**) with carbon disulphide in the absence of mono or dihalo-compounds gave bis-monopotassium salt thiohydantoindithione (**4**), which implies the reactivity of the methylene group and ability for dimerization.

In the previous examples, S- or N-alkylation was difficult to achieve due to the presence of active methylene, which can attack carbon disulphide under PTC conditions. Therefore, the authors attended to block the active methylene to enable N- or S-alkylation, and the formation of new thiohydantoin derivatives by blocking active methylene was achieved by condensation of 3-phenyl-2-thiohydantoin (**1**) with 3,4-dimethoxybenzaldehyde in catalytic piperidine, which afforded arylidene derivative (**5**). Alkylation of (**5**) with monohalocompounds, either ethyl bromide or benzyl chloride under PTC conditions, proceeded via S-alkylation to give thioethyl arylidene derivative (**6a**), or thiobenzyl arylidene derivative (**6b**), respectively.

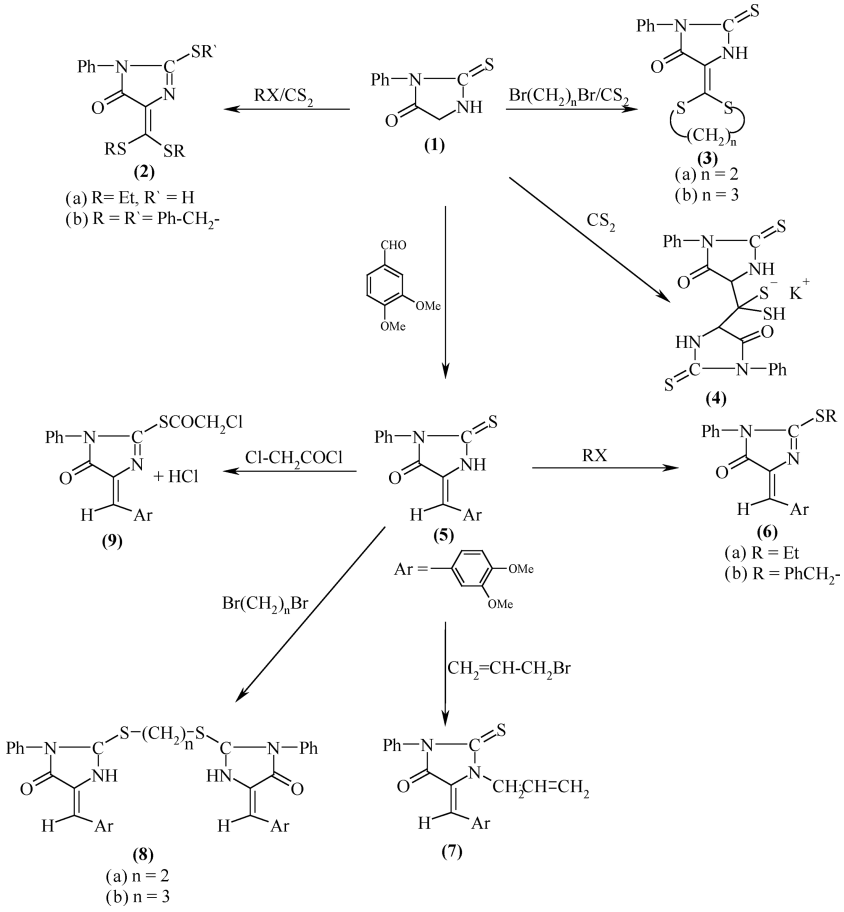
On the other hand, ally bromide alkylation proceeded via N-alkylation, yielding arylidene derivative (**7**).

PTC alkylation of arylidene derivative (**5**) using dihalo-compounds; namely ethylene dibromide or 1,3-dibromopropane, afforded thioalkylated dimers (**8a**) and (**8b**), respectively, which were produced according to S-alkylation followed by dimerization.

Acylation of (**5**) using chloroacetylchloride under PTC conditions yielded arylidene derivative salt (**9**), symbols, characterization, and spectral data of prepared compounds are listed in Scheme 1, Table I, and Table II, respectively.

CONCLUSION

From the previously discussed results, we concluded that position-5 of thiohydantoin (**1**) contains an active methylene group; which underwent nucleophilic displacement in the presence of a base and PTC catalyst with different electrophilic reagents as monoalkyl halides and dialkyl halides.



SCHEME 1

EXPERIMENTAL

Melting points were measured on an electrothermal melting point apparatus and are uncorrected. Elemental, analyses were carried out at the micro-analytical unit, Cairo University, Giza, Egypt. Infrared spectra were measured one Unicam SP-1200 spectrometer using KBr wafer technique. ^{1}HNMR spectra were measured in DMSO-d_6 or $CDCl_3$ on a Varian plus instrument (300 MHz). Mass spectra were determined using HP model MS-5988 at electron energy 70 eV.

TABLE I Characterization Data of Prepared Compounds

Compound No.	M. P. °C (Color)	Yield %, Solvent of Recryst.	Mol formula (M. Wt.)	Analysis Calculated/Found		
				C%	H%	N%
(**1**)	259–60	46	$C_9H_8N_2OS$	56.23	4.19	14.57
	yellow	A	(192.23)	56.26	4.16	14.55
(**2a**)	>300	70	$C_{12}H_{10}N_2OS_3$	48.96	3.42	9.51
	orange	D	(294.40)	49.36	3.22	9.50
(**2b**)	239–41	10–12	$C_{13}H_{12}N_2OS_3$	50.62	3.92	9.08
	brown	Ac	(308.44)	50.92	3.92	9.24
(**3a**)	154–58	50	$C_{14}H_{16}N_2OS_3$	51.82	4.97	8.63
	Yellow	P_a	(324.48)	51.80	4.95	8.63
(**3b**)	96–100	53	$C_{31}H_{26}N_2OS_3$	69.11	4.86	5.20
	Yellow	P_a	(538.75)	69.49	4.84	5.18
(**4**)	>300	81	$C_{19}H_{15}N_2O_2S_4K$	45.76	3.03	11.23
	Orange	D	(498.72)	45.70	3.00	11.11
(**5**)	190–91	97	$C_{18}H_{16}N_2O_3S$	63.51	4.74	8.23
	Orange	A	(340.40)	63.53	4.71	8.22
(**6a**)	121–123	70	$C_{20}H_{20}N_2O_3S$	65.19	5.47	7.60
	Yellow	E	(368.44)	65.59	5.44	7.62
(**6b**)	158–62	70	$C_{25}H_{22}N_2O_3S$	69.75	5.15	6.51
	Yellow	E	(430.51)	70.13	5.13	6.48
(**7**)	135–37	82	$C_{21}H_{20}N_2O_3S$	66.29	5.29	7.36
	Yellow	E	(380.44)	66.66	5.27	7.34
(**8a**)	228–30	40	$C_{39}H_{36}N_4O_6S_2$	64.98	5.03	7.77
	Yellow	D	(720.84)	64.94	5.00	7.73
(**8b**)	296–98	42	$C_{38}H_{34}N_4O_6S_2$	64.57	4.85	7.93
	Yellow	D	(706.81)	64.50	4.84	7.91
(**9**)	240–42	12	$C_{20}H_{18}N_2O_4SCl_2$	52.99	4.00	6.18
	Yellow	A	(453.32)	52.77	4.21	6.00

A = acetic acid; D = dimethyl formamide; Ac = acetone; P_a = Pet-ether 60–80; E = ethanol.

3-Phenyl-2-thiohydantoin (1)[21–23]

A mixture of phenylisothiocyanate (0.01 mole) (1.35 g) and ethyl glycinate hydrochloride (0.01 mole) (1.40 g) in the presence of ammonium acetate (0.15 mole) (1.16 g) in acetic acid (50 mL) was refluxed for 4 h. The solid formed after cooling was collected and crystallized to give (**1**).

3-Phenyl-2-thiohydantoin-4-arylidene Derivative (5)

A mixture of 3-phenyl-2-thiohydantoin (**1**) (0.01 mol) (1.92 g), 50 mL of ethanol, a catalytic amount of piperdine (2–3 drops), and (0.01 mol) (1.66 g) of 3,4-dimethoxy benzaldehyde was refluxed for 2–3 h. The

TABLE II IR, ^{1}HNMR, and MS Data of Prepared Compounds

Compound No.	^{1}HNMR (δ in ppm)	MS (m/z), %	IR cm^{-1}		
			OH	NH	C=O
(**1**)	9.1 (b, 1H), 7.41 (m, 5H), 4.34 (s, 2H)	193 (M+1, 20.3%), 192 (M^+, 38.7%), 135 (2.2%), 77(100%)	—	3145	1755
(**2a**)	9.16 (b, 1H), 7.54–7.3 (m, 5H), 3.1–2.95 (m, 4H), 1.4–1.3 (m, 6H)	325 (M + 1, 24.7%), 324 (M^+, 82.3%), 192 (3.8%), 77 (100%)	—	3184.1	1724
(**2b**)	7.49–7.29 (m, 20H), 4.52, 4.49 (2s, 4H), 4.29 (s, 2H)	538 (M^+, 3.5%), 448 (7.3%), 447 (20.0%), 77(100%)	—	—	1696
(**3a**)	12.52 (s, 1H), 7.5–7.3 (m, 5H), 3.6 (s, 4H)	295 (M + 1, 23%), 294 (M^+, 100%), 135 (21.4%), 77 (56.4%)	—	3103.1	1704
(**3b**)	12.24 (s, 1H), 7.5–7.3 (m, 5H), 3.2 (t, 2H), 3.04 (t, 2H), 2.2, 2.02 (m, 2H)	311 (M+3, 2.6%), 308 (M^+, 100%), 135 (3.8%), 77 (18.5%)	—	3108.4	1710
(**4**)	13.13 (b, 2H), 10.5 (s, 1H), 7.77–6.96 (m, 10H), 3.9 (s, 2H)	500 (M + 1, 30.8%), 192 (11.8%), 135 (55%), 77 (97%)	—	3099.9	1719
(**5**)	12.56 (s, 1H), 7.025–7.55 (m, 8H), 6.6 (s, 2H), 3.86–3.83 (2s, 6H)	341 (M + 1, 28.2%), 340 (M^+, 100%), 162 (30.6%), 77 (18.4%)	3576	3408	1705
(**6a**)	7.5–6.8 (m, 8H), 4.18 (s, 1H), 3.3 (Q, 2H), 1.65–1.47 (t, 3H)	368 (M^+, 100%), 340 (25.4%), 324 (42.3%), 77 (27.8%)	—	—	1713
(**6b**)	8.33 (s, 1H), 7.59–6.9 (m, 13H), 4.6 (s, 2H), 3.98–3.9 (2s, 6H)	430 (M^+, 68.2%), 340 (10.7%), 91 (100%), 77(22.3%)	—	—	1717
(**7**)	8.32 (s, 1H), 7.54–6.9 (m, 8H), 6.15 (m, 1H), 5.4–5.2 (two d, 2H), 4.02 (d, 2H), 3.98 (two s, 6H)	381 (M + 1, 25.8%), 380 (M^+, 100%), 340 (9%), 77 (33.1%)	—	—	1714
(**8a**)	8.09 (s, 1H), 7.5–6.85 (m, 16H), 3.9–3.85 (two s, 6H), 3.7 (s, 4H)	7.07 (M^+, 5.4%), 3.69 (M – 340, 7.3%), 367 (77.2%), 366 (100%)	3585.3	—	1631
(**8b**)	8.1 (s, 2H), 7.6–6.89 (m, 16H), 3.9, 3.7 (two s, 6H), 4.47 (t, 4H), 2.5–2.4 (m, 2H)	381 (M – 239, 98%), 380 (M- 340, 100%), 340 (76.4%), 77 (34.4%)	—	—	1711
(**9**)	8.19 (s, 1H), 7.6–6.96 (m, 8H), 4.17 (s, 2H), 3.86–3.85 (two s, 6H)	454 (M^+, 7.3%), 340 (99.6%), 324 (100%), 77 (71.3%)	—	—	1733

arylidene derivative formed during reflux, which was collected after cooling and recrystallized from the proper solvent.

3-Phenyl-2-thiohydantoin-4-diethylthiomethylidene (2a), 3-phenyl-2-thio-benzyl Hydantoin-4-dibenzylthiomethylidene (2b), 2-(3-phenyl-2-thiohydan-toin-4-ylidene)-1,3-dithiolidine (3a), and 2-(3-phenyl-2-thiohydantoin-4-ylidene)-1,3-dithioxane (3b)

To a solution of (**1**) (0.01 mol) (1.92 g) in dry dioxane (50 mL), potassium carbonate anhydrous (0.02 mol) (2.76 g), TBAB (0.003 mol) (0.97 g), and halogen compounds as ethyl bromide (0.02 mol) (1.1 g), benzyl chloride (0.02 mol) (2.5 g), ethylene dibromide (0.01 mol) (1.9 g), or 1,3-dibromopropane (0.01 mol) (2.02 g) were added in the presence of CS_2 (0.1 mol) (7.6 g). The reaction mixture was stirred at 25°C for 2–6 h. the organic layer was separated and the solvent was removed under reduced pressure; then the residue obtained was crystallized from the proper solvent to give (**2a**, **b**) and 3b. On the other hand, (**3a**) was precipitated during the reaction and was isolated from the solid carbonate phase, which was filtered and recrystallized from the proper solvent.

Bis-mono Potassium Salt Thiohydantoin Dithione (4)

To a solution of (**1**) (0.01 mol) (1.92 g) in dry dioxane (50 mL), potassium carbonate anhydrous (0.02 mol) (2.76 g), TBAB (0.003 mol) (0.97 g), and CS_2 (0.1 mol) (7.6 g) were added. The reaction mixture was stirred at 25°C for 2–3 h. The product was isolated from the carbonate phase and recrystallized from the proper solvent.

1-Phenyl-2-thioethyl-4-arylidene imidazole-5-one (6a), 1-phenyl-2-thiobenzyl-4-arylidene imidazole-5-one (6b), 1-allyl-3-phenyl-2-thiohydan-toin-4-arylidene (7), Thioalkated Dimers (8a), and (8b), and 1-phenyl-2-thiochloroacetate-4-arylidene Imidazole-5-one (9)

To a solution of (5) (0.01 mol) (3.40 g) in dry dioxane (50 mL), potassium carbonate anhydrous (0.02 mol) (2.76 g), TBAB (0.003 mol) (0.97 g), halogen compounds as ethyl bromide (0.02 mol) (1.1 g), benzyl chloride (0.02 mol) (2.5 g), allyl bromide (0.02 mol) (1.21 g), 1,2-dibromoethane (0.01 mol) (1.9 g), 1,3-dibromopropane (0.01 mol) (2.02 g), and chloroacetyl chloride (0.01 mol) (1.13 g) were added. The reaction mixture was stirred at 25°C for 2–6 h, the organic layer was separated, and the solvent was removed under reduced pressure; then

the residue obtained was crystallized from the proper solvent to give (**6a**, **b**), and (**7**). On the other hand, (**8a**, **b**) and (**9**) were isolated from the solid carbonate phase, filtered, and crystallized also from the proper solvent.

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