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Reactivity of 1-methylisoquinoline synthesis of pyrazolyl triazoloisoquinoline and thiadiazolyl isoquinoline derivatives

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ABSTRACT

The reaction of 1-methylisoquinoline 1 with hydrazonoyl halides 2 in ethanol in the presence of chitosan under microwave irradiation affords triazoloisoquinoline 4. Product 4 reacts with dimethylformamide-dimethylacetal to give enaminones 7 which react with hydrazonoyl halides to give pyrazolyl triazoloisoquinoline 13. Also, 1-methylisoquinoline 1 reacts with arylisothiocyanate to give thioanilide 15 which reacts with hydrazonoyl halides to give the corresponding thiadiazolyl isoquinoline derivatives 20, 24.

Keywords: [1,2,4] Triazolo [3,4-*a*] Isoquinolines; Enaminones; Hydrazonoyl Halides; Cycloaddition Reactions; Chitosan; Thioanilides; [1,3,4] Thiadiazolylisoquinoline Derivatives

1. INTRODUCTION

Within the class of fused isoquinoline with their cardiovascular [1], anti-inflammatory [2], and antidepressant activites [3], [1,2,4]triazolo [3,4-*a*]isoquinolines are of considerable pharmaceutical and agricultural interest [4-7]. Therefore, the synthesis of this ring system is an attractive goal. We have previously reported the syntheses of triazoloisoquinoline and fused isoquinoline compounds *via* reaction of 3,4-dihydro-6,7-dimethoxyisoquinoline derivatives with hydrazonoyl halides in chloroform in the presence of triethylamine or in pyridine as catalyst and solvent [8-12]. The aim of the present study is to introduce a new synthetic method by replacing triethylamine in chloroform by the ecologically more acceptable catalyst chitosan [13,14] and under microwave irradiation to enhance reaction rates [15-19] for the synthesis of [1,2,4]triazolo[3,4-*a*]isoquinolines which were found to be useful precursors for the synthesis of new enaminones 7. The latter compounds 7 were used to prepare carbonylpyrazolyl triazoloisoquinoline derivatives 13. Also, we synthesis thiadiazolyl isoquinoline derivatives 20, 24 *via* a reaction of thioanilide 15 with hydrazonoyl halides 16.

2. EXPERIMENTAL

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using a FTIR unit Bruker-vector 22 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 as solvents at 300 MHz on Varian Gemini NMR spectrometer using TMS as internal standard. Chemical shifts are reported in δ units (ppm). Mass spectra were measured on a Shimadzu GCMS-QP-1000 EX mass spectrometer at 70 eV. Microwave used was CEM Discover labmate™ microwave apparatus (300 W with ChemDriver™ software). The elemental analyses were performed at the Micro Analytical Center, Cairo University.

2.1. Synthesis of 1-(1-Aryl-8,9-Dimethoxy-10b-Methyl-1,5,6,10b-Tetrahydro [1,2,4] Triazolo [3,4-*a*]Isquinlin-3-yl) Ethanone-4a-c

Chitosan (0.1 g) was added to a solution of hydrazonoyl chloride 2 (1 mmol) and 1-methyl-3,4-dihydro-6,7-dimethoxyisoquinoline 1 (0.28 g, 1 mmol) in absolute ethanol (5 mL) at room temperature. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80˚C) for 10 min at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dilute HCl was added till pH became acidic and the solid was collected and crystallized from suitable solvent. The compounds prepared 4a-c with their physical data are listed in **Tables 1** and **2**.

2.2. Synthesis of (E)-1-(1-Aryl-8,9-Dimethoxy-10b-Methyl-1,5,6,10b-Tetrahydro [1,2,4] Triazolo-[3,4-*a*]Isoquinolin-3-yl)-3-Dimethylaminopropenone 7a-c

A mixture of 1-(1-aryl-8,9-dimethoxy-10b-methyl-1, 5,6,10b-tetra-hydro[1,2,4]triazolo[3,4-*a*]isoquinolin-3-yl) ethanone 4 (5 mmoles) and DMF-DMA (3 mL) was refluxed for 4 h. The solid that precipitated was collected and crystallized from suitable solvent. The compounds prepared 7 a-c with their physical data are listed in **Tables 1** and **2**.

2.3. Synthesis of Pyrazolyl Triazoloisoquinoline Derivatives 13a-i

To a solution of the appropriate hydrazonoyl chloride 2, 8, 9 (1 mmol) and enaminones 7 (1 mmol) in absolute ethanol (5 mL) was added chitosan (0.1 g) at room temperature. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80˚C) for 10 min at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dilute HCl was added till pH became acidic and the solid was collected and crystallized from suitable solvent. The compounds prepared 13a-i with their physical data are listed in **Tables 1** and **2**.

2.4. Synthesis of Thiadiazolyl Isoquinoline Derivatives 20a-j and 24a-g

Equimolar quantities of thioanilides 15 and the appropriate hydrazonoyl halides were dissolved in absolute ethanol (5 mL) in the presence of chitosan (0.1 g) at room temperature. The reaction mixture was irradiated under constant pressure (11.2 Bar, 80˚C) for 10 min at a power of 300 W. The hot solution was filtered to remove chitosan. After cooling, dilute HCl was added till pH became acidic and the solid was collected and crystallized from suitable solvent to give the corresponding 1, 3,4-thiadiazoles. The compounds prepared 20a-j and 24a-g with their physical data are listed in **Tables 1** and **2**.

3. RESULTS AND DISCUSSION

The reaction of hydrazonoyl halides 2 with 1-methyl-3, 4-dihydro-6, 7-dimethoxyisoquinoline 1 which has active group at C-1 was studied.

The capacity of this dipolarophile 1 to behave as cyclic ketimine 1 A or as a secondary enamine 1B has been discussed by many investigators [20,21]. Our aim point of interest whether addition of nitrilimines 3 occurred on the C = N double bond of ketimine structure 1 A or enamine double bond of 1 B (**Figure 1**). Thus, reaction of 1 with nitrilimines 3, generated in *situ* by treatment of hydrazonoyl chlorides 2 with chitosan [22] in ethanol under microwave irradiation, gave products whose elemental analyses were compatible with triazole derivatives 4, spyropyrazolines 5 or triazine derivatives 6. The structures 5 and 6 were discarded on the basis of ^{1}H NMR evidences. For example, structure 5 will reveal two singlet signals assignable to CH_2 and NH protons, while the other isomeric structure 6 is expected to reveal doublet and triplet assignable to C1-CH_2 and C11b-CH protons. Such signals were absent in the ^{1}H NMR spectra of the isolated products from reaction of 2 with 1. Instead of these signals, the ^{1}H NMR spectra of the latter products showed one singlet signal at δ 2.08 ppm. The presence of such signal is compatible with the assigned structure 4. Indeed the proton resonance of the moiety -N = C(CH_3)- appears in the ^{1}H NMR spectra of the dipolarophile 1 at δ 2.3 ppm [23]. This resonance was shifted to higher field in the ^{1}H NMR spectra (2.08 ppm) of the cycloadducts 4 indicating the conversion of such moiety to the saturated moiety -N-C(CH_3)- due to cycloaddition. Based on these findings the products isolated from the reaction mixture were assigned structure 4 (**Figure 1**).

Refluxing of 4a with DMFDMA for 4 h afforded a compound 7a which analyzed correctly for $C_{24}H_{28}N_4O_3$ (**Figure 2**). Similarly compounds 4b, c were also pre0 pared by reaction of the corresponding 3-acetylisoquinoline derivatives with DMFDMA. The structures of the products 7 were fully established on the basis of spectral (MS, IR, ^{1}H NMR and ^{13}C NMR) and elemental analyses. For example, the ^{1}H NMR spectrum of 7a showed two singlet signals at δ 2.96 and 3.72 ppm characteristic for -N(Me)$_2$ group, two doublet signals at δ about 5.75 and 7.64 ppm with coupling constant J = 13 Hz assignable to the two olefinic protons. The value of coupling constant is compatible with the *E*-configuration [24] depicted in **Figure 2**. Also its ^{13}C NMR spectrum showed two signals at δ 37.31 and 45.48 ppm assignable to -N(Me)$_2$ group [25], in addition to the signals of other carbon atoms.

Reaction of enaminones 7 with nitrilimines 10, generated in *situ* by the action of chitosan on the corresponding α-ketohydrazonoyl halides 2, 8, 9 in refluxed ethanol gave, in each case, one isolable product as evidenced by TLC analysis and ^{1}H NMR spectra of the crude reaction mixture (**Figure 3**).

All the isolated cycloadducts gave satisfactory elemental analyses and mass spectral data which were consistent with either one of the two isomeric structures 13 or 14. Structure 14 was ruled out on the basis of ^{1}H NMR spectra. For example, in the pyrazole ring system C (4) is the most electron rich carbon, thus, H (4) in is expected to appear at higher field at δ 6.31 ppm. On the

Table 1. Characterization data of the synthesized compounds.

Compd. no.	Mp (˚C), solvent	Yield (%), color	Mol. Formula	% Analyses calcd., found				
				C	H	N	Cl	S
4a	162 EtOH	72 Yellow	$C_{21}H_{23}N_3O_3$	69.02 68.83	6.34 6.13	11.50 11.67		
4b	142 EtOH	73 Yellow	$C_{22}H_{25}N_3O_3$	69.64 69.45	6.64 6.58	11.07 11.25		
4c	154 EtOH	73 Yellow	$C_{21}H_{22}ClN_3O_3$	63.08 62.93	5.55 5.75	10.51 10.66	8.87 8.63	
7a	192 CH_3CN	80 Yellow	$C_{24}H_{28}N_4O_3$	68.55 68.40	6.71 6.92	13.32 13.04		
7b	186 CH_3CN	79 Yellow	$C_{25}H_{30}N_4O_3$	69.10 68.87	6.96 7.03	12.89 13.06		
7c	212 DMF	78 Orange	$C_{24}H_{27}ClN_4O_3$	63.36 63.11	5.98 6.01	12.31 12.02	7.79 7.53	
13a	210 CH_3CN	75 Yellow	$C_{31}H_{29}N_5O_4$	69.52 69.31	5.46 5.18	13.08 12.96		
13b	170 EtOH	78 Yellow	$C_{32}H_{31}N_5O_4$	69.93 69.72	5.69 5.77	12.74 12.91		
13c	164 EtOH	76 Yellow	$C_{31}H_{28}ClN_5O_4$	65.32 65.05	4.95 5.11	12.29 12.38	6.22 6.16	
13d	150 EtOH	75 Yellow	$C_{32}H_{31}N_5O_5$	67.95 67.68	5.52 5.46	12.38 12.41		
13e	174 EtOH	73 Yellow	$C_{33}H_{33}N_5O_5$	68.38 68.15	5.74 5.94	12.08 11.93		
13f	158 EtOH	76 Yellow	$C_{32}H_{30}ClN_5O_5$	64.05 63.87	5.04 5.31	11.67 11.83	5.91 6.12	
13g	95 EtOH	72 Orange	$C_{36}H_{31}N_5O_4$	72.35 72.51	5.23 5.42	11.72 11.47		
13h	180 CH_3CN	73 Orange	$C_{37}H_{33}N_5O_4$	72.65 72.54	5.44 5.41	11.45 11.26		
13i	90 EtOH	72 Orange	$C_{36}H_{30}ClN_5O_4$	68.40 68.25	4.78 4.91	11.08 10.86	5.61 5.68	
20a	174 - 175 CH_3CN	81 Yellow	$C_{24}H_{25}N_3O_4S$	63.85 63.92	5.58 5.62	9.31 9.61		7.09 6.92
20b	208 - 210 DMF	81 Yellow	$C_{23}H_{22}ClN_3O_4S$	58.54 58.35	4.70 4.85	8.90 9.14	7.51 7.32	6.78 6.70
20c	201 - 202 DMF	82 Yellow	$C_{22}H_{21}N_3O_4S$	62.41 62.53	5.00 4.89	9.92 9.68		7.56 7.59
20d	210 - 211 DMF	81 Yellow	$C_{23}H_{23}N_3O_4S$	63.15 62.96	5.30 5.45	9.61 9.64		7.32 7.49
20e	210 - 220 DMF	79 Yellow	$C_{22}H_{20}ClN_3O_4S$	57.71 57.57	4.40 4.32	9. 18 8.88	7.74 7.45	6.99 7.18
20f	266 -268 DMF	80 Yellow	$C_{26}H_{22}N_4O_4S$	64.19 64.34	4.56 4.27	11.52 11.80		6.58 6.74
20g	279 - 280 DMF	79 Yellow	$C_{27}H_{24}N_4O_4S$	64.79 64.99	4.83 5.07	11.19 10.88		6.39 6.26
20h	276 - 278 DMF	82 Orange	$C_{26}H_{21}ClN_4O_4S$	59.95 60.22	4.06 3.89	10.76 10.53	6.81 7.04	6.14 6.07

20i	270 - 272 DMF	80 Yellow	$C_{24}H_{20}N_4O_4S_2$	58.54 58.58	4.09 4.25	11.38 11.17		13.00 13.23
20j	278 - 280 DMF	81 Yellow	$C_{24}H_{20}N_4O_5S$	60.50 60.42	4.23 3.98	11.76 11.63		6.72 6.81
24a	240 - 242 DMF	81 Yellow	$C_{23}H_{23}N_3O_3S$	65.55 65.32	5.50 5.57	9.97 10.21		7.59 7.74
24b	228 - 230 DMF	78 Orange	$C_{22}H_{20}ClN_3O_3S$	59.80 60.01	4.56 4.63	9.51 9.59	8.02 7.96	7.24 7.01
24c	200 - 201 DMF	84 Brown	$C_{28}H_{25}N_3O_3S$	69.55 69.64	5.21 4.93	8.69 8.44		6.62 6.68
24d	179 - 181 DMF	82 Red	$C_{27}H_{22}ClN_3O_3S$	64.35 64.42	4.40 4.72	8.34 8.48	7.04 6.83	6.35 6.57
24e	210-211 DMF	79 Yellow	$C_{27}H_{24}N_4O_3S$	66.93 67.11	4.99 5.07	11.56 11.31		6.60 6.53
24f	170 - 172 DMF	80 Yellow	$C_{28}H_{26}N_4O_3S$	67.46 67.26	5.26 4.95	11.24 11.13		6.42 6.51
24g	219 - 220 CH3CN	83 Yellow	$C_{27}H_{23}C_1N_4O_3S$	62.49 62.57	4.47 4.15	10.80 10.88	6.84 6.62	6.17 5.93

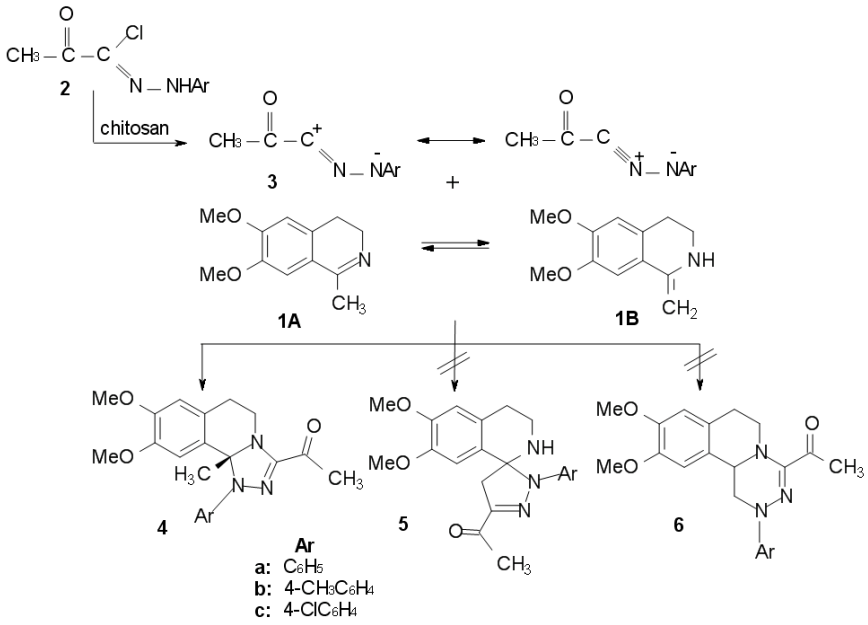

Figure 1. Synthesis of 3-acetyl-10b-methyl [1,2,4] triazolo [3,4-*a*] isoquinolines 4.

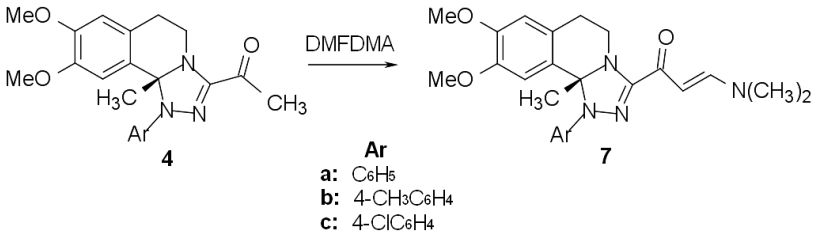

Figure 2. Synthesis of enaminones 7.

Table 2. Spectra of the synthesized compounds.

Compd. no.	Spectral data (IR, ^{1}H NMR, ^{13}C NMR and MS)
4a	IR (KBr) *v* 1670 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 2.08 (s, 3H), 2.37 (m, 1H), 2.38 (s, 3H), 2.80 (m, 1H), 3.18 (s, 3H), 3.2 (m, 1H), 3.73 (s, 3H), 4.60 (m, 1H), 5.85 (s, 1H), 6.40 (s, 1H), 7.13 - 7.28 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 26.21, 27.32, 29.24, 40.22, 54.9, 55.35, 90.09, 109.20, 111.04, 123.94, 125.09, 127.16, 127.69, 128.70, 143.19, 146.04, 147.75, 147.97, 189.88 ppm; MS, *m/z* (%): 365 (M$^+$, 10.9), 334 (100.0), 103 (22.0), 90 (38.4), 76 (30.8).
4b	IR (KBr) *v* 1662 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 2.05 (s, 3H), 2.29 (s, 3H), 2.34 (m, 1H), 2.38 (s, 3H), 2.84 (m, 1H), 3.14 (m, 1H), 3.23 (s, 3H), 3.75 (s, 3H), 4.65 (m, 1H), 5.79 (s, 1H), 6.41 (s, 1H), 7.09 - 7.12 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 20.61, 26.24, 27.40, 29.20, 40.35, 54.76, 55.40, 90.21, 109.45, 111.02, 124.39, 127.11, 127.86, 129.28, 135.16, 140.60, 145.96, 147.68, 147.95, 189.92 ppm; MS, *m/z* (%): 364 (M$^+$-15, 100.0), 104 (33.4), 90 (20.2).
4c	IR (KBr) *v* 1666 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 2.03 (s, 3H), 2.35 (m, 1H), 2.39 (s, 3H), 2.83 (m, 1H), 3.13 (m, 1H), 3.27 (s, 3H), 3.74 (s, 3H), 4.60 (m, 1H), 5.86 (s, 1H), 6.41 (s, 1H), 7.14-7.25 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 26.51, 27.70, 29.17, 40.61, 55.17, 55.63, 90.24, 109.39, 111.42, 125.16, 127.13, 128.17, 128.93, 130.49, 142.18, 146.44, 148.29, 148.40, 190.13 ppm; MS, *m/z* (%): 399 (M$^+$, 1.8), 384 (M$^+$-15, 100.0), 90 (8.6).
7a	IR (KBr) ν 1642 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.38 (m, 1H), 2.80 (s, 3H), 2.88 (m, 1H), 2.96 (s, 3H), 3.16 (s, 3H), 3.19 (m, 1H), 3.72 (s, 3H), 4.80 (m, 1H), 5.75 (d, 1H), 5.89 (s, 1H), 6.38 (s, 1H), 7.04 - 7.24 (m, 5H), 7.64 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 27.85, 29.10, 37.31, 40.42, 45.48, 54.95, 55.37, 88.63, 93.13, 109.52, 110.93, 123.80, 124.29, 128.02, 128.04, 128.50, 144.36, 145.88, 147.67, 150.13, 152.23, 179.19 ppm; MS, m/z (%): 420 (M+, 3.2), 405 (M+-15, 87.9), 322 (11.0), 98 (100.0).
7b	IR (KBr) ν 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.26 (s, 3H), 2.35 (m, 1H), 2.80 (s, 3H), 2.87 (m, 1H), 2.95 (s, 3H), 3.16 (m, 1H), 3.20 (s, 3H), 3.71 (s, 3H), 4.80 (m, 1H), 5.74 (d, 1H), 5.81 (s, 1H), 6.37 (s, 1H), 7.01-7.10 (m, 4H), 7.63 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.77, 28.10, 29.25, 37.38, 42.71, 45.49, 54.96, 55.58, 88.96, 93.40, 109.94, 111.08, 124.49, 128.13, 128.38, 129.25, 134.42, 141.99, 145.97, 147.82, 150.18, 152.37, 179.46 ppm; MS, m/z (%): 434 (M+, 2.0), 419 (M+-15, 46.7), 336 (10.5), 98 (100.0).
7c	IR (KBr) ν 1640 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.98 (s, 3H), 2.37 (m, 1H), 2.79 (s, 3H), 2.87 (m, 1H), 2.94 (s, 3H), 3.15 (m, 1H), 3.28 (s, 3H), 3.71 (s, 3H), 4.67 (m, 1H), 5.75 (d, 1H), 5.90 (s, 1H), 6.38 (s, 1H), 7.13-7.19 (m, 4H), 7.63 (d, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 28.17, 28.99, 37.42, 40.77, 44.98, 55.18, 55.61, 88.71, 93.22, 109.68, 111.30, 124.97, 127.99, 128.48, 128.67, 129.48, 143.35, 146.25, 148.08, 150.81, 152.68, 179.17 ppm; MS, m/z (%): 454 (M+, 1.9), 439 (M+-15, 29.2), 285 (31.5), 98 (100.0).
13a	IR (KBr) ν 1692 (C=O), 1645 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 3H), 2.52 (m, 1H), 2.63 (s, 3H), 3.24 (s, 3H), 3.38 (m, 1H), 3.41 (m, 1H), 3.81 (s, 3H), 4.79 (m, 1H), 5.87 (s, 1H), 6.53 (s, 1H), 7.15 - 7.68 (m, 10H), 8.33 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 27.93, 28.12, 29.65, 40.92, 55.23, 55.64, 90.27, 109.58, 111.46, 119.85, 122.74, 124.95, 125.70, 127.27, 127.88, 128.77, 128.91, 129.54, 131.01, 138.98, 143.35, 146.17, 148.24, 149.04, 151.56, 178.11, 193.99 ppm; MS, m/z (%): 535 (M+, 1.8), 520 (M+-15, 100.0), 303 (21.1), 213 (13.9), 77 (33.8).
13b	IR (KBr) ν 1694 (C=O), 1645 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.31 (s, 3H), 2.52 (m, 1H), 2.63 (s, 3H), 3.26 (s, 3H), 3.30 (m, 1H), 3.34 (m, 1H), 3.83 (s, 3H), 4.80 (m, 1H), 5.82 (s, 1H), 6.54 (s, 1H), 7.01 - 7.69 (m, 9H), 8.34 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.85, 27.97, 28.14, 29.59, 40.97, 55.04, 55.63, 90.32, 109.75, 111.38, 119.89, 122.77, 125.34, 127.20, 127.87, 128.86, 129.43, 129.54, 131.04, 135.78, 139.02, 140.71, 146.05, 148.17, 148.86, 151.60, 178.01, 194.10 ppm; MS, m/z (%): 549 (M+, 1.1), 534 (M+-15, 100.0), 317 (13.2), 213 (23.9), 91 (11.8).
13c	IR (KBr) ν 1692 (C=O), 1650 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.52 (m, 1H), 2.62 (s, 3H), 3.31 (m, 1H), 3.33 (m, 1H), 3.35 (s, 3H), 3.82 (s, 3H), 4.78 (m, 1H), 5.90 (s, 1H), 6.55 (s, 1H), 7.06 - 7.69 (m, 9H), 8.32 (s, 1H) ppm; MS, m/z (%): 581 (M+, 1.0), 557 (17.1), 556 (46.1), 555 (45.9), 554 (100.0), 337 (15.0), 213 (43.8), 98 (13.6).
13d	IR (KBr) ν 1728 (C=O), 1635 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3H), 2.17 (s, 3H), 2.45 (m, 1H), 3.20 (m, 1H), 3.24 (s, 3H), 3.30 (m, 1H), 3.80 (s, 3H), 4.36 (q, 2H), 4.81 (m, 1H), 5.95 (s, 1H), 6.50 (s, 1H), 7.16-7.69 (m, 10H), 8.44 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.13, 27.82, 29.57, 40.66, 55.22, 55.69, 61.52, 90.21, 109.37, 111.37, 120.17, 123.14, 124.02, 125.36, 127.64, 127.94, 128.27, 129.01, 129.46, 131.10, 138.94, 144.05, 145.92, 147.65, 148.81, 149.22, 162.54, 176.33 ppm; MS, m/z (%): 550 (M+-15, 100.0), 474 (30.1), 103 (45.1), 76 (82.4), 56 (47.6).
13e	IR (KBr) ν 1720 (C=O), 1639 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (t, 3H), 2.12 (s, 3H), 2.30 (s, 3H), 2.49 (m, 1H), 3.18 (m, 1H), 3.25 (s, 3H), 3.13 (m, 1H), 3.79 (s, 3H), 4.36 (q, 2H), 4.77 (m, 1H), 5.88 (s, 1H), 6.48 (s, 1H), 7.10 - 7.67(m, 9H), 8.43 (s, 3H) ppm;

13f	IR (KBr) ν 1720 (C=O), 1639 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, 3H), 2.12 (s, 3H), 2.46 (m, 1H), 3.09 (m, 1H), 3.18 (m, 1H), 3.35 (s, 3H), 3.79 (s, 3H), 4.39 (q, 2H), 4.72 (m, 1H), 5.98 (s, 1H), 6.51 (s, 1H), 7.15 - 7.71 (m, 9H), 8.42 (s, 1H) ppm; MS, m/z (%): 584 (M+-15, 100.0), 148 (21.1), 127 (22.1), 103 (61.5), 76 (67.1).
13g	IR (KBr) ν 1675 (C=O), 1631 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10 (s, 3H), 2.44 (m, 1H), 3.21 (s, 3H), 3.24 (m, 1H), 3.28 (m, 1H), 3.82 (s, 3H), 4.77 (m, 1H), 5.83 (s, 1H), 6.51 (s, 1H), 7.02-8.04 (m, 15H), 8.61 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 27.75, 29.40, 40.52, 55.06, 55.59, 89.90, 109.26, 111.36, 119.79, 123.67, 124.39, 125.29, 127.28, 127.72, 128.19, 128.33, 128.73, 129.43, 130.15, 130.86, 133.13, 136.51, 138.88, 143.03, 146.07, 148.12, 148.54, 152.01, 176.64, 189.11 ppm; MS, m/z (%): 582 (M+-15, 100.0), 104 (81.6), 76 (94.3).
13h	IR (KBr) ν 1678 (C=O), 1624 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.07 (s, 3H), 2.29 (s, 3H), 2.44 (m, 1H), 3.20 (m, 1H), 3.23 (s, 3H), 3.28 (m, 1H), 3.83 (s, 3H), 4.78 (m, 1H), 5.79 (s, 1H), 6.51 (s, 1H), 6.90 - 8.04 (m, 14H), 8.62 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 20.78, 27.83, 29.39, 40.65, 54.95, 55.66, 90.03, 109.51, 111.34, 119.89, 123.72, 124.83, 127.26, 127.75, 128.25, 128.51, 129.33, 129.48, 130.21, 130.97, 133.15, 135.41, 136.61, 139.00, 140.51, 146.02, 148.13, 148.40, 152.10, 176.55, 189.29 ppm; MS, m/z (%): 611 (M+, 1.1), 596 (M+-15, 100.0), 324 (49.7), 104 (21.7), 76 (25.7).
13i	IR (KBr) ν 1678 (C=O), 1639 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.50 (m, 1H), 3.20 (m, 1H), 3.30 (s, 3H), 3.36 (m, 1H), 3.83 (s, 3H), 4.79 (m, 1H), 5.83 (s, 1H), 6.53 (s, 1H), 6.87 - 8.03 (m, 14H), 8.57 (s, 1H) ppm; MS, m/z (%): 632 (M+, 2.9), 617 (M+-15, 100.0), 275 (21.8), 104 (59.2), 76 (44.3).
20a	IR (KBr) ν 1732 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (t, 3H), 2.43 (s, 3H), 2.66 (t, 2H), 3.79 (s, 3H), 3.84 (t, 2H), 3.88 (s, 3H), 4.44 (q, 2H), 6.22 (s, 1H), 6.69 (s, 1H), 6.81 (s, 1H), 7.30 - 7.48 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.18, 21.14, 26.92, 45.84, 55.81, 56.43, 62.19, 85.56, 108.46, 110.49, 122.59, 125.39, 130.06, 131.78, 136.88, 138.71, 143.14, 147.37, 149.93, 150.56, 157.96, 160.06 ppm; MS, m/z (%): 451 (M+, 8.9), 293 (100.0), 91 (18.3).
20b	IR (KBr) *ν* 1734 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 1.43 (t, 3H), 2.65 (t, 2H), 3.78 (s, 3H), 3.84 (t, 2H), 3.88 (s, 3H), 4.46 (q, 2H), 6.20 (s, 1H), 6.67 (s, 1H), 6.78 (s, 1H), 7.31 - 7.52 (m, 4H) ppm; MS, *m/z* (%):473 (M^+ + 2, 3.5), 471 (M^+, 10.1), 293 (100.0), 91 (18.9).
20c	IR (KBr) *ν* 1708 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.66 (t, 2H), 3.79 (s, 3H), 3.84 (t, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 6.23 (s, 1H), 6.69 (s, 1H), 6.81 (s, 1H), 7.31 - 7.48 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 27.00, 45.79, 52.86, 55.83, 56.45, 85.82, 108.41, 110.66, 121.58, 125.01, 130.22, 131.90, 136.85, 138.88, 142.83, 147.58, 149.67, 150.70, 158.01, 160.64 ppm; MS, *m/z* (%): 423 (M^+, 8.9), 293 (100.0), 91 (21.4).
20d	IR (KBr) *ν* 1705 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.43 (s, 3H), 2.66 (t, 2H), 3.79 (s, 3H), 3.84 (t, 2H), 3.88 (s, 3H), 3.96 (s, 3H), 6.23 (s, 1H), 6.69 (s, 1H), 6.81 (s, 1H), 7.31 - 7.48 (m, 4H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 21.15, 26.92, 45.78, 52.86, 55.82, 56.44, 85.68, 108.47, 110.51, 122.54, 125.36, 130.10, 131.79, 136.83, 138.78, 142.83, 147.39, 149.86, 150.61, 157.92, 160.51 ppm; MS, *m/z* (%): 437 (M^+, 9.3), 293 (100.0), 91 (20.3).
20e	IR (KBr) *ν* 1704 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) *δ* 2.62 (t, 2H), 3.75 (s, 3H), 3.84 (t, 2H), 3.88 (s, 3H), 3.95 (s, 3H), 6.21 (s, 1H), 6.75 (s, 1H), 7.01 (s, 1H), 7.25 - 7.49 (m, 4H) ppm; MS, *m/z* (%): 459 (M^+ + 2, 4.1), 457 (M^+, 10.2), 293 (100.0), 91 (20.9).
20f	^1H NMR ($CDCl_3$) *δ* 2.90 (t, 2H), 3.86 (s, 3H), 3.98 (s, 3H), 4.09 (t, 2H), 6.62 (s, 1H), 7.07 - 8.11 (m, 11H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 26.16, 47.94, 56.01, 56.16, 86.68, 107.02, 111.55, 116.32, 123.02, 125.85, 127.32, 127.64, 128.66, 129.68, 141.00, 141.42, 142.82, 144.47, 148.48, 151.12, 161.81, 168.40 ppm; MS, *m/z* (%): 486 (M^+, 8.2), 324 (100.0).
20g	^1H NMR ($CDCl_3$) *δ* 2.35 (s, 3H), 2.89 (t, 2H), 3.88 (s, 3H), 4.00 (s, 3H), 4.08 (t, 2H), 6.57 (s, 1H), 7.07-8.07 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) *δ* 21.43, 26.16, 47.84, 55.96, 56.15, 86.65, 107.06, 111.44, 116.32, 123.06, 125.84, 127.30, 127.59, 128.86, 129.68, 140.95, 141.41, 142.82, 144.38, 148.34, 151.06, 161.80, 168.39 ppm; MS, *m/z* (%): 500 (M^+, 6.7), 324 (100.0).
20h	^1H NMR ($CDCl_3$) *δ* 2.91 (t, 2H), 3.86 (s, 3H), 3.88 (s, 3H), 4.01 (t, 2H), 6.59 (s, 1H), 7.07 - 8.10 (m, 10H) ppm; MS, *m/z* (%): 522 (M^+ + 2, 3.9), 520 (M^+, 9.6), 324 (100.0).
20i	^1H NMR (DMSO-d_6) *δ* 2.82 (t, 2H), 3.75 (s, 3H), 3.90 (s, 3H), 4.12 (t, 2H), 6.75 (s, 1H), 7.12 - 8.07 (m, 9H) ppm; ^{13}C NMR (DMSO-d_6) *δ* 25.54, 47.01, 55.51, 55.86, 108.17, 111.12, 111.64, 111.82, 112.78, 116.30, 122.70, 125.61, 129.04, 130.01, 139.98, 144.92, 146.08, 147.80, 150.67, 151.12, 161.21, 161.54 ppm; MS, *m/z* (%): 492 (M^+, 7.9), 324 (100.0), 127 (22.1), 73 (25.0).
20j	^1H NMR (DMSO-d_6) *δ* 2.82 (t, 2H), 3.75 (s, 3H), 3.90 (s, 3H), 4.13 (t, 2H), 6.68 (s, 1H), 6.76-8.08 (m, 9H) ppm; ^{13}C NMR (DMSO-d_6) *δ* 25.54, 46.92, 55.51, 55.86, 108.19, 111.12, 111.63, 111.84, 112.78, 116.19, 122.70, 125.67, 129.05, 130.01, 140.01, 144.96, 146.07, 147.80, 150.68, 151.06, 157.46, 161.10 ppm; MS, *m/z* (%): 476 (M^+, 10.6), 324 (100.0).
24a	IR (KBr) *ν* 1647 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) *δ* 2.40 (s, 3H), 2.48 (s, 3H), 2.71 (t, 2H), 3.79 (s, 3H), 3.92 (t, 2H), 3.98 (s, 3H), 6.24 (s, 1H), 6.82 (s, 1H), 6.88 (s, 1H), 7.42 - 7.93 (m, 4H) ppm; MS, *m/z* (%): 421 (M^+, 10.4), 293 (100.0), 91 (19.1).
24b	IR (KBr) *ν* 1649 (C=O) cm^{-1}; ^1H NMR (DMSO-d_6) *δ* 2.42 (s, 3H), 2.68 (t, 2H), 3.78 (s, 3H), 3.90 (t, 2H), 3.95 (s, 3H), 6.24 (s, 1H), 6.83 (s, 1H), 6.88 (s, 1H), 7.48 - 7.91 (m, 4H) ppm; MS, *m/z* (%): 443 (M^+ + 2, 5.1), 441(M^+, 12.8), 293 (100.0), 91 (22.9).

24c	IR (KBr) ν 1616 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.68 (t, 2H), 3.81 (s, 3H), 3.87 (t, 2H), 3.90 (s, 3H), 6.32 (s, 1H), 6.71 (s, 1H), 6.84 (s, 1H), 7.36-8.30 (m, 9H) ppm; ^{13}C NMR ($CDCl_3$) δ 21.26, 26.95, 46.00, 55.92, 56.53, 86.65, 108.62, 110.62, 122.67, 125.29, 126.01, 128.25, 130.25, 130.26, 131.98, 133.14, 135.55, 137.11, 138.89, 147.46, 150.72, 151.28, 158.22, 184.25 ppm; MS, *m/z* (%): 483 (M^+, 6.7), 293 (100.0), 91 (16.8), 105 (66.8).
24d	IR (KBr) ν 1616 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (t, 2H), 3.79 (s, 3H), 3.87 (t, 2H), 3.91 (s, 3H), 6.34 (s, 1H), 6.70 (s, 1H), 6.84 (s, 1H), 7.35 - 8.32 (m, 9H) ppm; MS, *m/z* (%): 505 ($M^+ + 2$, 3.9), 503(M^+, 9.5), 293 (100.0), 91 (17.2), 105 (67.8).
24e	IR (KBr) ν 1672 (C=O), 3385 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (t, 2H), 3.81 (s, 3H), 3.83 (t, 2H), 3.91 (s, 3H), 6.29 (s, 1H), 6.63 - 8.70 (m, 12H), 11.75 (s, 1H) ppm; MS, *m/z* (%): 484 (M^+, 7.6), 293 (100.0).
24f	IR (KBr) ν 1670 (C=O), 3386 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 2.68 (t, 2H), 3.80 (s, 3H), 3.85 (t, 2H), 3.89 (s, 3H), 6.22 (s, 1H), 6.66-8.65 (m, 11H), 11.73 (s, 1H) ppm; MS, *m/z* (%): 498 (M^+, 9.5), 293 (100.0).
24g	IR (KBr) ν 1670 (C=O), 3388 (NH) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.66 (t, 2H), 3.81 (s, 3H), 3.83 (t, 2H), 3.89 (s, 3H), 6.32 (s, 1H), 6.66 - 8.66 (m, 11H), 11.74 (s, 1H) ppm; MS, *m/z* (%): 520 ($M^+ + 2$, 2.7), 518 (M^+, 8.3), 293 (100.0).

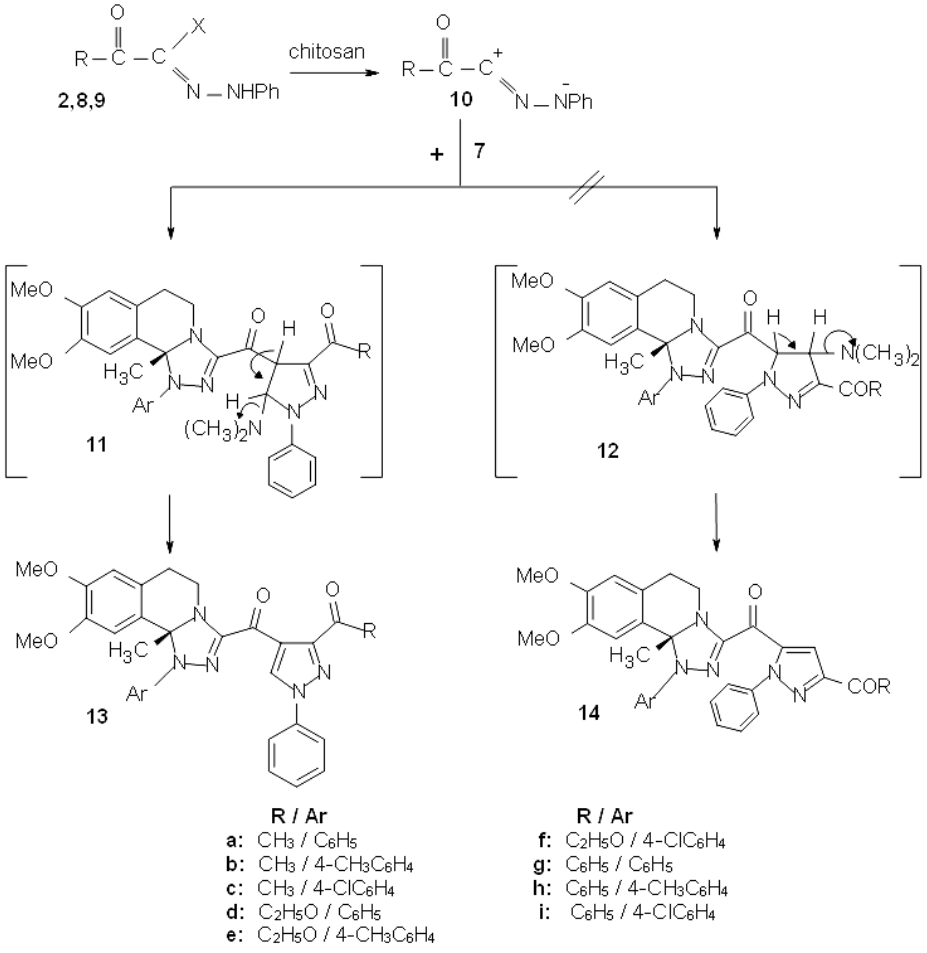

Figure 3. Synthesis of pyrazoles 13.

other hand, H (5) is linked to the carbon attached to nitrogen atom and thus it's deshielded to appear in the region δ 7.5 - 8.5 ppm [26-28]. The ^1H NMR spectra of isolated reaction products revealed, in each case, a singlet signal at δ 8.5 ppm which indicates the presence of the pyrazole H (5) rather than H (4) in the structure of the isolated products.

The proposed mechanism leading to the formation of the latter product suggested that the studied reaction starts with regioselective 1, 3-dipolar cycloaddition of nitrilimines 10 to C=C of the enaminones 7 to afford the cycloadducts 11 which gave the pyrazole derivatives 13

via elimination of dimethylamine and the other isomer 14 resulting from 12 was discarded (**Figure 3**).

Treatment of thioanilide [9] 15a with hydrazonoyl halides 16 in refluxing ethanol in the presence of chitosan under microwave irradiation for 10 min yielded only one isolable product 20 as indicated by TLC and ^{1}H NMR of the crude reaction product (**Figure 4**).

The structure of the products was inferred from their elemental analyses, spectral data and by their alternative synthesis. Thus reaction of 15b with 16 gave products identical in all respects (mp, IR, ^{1}H NMR, MS) with products 20 which formed by the reaction of 15a with 16, respectively (**Figure 4**). For example, the ^{1}H NMR of 20a showed triplet and quartet signals at δ 1.41 and at δ 4.44 ppm respectively, assignable to the ethoxycarbonyl group, and a singlet signal at δ 6.81 ppm assignable to methylidene proton in addition to the signals of the isoquinoline moiety. Its IR spectrum showed the characteristic ester carbonyl absorption band at 1732 cm^{-1}.

Two possible structures 20 and 21 can be suggested for the products resulting from the reaction of 15 with hydrazonoyl halides 16 or nitrilimine 17. Structure 21 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 20, two possible pathways are proposed. In the first way (path A), the reaction led to the formation of thiohydrazones 18 followed by elimination of arylamine to give 20. The second path (path B), nitrilimines 17 cycloadded to the C = S double bond to give the intermediate 19 which upon elimination of arylamine led to 20.

To study the effect of the carbonyl group on the reactivity of the hydrazonoyl halides, we investigated the reaction of α-ketohydrazonoyl halides 2, 9, 22 with thioanilides 15. Thus treatment of 15a or 15b with hydrazonoyl halides 2, 9, 22 in refluxing ethanol in the presence of chitosan under microwave irradiation for 10 min gave the corresponding thiadiazole derivatives 24 (**Figure 5**).

The structures of the products 24 were supported by their elemental analyses and spectral data. The other possible structures 25 and 26 were excluded on the basis of elemental analysis and spectral data. For example, their IR spectra lacked the carbonyl absorption band while such band is present in the spectra of the product

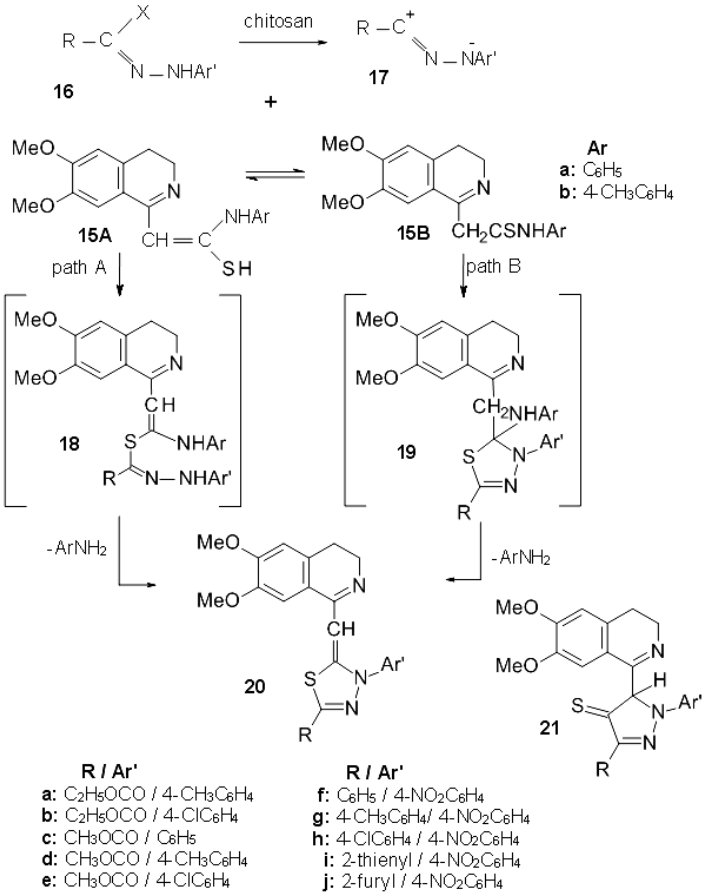

Figure 4. Synthesis of [1,3,4]thiadiazolyl isoquinolines 20.

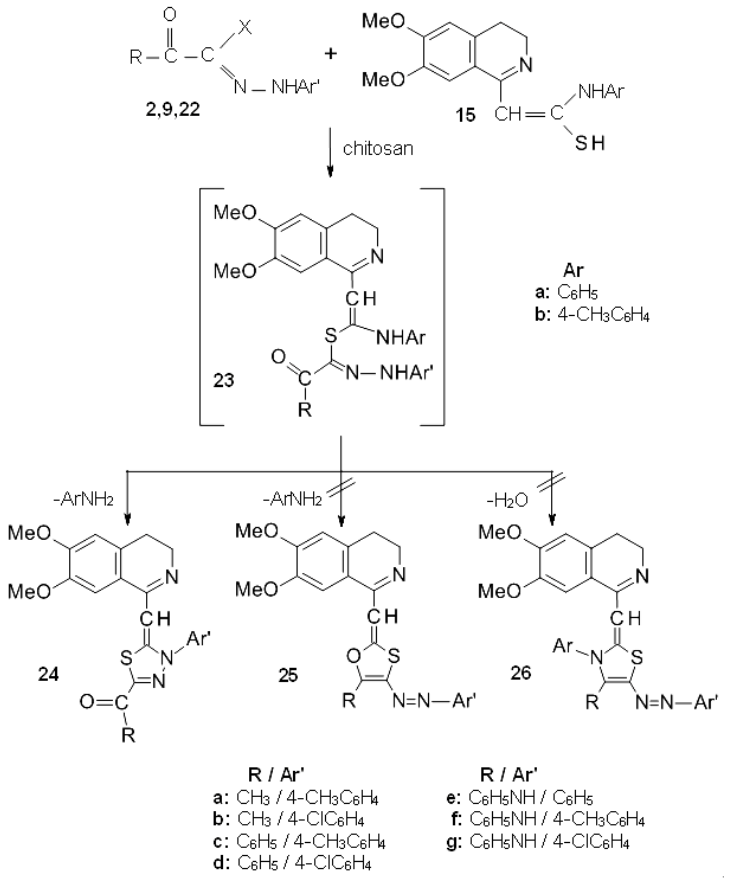

Figure 5. Synthesis of [1,3,4]thiadiazolyl isoquinolines 24.

24. The structure of the latter products proved that the carbonyl group has no effect on the course of this reaction.

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