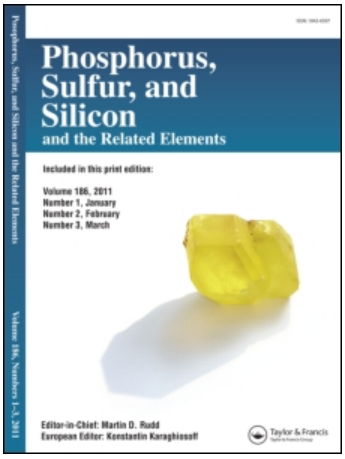

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REACTIVITY OF 1-METHYLISOQUINOLINE. SYNTHESIS OF 2-(1-ISOQUINOLINEMETHYLIDENE)-1,3,4-THIADIAZOLE DERIVATIVES

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1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline reacts with arylisothiocyanates to give the corresponding thioanilides ***2****. Treatment of the latter compounds* ***2*** *with hydrazonoyl halides* ***3*** *and* ***10*** *leads to the formation of thiadiazoles* ***7*** *and* ***12****.*

Keywords: 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline; hydrazonoyl halides; nitrilimines; thiadiazoles; thioanilides

The considerable biological and medicinal activities of isoquinoline derivatives[1–3] have stimulated the interest in the synthesis and chemistry of these compounds. As a part of our program aimed of developing synthesis of new isoquinoline derivatives as potential pharmaceutical and/or agrochemicals, we have recently reported on the utility of the reaction of 1-methylisoquinoline and 1-cyanomethylisoquinoline with hydrazonoyl halides as a route to pyrroloisoquinolines.[4,5]

Previously, it was reported that thioanilides react with α-ketohydrazonoyl halides **10** to give the thiazole derivatives.[6,7] Recently, we proved that the products resulting from such reaction have 1,3,4-thiadiazoline and not thiazole structures.[8,9]

In continuation of this work, we report on the utility of reaction of 1-methylisoquinoline with arylisothiocyanate and studies on the reactivity of the resulting thioanilides with hydrazonoyl halides.

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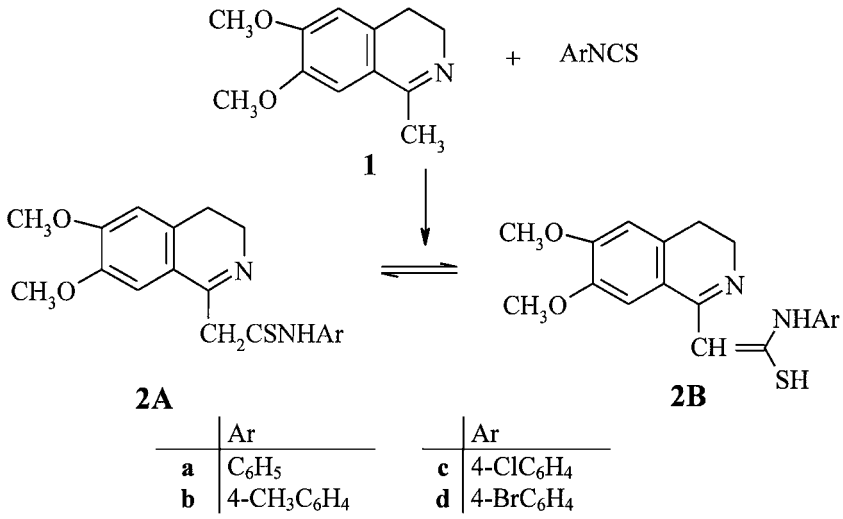
RESULTS AND DISCUSSION

The preparation of the starting thioanilides **2a–d** was accomplished by refluxing equimolecular amounts of 1-methylisoquinoline **1** with arylisothiocyanate in toluene (Scheme 1). The structure of thioanilides **2**

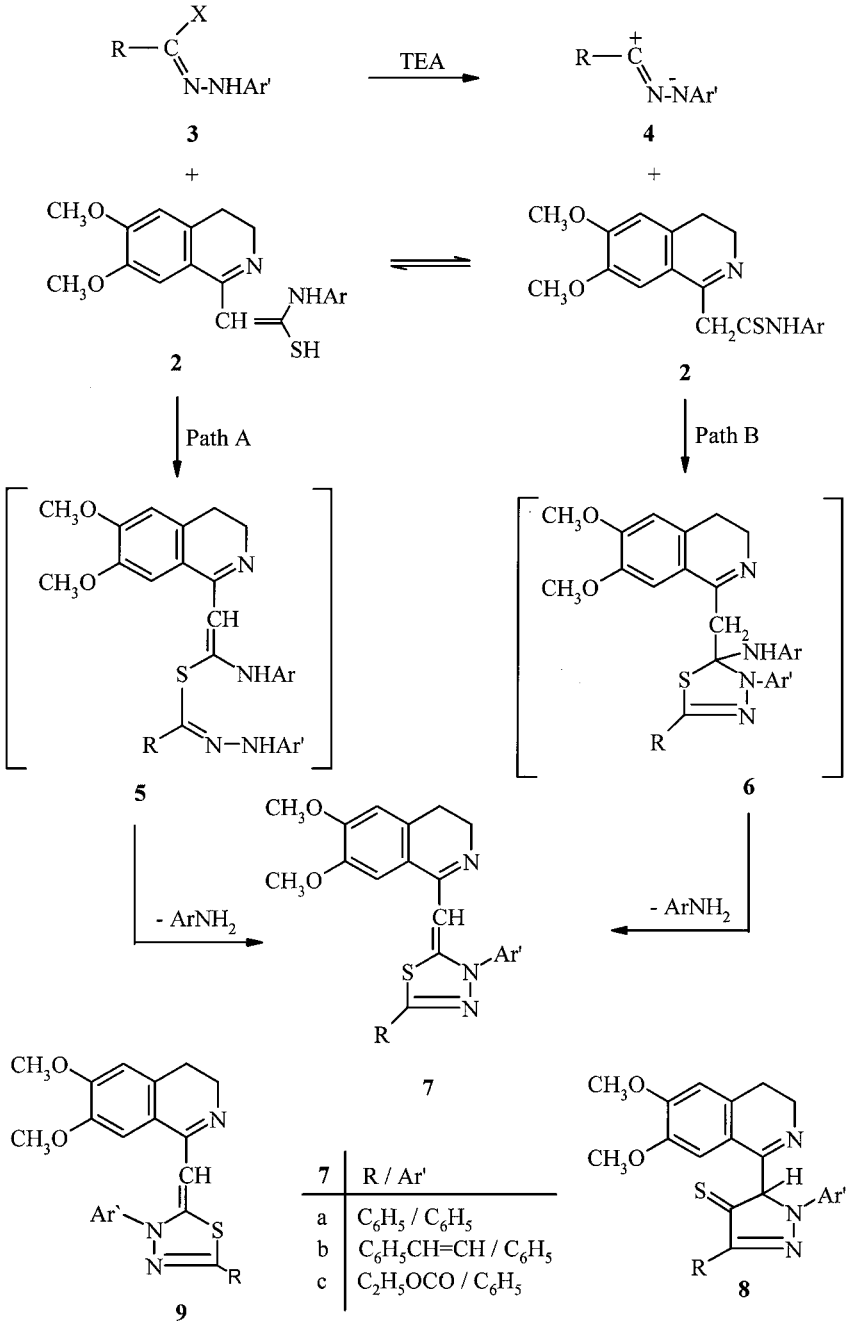


	Ar		Ar
a	C_6H_5	**c**	4-ClC_6H_4
b	4-$CH_3C_6H_4$	**d**	4-BrC_6H_4

SCHEME 1

were established on the basis of elemental and spectral analyses data. For example, the ^{1}H NMR spectra of thioanilides **2** reveal three singlet signals at δ 6.0, 7.9, and 12.1 ppm assignable to the =CH, SH, and NH protons in addition to the protons of isoquinoline moiety, which confirm the structure **2b**. Also, the structures were inferred from their reactions with hydrazonoyl halides.

Treatment of thioanilide **2** with C-ethoxycarbonyl-N-phenyl hydrazonoyl halides **3c** in refluxing chloroform in the presence of triethylamine yielded only one isolable product as indicated by TLC and ^{1}H NMR spectrum of the crude reaction product (Scheme 2). The structure of the product **7c** was inferred from its elemental and spectral analyses. For example, the ^{1}H NMR spectrum of **7c** shows triplet and quartet signals at δ 1.4 and 4.5 ppm, respectively, assignable to ethyl group, in addition to the signals of isoquinoline moiety. Its IR spectrum shows the characteristic ester carbonyl absorption band at 1715 cm.$^{-1}$ Also, the mass spectrum gives a molecular ion peak at m/z 437 with high intensity. Similarly, hydrazonoyl halides **3a**,**b** react with thioanilides **2** to give the corresponding 1,3,4-thiadiazole derivatives



7	R / Ar'
a	C_6H_5 / C_6H_5
b	$C_6H_5CH{=}CH$ / C_6H_5
c	C_2H_5OCO / C_6H_5

SCHEME 2

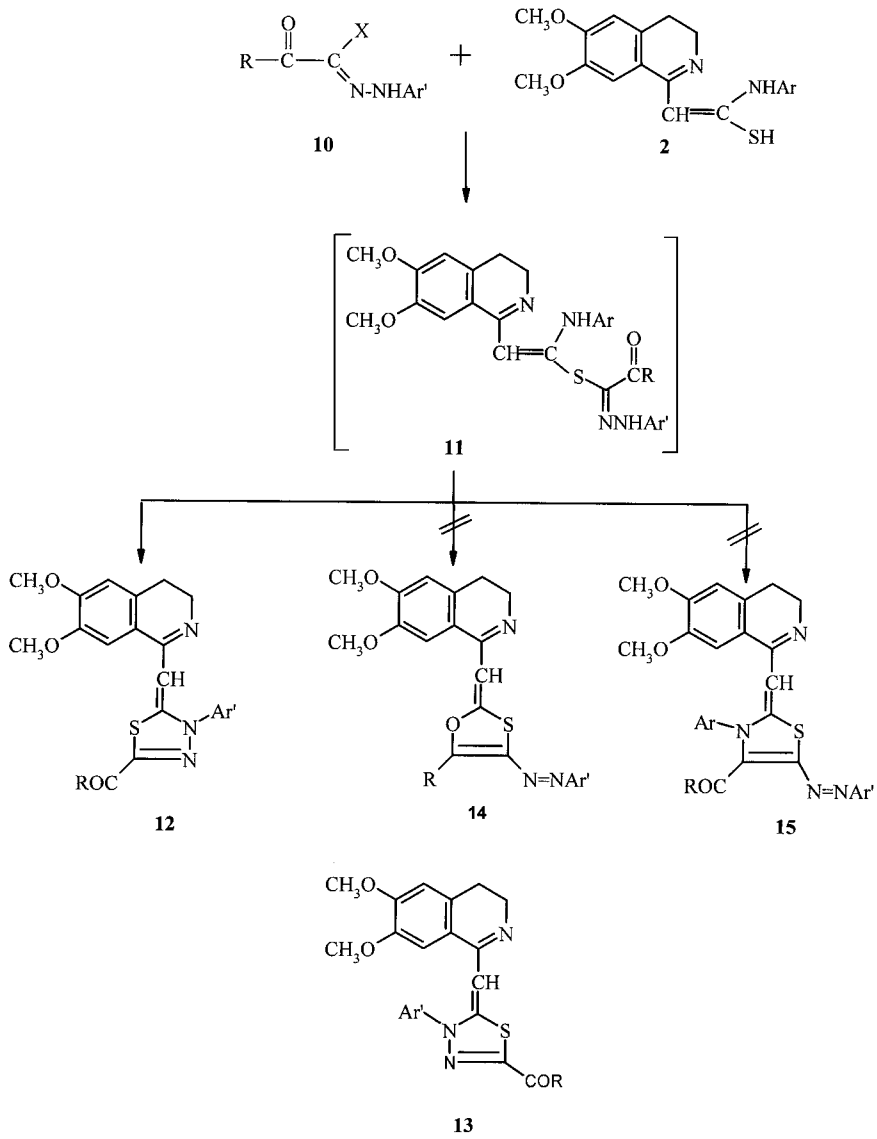
7a,**b** respectively. The structure of the products of **7a**,**b** were confirmed from their elemental and spectral data.

Two possible structures can be suggested for the products **7** or **8**. Structure **8** was ruled out because the reaction product was recovered unchanged after treatment with mercuric oxide in boiling acetic acid. To account for the formation of **7** two possible pathways are proposed. In the first way, the reaction leads to the formation of thiohydrazones **5** followed by elimination of aryl amine to give **7**. In second path, nitrilimines **4**, generated in situ from reaction of hydrazonoyl chlorides **3** with triethylamine in chloroform, cycloadd to C=S of thioanilideto give the intermediate **6** which upon elimination of aryl amine leads to **7** (Scheme 2).

In order to study the effect of a carbonyl group on the reactivity of the hydrazonoyl halides, we investigated the reaction of α-ketohydrazonoyl halides **10** with thioanilides **2**. Thus, treatment of **2** with hydrazonoyl halides **10** in refluxing chloroform in the presence of triethylamine gave the corresponding thiadiazole derivatives **12** (Scheme 3). The structure of the products **12** were supported by their spectra and by alternative syntheses, thus reaction of **2b** with **10a–d** gave products identical in all respects (mp, IR, ^{1}H NMR, MS) with **12a–d**, respectively (Scheme 3).

TABLE I Melting points and analytical data of products

				Analysis		Calcd/Found	
No.	m.p.(°C)	Solvent	mol formula	C%	H%	N%	S%
2a[17]	185						
2b	195	EtOH	$C_{20}H_{22}N_2O_2S$	67.8	6.3	7.9	9.0
				67.5	6.1	7.6	8.9
2c	209	EtOH/DMF	$C_{19}H_{19}N_2O_2SCl$	60.9	5.1	7.5	8.5
				60.5	4.8	7.2	8.3
2d	208	AcOH	$C_{19}H_{19}N_2O_2SBr$	54.4	4.6	6.6	7.7
				54.3	4.3	6.4	7.5
7a	173–174	EtOH/DMF	$C_{26}H_{23}N_3O_2S$	70.7	5.3	9.5	7.3
				70.9	5.2	9.3	7.1
7b	195–197	EtOH/DMF	$C_{28}H_{25}N_3O_2S$	71.9	5.4	8.9	6.9
				72.2	5.2	8.7	6.7
7c	229–230	EtOH/DMF	$C_{23}H_{23}N_3O_4S$	63.1	5.3	9.6	7.4
				63.0	5.2	9.5	7.0
11a	173–175	EtOH	$C_{22}H_{21}N_3O_3S$	64.8	5.2	10.3	7.8
				64.7	5.2	10.1	7.6
11b	218–220	EtOH/DMF	$C_{27}H_{23}N_3O_3S$	69.0	4.9	8.9	6.8
				69.2	5.2	8.7	6.5
11c	230–233	EtOH/DMF	$C_{31}H_{25}N_3O_3S$	71.6	4.8	8.1	6.2
				71.4	4.9	7.8	6.0
11d	247–249	DMF	$C_{25}H_{21}N_3O_3S_2$	63.1	4.5	8.8	13.4
				63.3	4.7	8.5	13.1



	R / Ar`		R / Ar`
a	CH_3 / C_6H_5	**c**	2-naphthyl / C_6H_5
b	C_6H_5 / C_6H_5	**d**	2-thienyl / C_6H_5

SCHEME 3

Other possible structures **14** and **15** excluded on the basis of elemental analyses and spectral data.

Stereochemically, the isolated products can have either the configuration **7**/**12** or **9**/**13**. Molecular models indicate that structures **9** and **13** suffer severe steric interactions due to the close proximity of the Ar′ and isoquinoline moiety. On these basis we suggest that the configuration of the products isolated are the less hindered structures **7** and **12**.

EXPERIMENTAL

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Infrared spectra (KBr) were determined on a Pye Unican

TABLE II Characteristic IR, ^{1}HNMR and MS spectral data of products

No.	ν_{max}/cm^{-1}	δ_H ppm	m/z
2b	3218 (NH)	2.3 (s, 3H), 2.8 (t, 2H), 3.5 (t, 2H), 3.7 (s, 3H), 3.9 (s, 3H), 6.0 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2 (m, 4H), 7.7 (s, 1H), 12.0 (s, 1H)	354, 321, 248, 205, 190, 149, 77, 51
2c	3326 (NH)	2.8 (t, 2H), 3.5 (t, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 5.9 (s, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.3 (m, 4H), 7.7 (s, 1H), 12.1 (s, 1H)	
2d	3325 (NH)	2.8 (t, 2H), 3.5 (t, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 6.0 (s, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.2 (d, 2H), 7.5 (d, 2H), 7.7 (s, 1H), 12.1 (s, 1H)	
7a	1610 (C═N)	2.7 (m, 2H), 3.8 (s, 3H), 3.9 (m, 2H), 4.0 (s, 3H), 6.3 (s, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.2–8.0 (m, 10H)	441, 338, 279, 264, 220, 175, 132, 91, 77
7b	1600 (C═N)	2.6 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (m, 2H), 6.2 (s, 1H), 6.7 (s, 1H), 6.9 (s, 1H), 7.0–7.9 (m, 12H)	
7c	1715 (C═O)	1.4 (t, 3H), 2.7 (t, 2H), 3.7 (s, 3H), 3.8 (t, 2H), 3.9 (s, 3H), 4.5 (q, 2H), 6.3 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.4–7.7 (m, 5H)	437, 338, 279, 77, 51
11a	1681 (C═O)	2.6 (s, 3H), 2.7 (t, 2H), 3.8 (s, 3H), 3.9 (t, 2H), 3.9 (s, 3H), 6.3 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.2–7.5 (m, 5H)	407, 338, 279, 131, 77
11b	1665 (C═O)	2.7 (m, 2H), 3.8 (s, 3H), 3.9 (m, 2H), 4.0 (s, 3H), 6.4 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.4–8.3 (m, 10H)	469, 328, 281, 214, 135, 79
11c	1650 (C═O)	2.3 (m, 2H), 3.9 (s, 3H), 4.0 (s, 3H), 4.0 (m, 2H), 6.4 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.4–8.4 (m, 11H), 9.0 (s, 1H)	519, 338, 279, 127, 77
11d	1645 (C═O)	2.6 (m, 2H), 3.8 (s, 3H), 3.9 (s, 3H), 4.0 (m, 2H), 6.4 (s, 1H), 6.7 (s, 1H), 6.8 (s, 1H), 7.0–8.4 (m, 8H)	475, 338, 279, 111, 77

SP-3000 infrared spectrophotometer. The ^{1}H NMR spectra in $CDCl_3$ or DMSO-d_6 were recorded on a Varian Gemini 200 instrument (200 MHz) with TMS as the internal standard. Mass spectra were recorded on GCMS-QP 1000EX Shimadzu, Japan. Elemental analyses were carried out at the University of Cairo, Giza, Egypt. The hydrazonoyl halides **3a**,[10] **3b**,[11] **3c**,[12] **10a**,[13] **10b**,[14] **10c**,[15] **10d**,[16] were prepared as previously described.

Synthesis of Thioanilides 2

A mixture of 1-methylisoquinoline (3.5 g, 10 mmol) and arylisothiocyanate (10 mmol) was refluxed in dry toluene (40 ml) for 2 h. The solid that formed was collected and recrystallized from the suitable solvent to give the corresponding thioanilides **2a–d** (Tables I and II).

Preparation of 1,3,4-Thiadiazoles 7 and 12

Equimolecular quantities of **2** and **3** or **10** and triethylamine (5 mmol each) were dissolved in chloroform (30 ml). The reaction mixture was refluxed for 3 h the excess solvent was evaporated under reduced pressure and the residue was triturated with methanol (10 ml) until it solidified. The solid formed was collected, washed with water, and finally crystallised from suitable solvent to give the corresponding 1,3,4-thiadiazolines **7** or **12**. The physical properties and elemental analysis of **7** and **12** are summarised in Tables I and II.

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