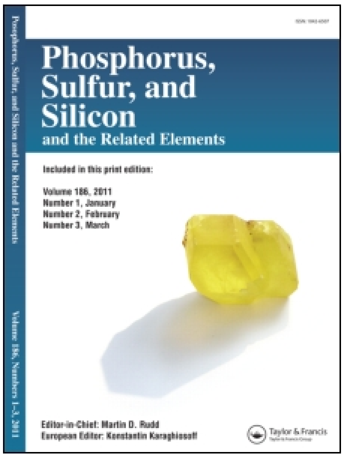

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ACTIVATED NITRILES IN HETEROCYCLIC SYNTHESIS NOVEL SYNTHESES OF IMIDAZO (2,1-b)-1,3-THIAZINE DERIVATIVES

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Communication

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 4,5-diphenyl imidazole-2-thiol (**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.

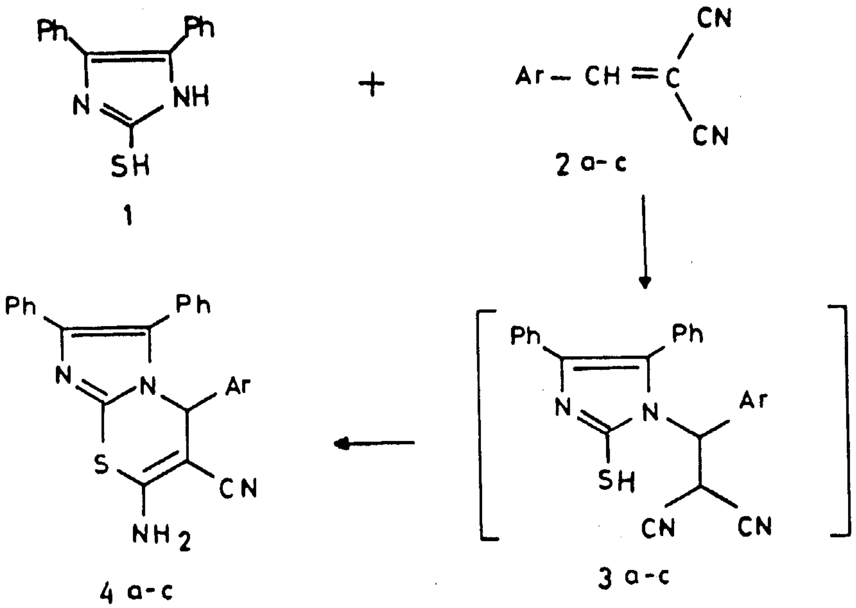
Key words: 4,5-Diphenylimidazole-2-thiol; α,β-unsaturated nitriles.

INTRODUCTION

A number of imidazole-2-thiols have found an 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 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.

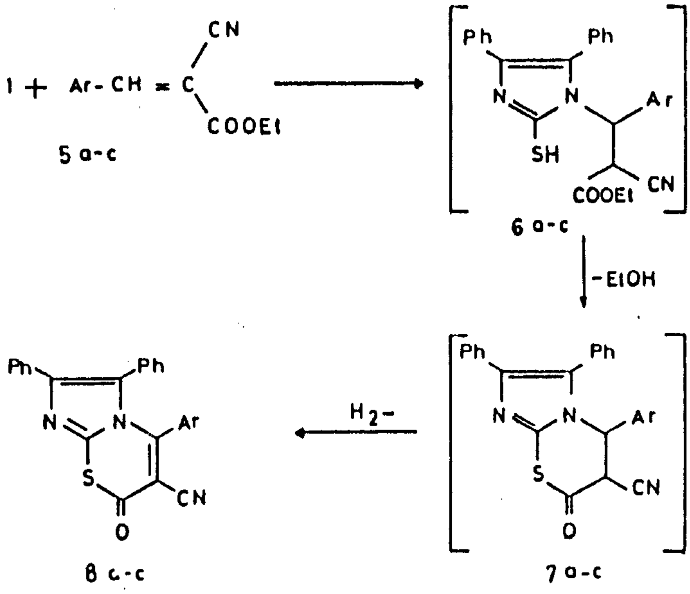
RESULTS AND DISCUSSION

It has been found that, when a mixture of equimolecular amounts of 4,5-diphenyl imidazole-2-thiol-(**1**) and of arylidene malononitriles (**2a–c**) in absolute ethanol were refluxed in the presence of triethylamine as catalyst, products corresponding to addition of one molecule of (**1**) to one molecule of **2a–c** followed by cyclization were obtained. Their constitution of 2-amino-4-aryl-3-cyano-6,7-diphenyl imidazo-(2,1-b)-1,3-thiazines (**4a–c**) was established by elemental analyses and spectral data (cf. Experimental Part). The IR spectra of **4a–c** showed absorption bands of one NH_2 group and one CN 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 initial Michael addition of the hydrogen atom of the imino group of (**1**) to the activated double bond of arylidene



2-4 a, Ar= C_6H_5
b, Ar= $C_6H_4 \cdot OCH_3$-p
c, Ar = $C_6H_4 \cdot Cl$-p

CHART I



5 - 8 a, Ar= C_6H_5
b, Ar= $C_6H_4 \cdot OCH_3$-p
c, Ar= $C_6H_4 \cdot Cl$-p

CHART II

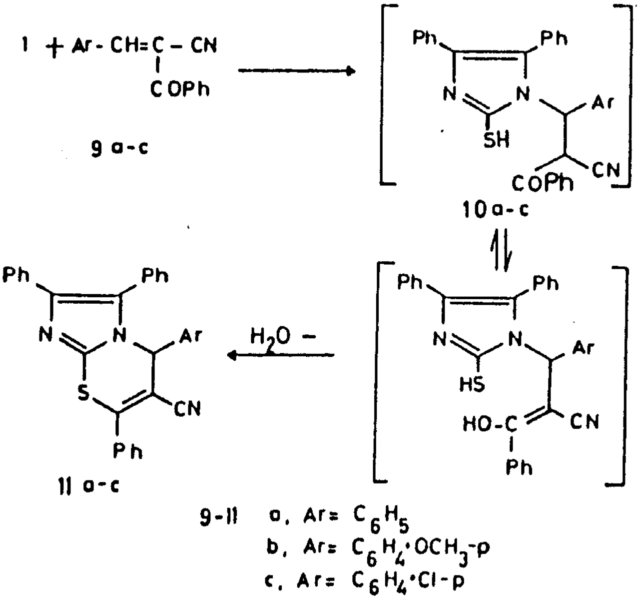


CHART III

malononitriles **2a–c** to yield the acyclic intermediates (**3a–c**) which then cyclized under the applied reaction conditions to the final isolable products (**4a–c**) (cf. Chart I).

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-6,7-diphenyl imidazo (2,1-b)-1,3-thiazine-2-ones (**8a–c**) (cf. Chart II). Autoxidation of similar ring systems has been previously reported.[7,8]

(**1**) also reacted with the 2-aroylcinnamonitrile 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 in experimental part).

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 nonisolable. Michael adducts (**10a–c**) which subsequently cyclized via water elimination to give 4-aryl-3-cyano-2,6,7-triphenyl imidazo (2,1-b)-1,3-thiazines (**11a–c**). (cf. Chart III).

EXPERIMENTAL

All melting points are 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 (δppm units). Microanalytical data were performed by the Microanalytical Center at the Faculty of Science, Cairo University.

Preparation of 2-amino-4-aryl-3-cyano-6,7-diphenyl imidazo[2,1-b]-1,3-thiazines (**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 hours. The solid products thus obtained while the reaction mixtures were still boiling were filtered off and crystallized from ethanol as yellow crystals of (**4a–c**) (cf. Tables I and II).

TABLE I

Synthetic data of imidazo[2,1-b]-1,3-thiazine derivatives (**4a–c**), (**8a–c**), and (**11a–c**)

Compound	M·P· (°C)	Yield (%)	Formula	Elemental analysis (%) Calcd·/Found				
				C	H	N	S	Cl
4a	263	74	$C_{25}H_{18}N_4S$	73·89 73·70	4·43 4·60	13·79 13·60	7·88 8·10	-- --
4b	245	71	$C_{26}H_{20}N_4OS$	71·56 71·80	4·59 4·90	12·84 12·60	7·34 7·50	-- --
4c	292-3	78	$C_{25}H_{17}N_4SCl$	68·10 67·90	3·85 3·60	12·71 12·50	7·26 7·50	8·05 8·20
8a	281	68	$C_{25}H_{15}N_3OS$	74·07 74·20	3·70 3·90	10·30 10·50	7·90 7·60	-- --
8b	258-9	65	$C_{26}H_{17}N_3O_2S$	71·72 71·50	3·90 4·10	9·75 9·90	7·35 7·50	-- --
8c	286	71	$C_{25}H_{14}N_3OSCl$	68·25 68·50	3·18 3·00	9·55 9·20	7·28 7·50	8·07 8·30
11a	276	66	$C_{31}H_{21}N_3S$	79·67 79·50	4·49 4·70	8·99 8·60	6·85 7·00	-- --
11b	262-4	62	$C_{32}H_{23}N_3OS$	77·26 77·50	4·63 4·80	8·45 8·70	6·44 6·20	-- --
11c	282-4	69	$C_{31}H_{20}N_3SCl$	74·17 74·00	3·98 4·02	8·37 8·50	6·38 6·10	7·07 7·30

TABLE II

The IR and ^{1}H NMR data of compounds (**4a–c**), (**8a–c**) and (**11a–c**)

Compound	IR [cm^{-1}]	^{1}H NMR (δ ppm)
4a	3300, 3220 (NH_2); 2220 (C≡N) and 1640 (C=N).	4·0 (s, 1H, thiazine H-4);5.8(s, br, 2H, NH_2 exchangeable with D_2O) and 7·1-7·4 (*m*, 15H, Ar-H).
4b	3320, 3280 (NH_2); 2225 (C≡N) and 1640 (C=N).	3·8 (s, 3H, OCH_3); 4·1 (s, 1H thiazine H-4); 6·1 (s, br, 2H, NH_2) and 7·2-7·5 (m, 14H, Ar-H).
4c	3350, 3310 (NH_2); 2230 (C≡N) and 1645 (C=N).	4·3 (s, 1H .thiazine H-4);6.3(s,br, 2H, NH_2) and 7·2-7·6 (m, 14H, Ar-H).
8a	2210 (C≡N); 1690 (C=O) and 1640 (C=N).	
8b	2220 (C≡N); 1685 (C=O) and 1635 (C=N).	3·9 (s, 3H, OCH_3); 7·2-7·6 (m, 14H, Ar-H).
8c	2230 (C≡N); 1690 (C=O) and 1640 (C=N).	

TABLE II (*Continued*)

Compound	IR [cm^{-1}]	^{1}H NMR (δ ppm)
11a	2220 (C≡N) and 1640 (C=N)	4.0 (s, 1H thiazine H-4) and 7.1-7.4 (m, 20 H, Ar-H).
11b	2225 (C≡N) and 1635 (C=N)	3.8 (s, 3H, OCH$_3$); 4.1 (s, 1H thiazine H-4) and 7.2-7.5 (m,19 H, Ar-H).
11c	2230 (C≡N) and 1640 (C=N).	4.3 (s, 1H thiazine H-4) and 7.2-7.6 (m, 19H, Ar-H).

Preparation of 4-aryl-3-cyano-6,7-diphenylimidazo[2,1-b]-1,3-thiazin-2-one (**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 hours. The solid products thus obtained after cooling were filtered off and crystallized from ethanol as yellow crystals of (**8a–c**) (cf. Tables I and II).

Synthesis of 4-aryl-3-cyano-2,6,7-triphenylimidazo[2,1-b]-1,3-thiazines (**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 hours. After cooling the reaction mixture was poured onto ice-cold water. The solid products thus obtained were filtered off and crystallized from ethanol as yellow crystals of **11a–c** (cf. Tables I and II).

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