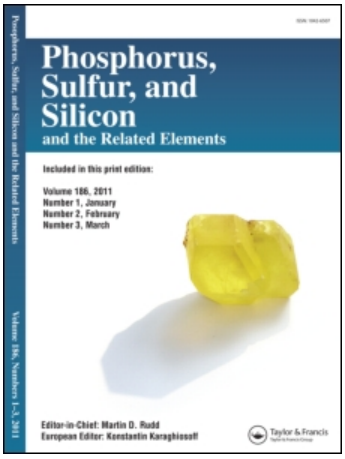

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Activated Nitriles in Heterocyclic: Synthesis Novel Syntheses of Imidazo[2,1-*b*]-1,3-Thiazine Derivatives

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*Several new imidazo[2,1-*b*]-1,3-thiazine derivatives **4a–c**, **8a–c**, and **11a–c** were synthesised via the reaction of 5,5-diphenyl-2-thiohydantoin (**1**) with α,β-unsaturated nitriles **2a–c**, **5a–c**, and **9a–c**. The structures of the products were established on the basis of elemental analyses, IR, and ^{1}H-NMR spectral data.*

Keywords 5,5-Diphenyl-2-thiohydantoin; α,β-unsaturated nitriles

INTRODUCTION

A number of imidazole-2-thiols have found application in clinical medicine due to their pronounced antithyroid activity.[1,2] On the other hand, 1,3-thiazines possess considerable strong analgesic[3] and muscle relaxing properties,[4] stimulation of the entire sympathetic system,[5] and hypothermic activities.[6] This present work was done with the aim of synthesis of several new condensed heterocyclic compounds containing both imidazole and 1,3-thiazine moieties for pharmacological studies.

RESULTS AND DISCUSSION

When a mixture of equimolecular amounts of 5,5-diphenyl-2-thiohydantoin (**1**) and of arylidene malononitriles **2a–c** in absolute ethanol were refluxed in the presence of triethylamine as catalyst, products **4a–c** corresponding to the addition of one molecule of **1** to

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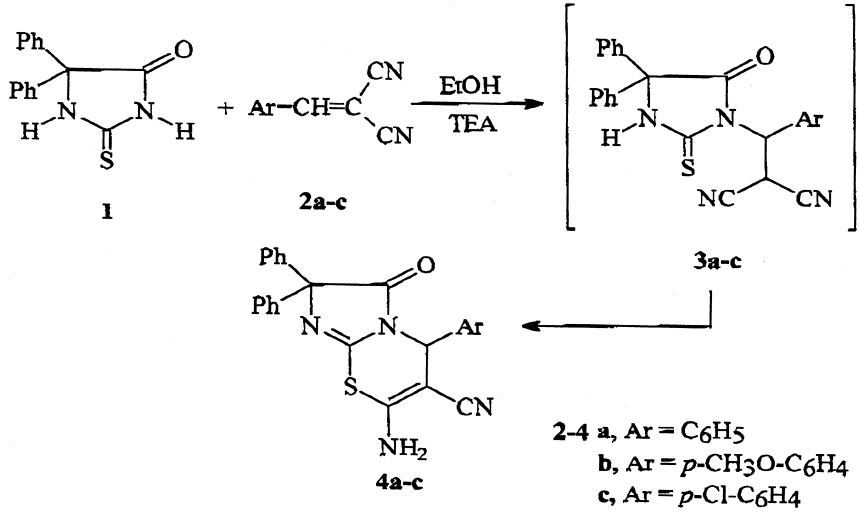
one molecule of **2a–c** were obtained. The constitution of 2-amino-4-aryl-3-cyano-7,7-diphenylimidazo[2,1-*b*]-1,3-thiazine-6-ones **4a–c** was established by elemental analyses and spectral data (cf. Experimental Section).

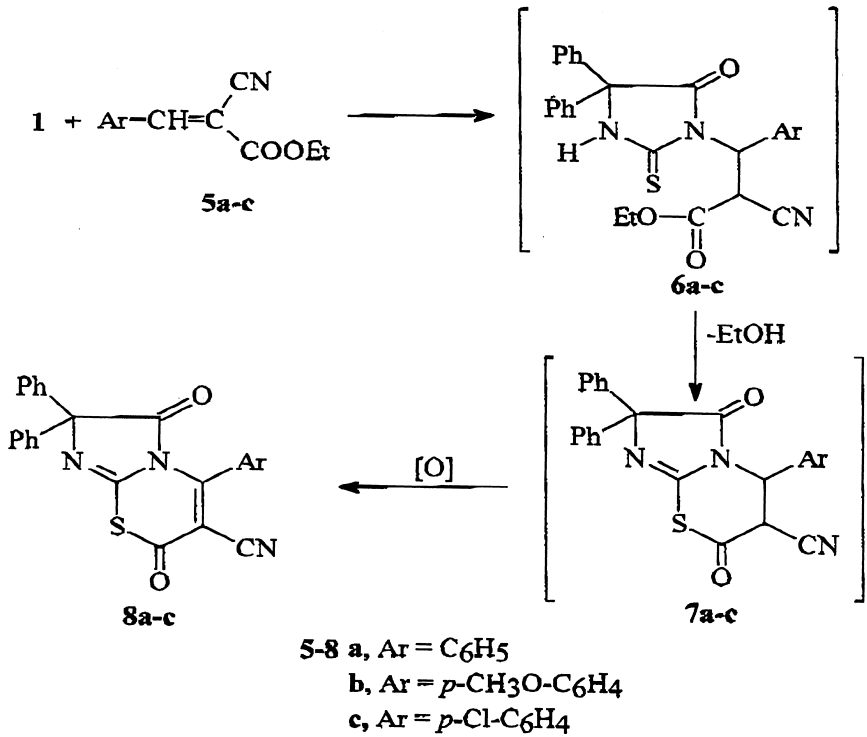
The IR spectra of **4a–c** showed absorption bands for one NH_2 group, one CN group, and one ring C=C group in each case while their ^{1}H-NMR spectra revealed signals corresponding to the presence of 1,3-thiazine H-4, aromatic, and NH_2 protons. The reaction was assumed to proceed via an initial Michael addition of the active hydrogen atom attached to N-3 of compound **1** to the activated double bond of arylidene malononitriles **2a–c** to yield the acyclic intermediates **3a–c**. The latter then cyclized under the applied reaction conditions to the final isolable products **4a–c** (cf. Scheme 1).



SCHEME 1

The study was extended to investigate the behaviour of **1** towards arylidene ethyl cyanoacetates **5a–c** and of 2-aroylcinnamonitriles **9a–c**. The (nonisolated) intermediates are autoxidized under the applied reaction conditions to give 4-aryl-3-cyano-7,7-diphenylimidazo[2,1-*b*]-1,3-thiazine-2,6-diones **8a–c** (cf. Scheme 2). Autoxidation of similar ring systems has been previously reported.[7,8]

Compound **1** also reacted with the 2-aroylcinnamonitriles derivatives **9a–c** to yield the imidazo[2,1-*b*]-1,3-thiazine derivatives **11a–c**. The elemental analysis and spectral data were in a good agreement with the assigned structures **11a–c** (cf. Tables I and II).



SCHEME 2

Compounds **11a–c** were most likely formed via the initial addition of one molecule of **1** to one molecule of each of **9a–c** to yield the non-isolable **10a–c**. Michael adducts **10a–c** subsequently cyclized via water elimination to give 4-aryl-3-cyano-6-oxo-2,7,7-triphenylimidazo-[2,1-*b*]-1,3-thiazines **(11a–c)**. (cf. Scheme 3).

EXPERIMENTAL

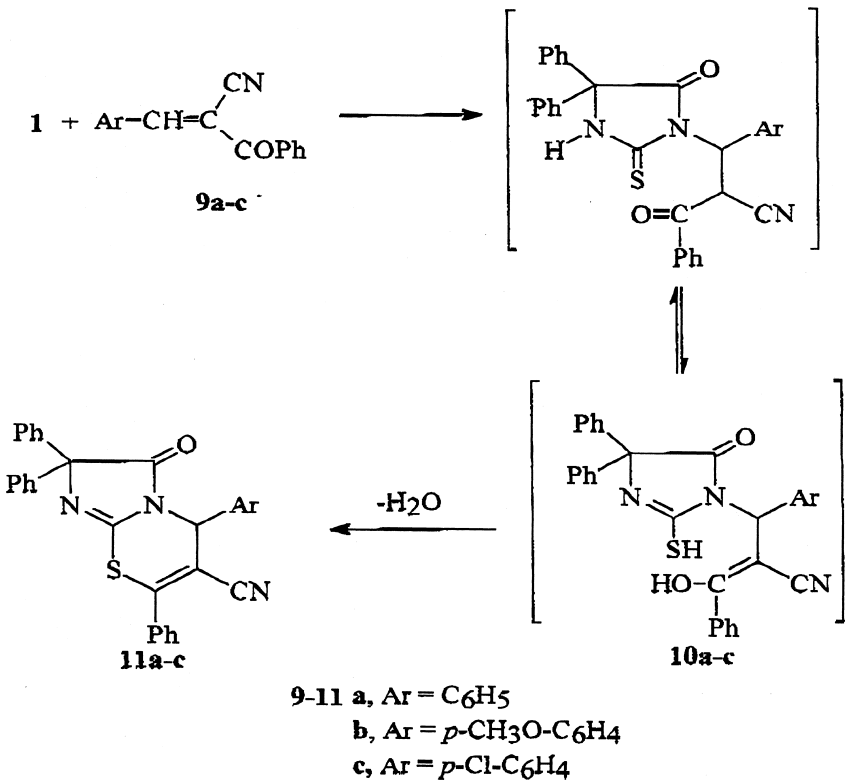
All melting points were uncorrected. IR spectra were recorded on a Pye Unicam SP 3-300 spectrophotometer in KBr discs. The ^{1}H-NMR spectra were recorded on a Varian EM 390-90 MHz spectrometer in deuterated DMSO-d_6 as a solvent and TMS as internal standard. Chemical shifts are expressed as (δ ppm). Microanalytical data were performed by the Microanalytical Center at the Faculty of Science, Cairo University.

TABLE I Synthetic Data of Imidazo[2,1-*b*]-1,3-thiazine Derivatives 4a–c, 8a–c, and 11a–c

Comp. no.	M.P. (°C)	Yield (%)	Formula	Elemental analysis (%) calcd./found				
				C	H	N	S	Cl
4a	188	78	$C_{25}H_{18}N_4OS$	71.09	4.26	13.27	7.58	
				71.20	4.04	13.50	7.43	
4b	198	74	$C_{26}H_{20}N_4O_2S$	69.02	4.42	12.38	7.07	
				68.80	4.20	12.14	6.83	
4c	208	71	$C_{25}H_{17}N_4OSCl$	65.71	3.72	12.26	7.0	7.77
				65.53	3.60	12.40	7.22	7.65
8a	205	76	$C_{25}H_{15}N_3O_2S$	71.25	3.56	9.97	7.60	
				71.11	3.40	10.20	7.52	
8b	192	79	$C_{26}H_{17}N_3O_3S$	69.17	3.76	9.31	7.09	
				69.04	3.54	9.52	6.90	
8c	210	82	$C_{25}H_{14}N_3O_2SCl$	65.86	3.07	9.22	7.02	7.79
				65.63	2.84	9.50	7.30	7.63
11a	202	64	$C_{31}H_{21}N_3OS$	77.01	4.34	8.69	6.62	
				77.22	4.52	8.50	6.90	
11b	213	72	$C_{32}H_{23}N_3O_2S$	74.85	4.48	8.18	6.24	
				74.64	4.74	8.00	6.51	
11c	222	70	$C_{31}H_{20}N_3OSCl$	71.88	3.87	8.12	6.18	6.86
				71.62	4.01	8.40	6.00	6.62

TABLE II The IR and ^{1}H NMR Data of Compounds 4a–c, 8a–c, and 11a–c

Comp. no.	IR (cm^{-1})	^{1}H NMR (δ ppm)
4a	3300, 3220 (NH_2); 2220 (C≡N); 1720 (C=O) and 1640 (C=N).	4.0 (s, 1H, thiazine H-4), 5.6 (s, br, 2H, NH_2 exchangeable with D_2O), and 7.2–7.5 (m, 15H, Ar-H)
4b	3320, 3280 (NH_2); 2225 (C≡N); 1725 (C=O) and 1640 (C=N).	3.8 (s, 3H, OCH_3), 4.2 (s, 1H, thiazine H-4), 5.8 (s, br, 2H, NH_2), and 7.2–7.5 (m, 14H, Ar-H)
4c	3350, 3310 (NH_2); 2230 (C≡N); 1720 (C=O) and 1645 (C=N).	4.3 (s, 1H, thiazine H-4), 6.1 (s, br, 2H, NH_2), and 7.2–7.6 (m, 14H, Ar-H)
8a	2210 (C≡N); 1725, 1690 (2 C=O) and 1640 (C=N).	
8b	2220 (C≡N); 1720, 1685 (2 C=O) and 1635 (C=N).	3.9 (s, 3H, OCH_3), and 7.1–7.4 (m, 14H, Ar-H)
8c	2230 (C≡N); 1730, 1690 (2 C=O) and 1640 (C=N).	
11a	2220 (C≡N); 1720 (C=O) and 1640 (C=N).	4.1 (s, 1H, thiazine H-4), and 7.3–7.6 (m, 20H, Ar-H)
11b	2225 (C≡N); 1730 (C=O) and 1635 (C=N).	3.8 (s, 3H, OCH_3), 4.2 (s, 1H, thiazine H-4), and 7.2–7.6 (m, 19H, Ar-H)
11c	2230 (C≡N); 1725 (C=O) and 1640 (C=N).	4.2 (s, 1H, thiazine H-4), and 7.2–7.6 (m, 19H, Ar-H)



SCHEME 3

Preparation of 2-Amino-4-aryl-3-cyano-7,7-diphenylimidazo-[2,1-*b*]-1,3-thiazines-6-one 4a–c

A solution of **1** (0.01 mole) and each of **2a–c** (0.011 mole) in absolute ethanol (50 mL) and triethylamine (0.5 mL) was heated under reflux for 5 h. The solid products obtained, while the reaction mixtures were boiling, filtered off, and crystallized from ethanol as yellow crystals of **4a–c** (cf. Tables I and II).

Preparation of 4-Aryl-3-cyano-7,7-diphenylimidazo[2,1-*b*]-1,3-thiazin-2,6-diones 8a–c

A solution of **1** (0.01 mole) and each of **5a–c** (0.011 mole) in absolute ethanol (60 ml) and triethylamine (0.6 mL) was heated under reflux for 5 h. The solid products obtained after cooling were filtered off and crystallized from ethanol as yellow crystals of **8a–c** (cf. Tables I and II).

Preparation of 4-Aryl-3-cyano-2,7,7-triphenylimidazo[2,1-*b*]-1,3-thiazin-6-one 11a–c

A solution of **1** (0.01 mole) and each of **9a–c** (0.011 mole) in absolute ethanol (100 mL) and triethylamine (1 mL) was heated under reflux for 6 h. After cooling, the reaction mixture was poured onto icecold water. The solid products were filtered off and crystallized from ethanol as yellow crystals of **11a–c** (cf. Tables I and II).

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