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Synthesis and Reactions of Indane-1,3-dione-2-thiocarboxanilides with Hydrazonoyl Halides and Active Chloromethylene Compounds

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ABSTRACT: *A novel synthesis of thiadiazoline derivatives* **12** *and* **14** via *treatment of indane-1,3-dione-2-thiocarboxanilides (***5***) with hydrazonoyl halides* **1** *and* **2** *is reported. Also, active chloromethylene compounds* **15** *react with* **5** *to give thiazole derivatives* **19**. © 2002 Wiley Periodicals, Inc. Heteroatom Chem 13:585–591, 2002; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.10132

INTRODUCTION

The high dipolarophilic activity of the C=S double bond towards 1,3-dipoles is known [1]. Recently, it was indicated that the reactions of *C*-acyl-*N*-arylnitrilimines with active methine thioanilides yield the corresponding thiazoline derivatives [2,3]. More recently, Hassaneen et al. reported that hydrazonoyl halides **1** and **2** reacted with thioanilides to give the corresponding thiadiazoles *via* elimination of the arylamine moiety [4–6]. Inspired by these different results, we thought it necessary to explore further the reactions of active methine thioanilides with different nitrilimines. For this purpose, indane-1,3-dione-2-thiocarboxanilides (**5**) were prepared (Scheme 1) and their reactions with different nitrilimines were investigated under different reaction conditions. The objective of this work was to shed more light on the actual pathway of the reactions in question and the factors influencing it. In addition, this investigation led to a one-step synthesis of 2,3-dihydrothiadiazole derivatives.

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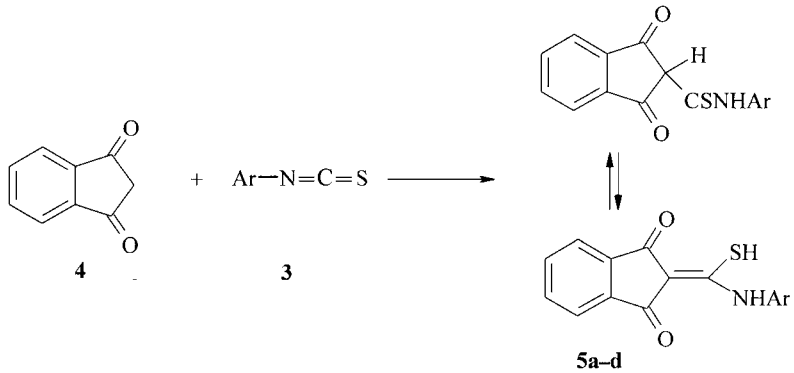
RESULTS AND DISCUSSION

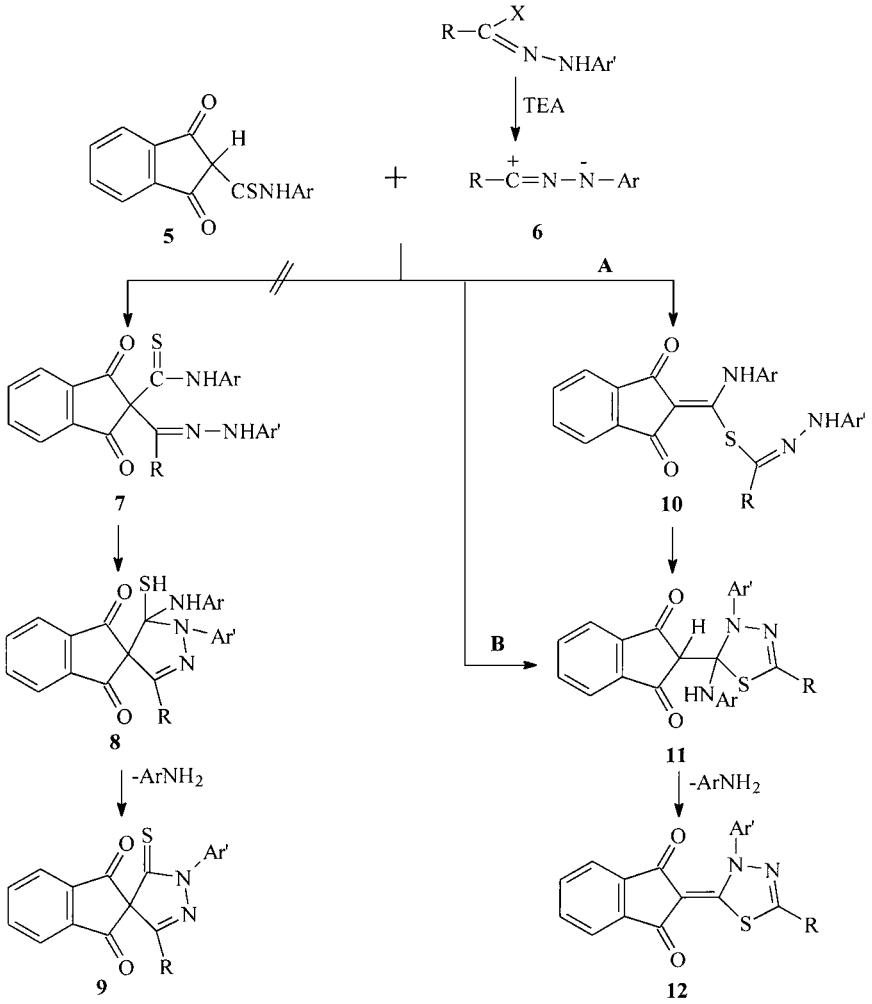
The preparation of the starting thioanilides (**5**) was accomplished by addition of each aryl isothiocyanate (**3**) to a solution of indane-1,3-dione (**4**) in dimethylformamide in the presence of potassium hydroxide at room temperature, followed by acidification with dilute hydrochloric acid. The structures of thioanilides **5a–d** were established on the basis of elemental analysis and spectral data (IR, ^{1}H NMR, MS). For example, the mass spectrum of **5a** showed an intense molecular ion peak at m^+/z 281. The IR spectrum revealed two absorption bands at 1697 and 1664 cm^{-1} assignable to indane-1,3-dione carbonyl groups and a band at 3217 cm^{-1} assignable to an NH group. Its ^{1}H NMR spectrum showed two singlet signals at δ 11.7 and 14.1 assignable to NH and SH protons, respectively, as well as a multiplet signal due to aromatic protons at δ 7.0–7.4.

Moreover, the structures of thioanilides **5** were confirmed by their reactions with hydrazonoyl halides **1** and **2** and with active chloromethylene compounds **15a–d** as described later. The reaction of *N*-phenylbenzohydrazonoyl chloride (**1a**) with indane-1,3-dione-2-thiocarboxanilide (**5a**) in



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

SCHEME 1



	R / Ar
a	C_6H_5/C_6H_5
b	$C_6H_5CH{=}CH/C_6H_5$
c	C_6H_5/4-$NO_2C_6H_4$

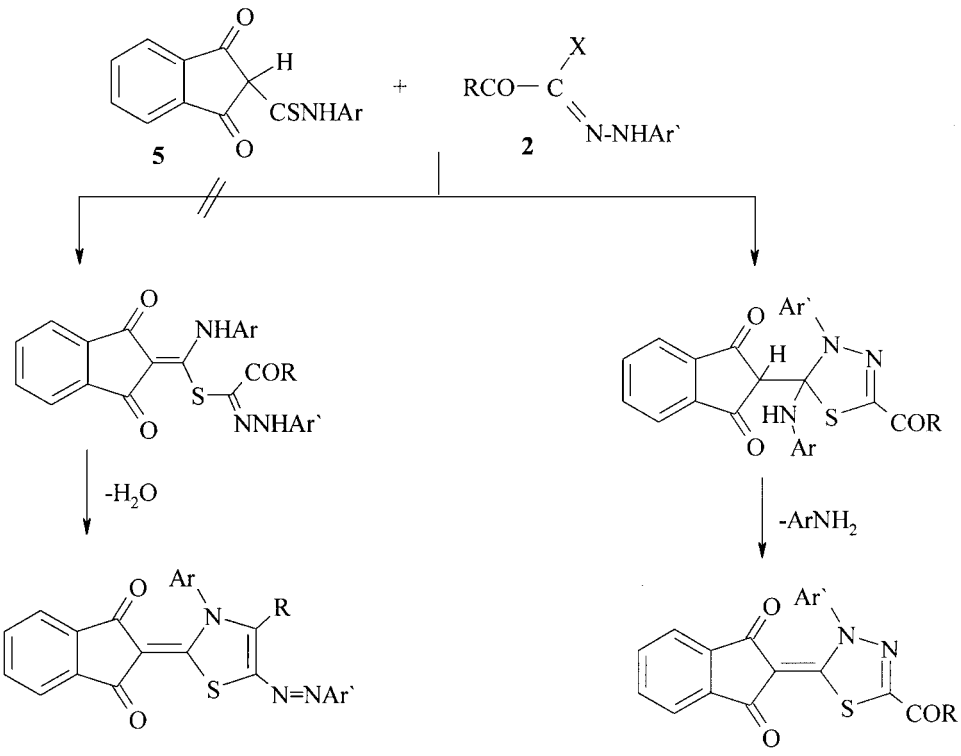
SCHEME 2

chloroform in the presence of triethylamine afforded a product which analyzed correctly for $C_{23}H_{14}N_2O_2S$. Two possible structures can be suggested for this product—**9a** and **12a** (Scheme 2).

Structure **9a** was rejected for the following reasons: (i) the reaction product was recovered unchanged after treatment with mercuric oxide in boiling acetic acid; (ii) the C=S double bond is known to be more reactive as a 1,3-dipolarophile than is the C=C double bond; [7] and (iii) reaction of nitrilimines with β-ketothioanilide in the presence of triethylamine has been reported to yield 2-alkylidene-1,3,4-thiadiazoline derivatives with the elimination of the arylamine moiety [8].

To account for the formation of **12a**, two alternative pathways (route A and route B outlined in Scheme 2) are proposed. In route A it was suggested that the reaction starts with the formation of thiohydrazonate ester (**10**) followed by intramolecular cyclization to give **11** which in turn eliminates arylamine to afford **12**. Alternatively, cycloaddition of nitrilimine (**6**), generated in situ from **1** by the action of triethylamine, to the C=S double bond of **5a** would give **11** directly, which upon elimination of arylamine would lead to **12a**. Similarly, hydrazonoyl halides **1b** and **c** were reacted with 2-thiocarboxanilide (**5**) to give the corresponding 1,3,4-thiadiazoline derivatives **12b** and **c**.

Next, reaction of α-ketohydrazonoyl halides **2** with thioanilide **5** was then studied to investigate the effect of the presence of a carbonyl group on the course of the reaction. Compound **5** reacted with α-ketohydrazonoyl halides (**2**) in refluxing chloroform in the presence of triethylamine to give the corresponding thiadiazoline derivatives **14** (Scheme 3). Compound **13** was discarded from consideration on the basis of elemental analysis and



	R / Ar`
a	OC_2H_5/C_6H_5
b	CH_3/C_6H_5
c	C_6H_5/C_6H_5
d	2-thienyl/C_6H_5
e	CH_3/4-ClC_6H_4
f	CH_3/4-$NO_2C_6H_4$

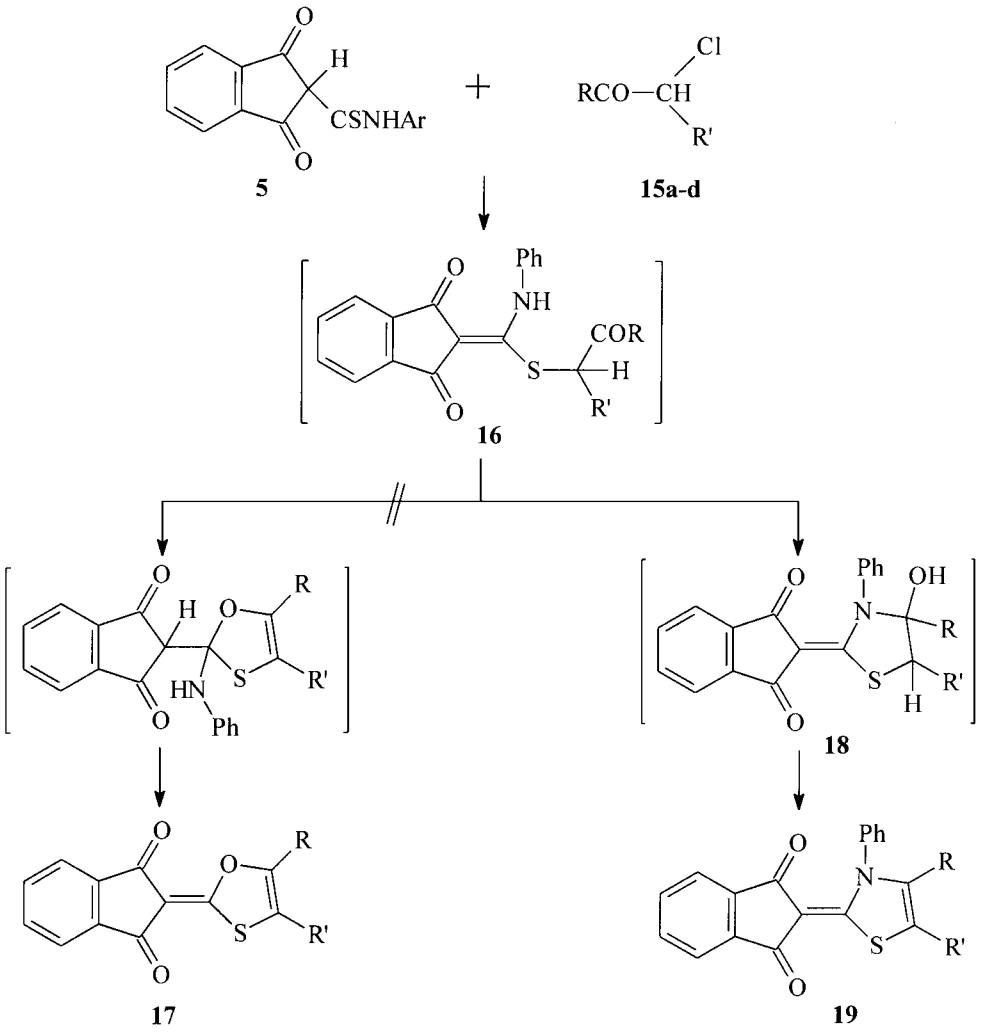
	R / Ar`
g	OC_2H_5/4-ClC_6H_4
h	OC_2H_5/4-$CH_3C_6H_4$
i	C_6H_5/4-ClC_6H_4
j	C_6H_5/4-$CH_3C_6H_4$
k	2-thienyl/4-$CH_3C_6H_4$

SCHEME 3

spectral data. For example, the IR spectra of the product **13** would reveal only two carbonyl absorption bands of indane-1,3-dione and the absence of the carbonyl absorption band of the aryl group; such a band is present in the spectrum of each product **14**.

The structures of **12** and **14** were confirmed on the basis of elemental analyses and spectral data (IR,^{1}H NMR, MS). For example, the IR spectrum of compound **14a** showed absorption bands at 1742, 1697, and 1645cm^{-1} corresponding to the (three CO) groups. Its ^{1}H NMR spectrum revealed the signals of a triplet at δ 1.5 (3H), a quartet at δ 4.5 (2H), and a multiplet at δ 7.3–7.6 (9H). The mass spectrum of **14a** showed an intense molecular ion peak at m^+/z 378. The structure of **14a** was further confirmed by an alternative synthesis. Thus, reaction of **3a** with **5b** or **5c** or **5d** gave a product identical in all respects (mp., mmp., IR, ^{1}H NMR, MS) with **14a** (Scheme 3).

In the course of our study of the reaction of indane-1,3-dione-2-thiocarbox-anilides (**5**) with hydrazonoyl halides **1** and **2**, it was found that the reactions proceed via elimination of an arylamine to give **12** and **14**, respectively. This finding influenced us to investigate the reaction of **5** with active chloromethylene compounds **15a–d** to see if such reactions will lead to thiazolines and/or 1,3-oxathioles. Previous literature reports indicated that reactions of α-halo derivatives of simple ketones and



	R / R`		R / R`
a	$CH_3/CONHC_6H_5$	**c**	$CH_3/COOC_2H_5$
b	C_6H_5/COC_6H_5	**d**	C_6H_5/H

SCHEME 4

esters with potassium salts of acyclic thioamides [2,3,9] afforded the thiazolines and/or 1,3-oxathioles [10].

Treatment of **5a** with **15a–d** in dimethylformamide afforded a single product, in each case, as evidenced by TLC and ^{1}H NMR spectral analyses of the crude products. Both elemental analyses and spectral data were found compatible with 2,3-dihydro-3-phenylthiazole derivatives **19** but not with 1,3-oxathiole-2-ylidene derivative **17**. To account for the formation of **19**, we suggest the mechanism outlined in Scheme 4. The reaction is initiated by a nucleophilic addition of the sulfur atom of **5** to the carbonyl group of **15** to give the ketene *N*,*S*-acetal (**16**). Then, **16** undergoes cyclization to yield the intermediate **18** which then eliminates a water molecule to afford **19** (Scheme 4). The elemental analyses and spectral data (IR, ^{1}H

TABLE 1 Characterization Data of the Newly Synthesized Compounds

				% Analysis		Calculated/Found	
Comp. No.	*m. p. (°C)*	*Yield (%)*	*Mol. Formula [Mol. Wt.]*	*C*	*H*	*N*	*S*
5a[a]	135	78	$C_{16}H_{11}NO_2S$[281]	68.3	3.9	5.0	11.4
				68.2	3.8	4.9	11.4
5b[a]	151	70	$C_{17}H_{13}NO_2S$[295]	69.2	4.4	4.7	10.8
				70.1	4.5	4.8	10.8
5c[a]	182	69	$C_{16}H_{10}NClO_2S$[315.5]	60.9	3.2	4.4	10.1
				61.0	3.3	4.5	10.1
5d[a]	186	75	$C_{16}H_{10}NbrO_2S$[360]	53.3	2.8	3.9	8.9
				53.2	3.1	3.8	8.8
12a[a]	310	80	$C_{23}H_{14}N_2O_2S$[382]	72.2	3.7	7.3	8.4
				72.3	3.9	7.1	8.2
12b[b]	250	78	$C_{25}H_{16}N_2O_2S$[408]	73.5	3.9	6.9	7.8
				73.4	4.1	6.8	7.9
12c[b]	300	76	$C_{23}H_{13}N_3O_4S$[427]	64.6	3.1	9.8	7.5
				64.7	3.1	9.7	7.3
14a[a]	262	80	$C_{20}H_{14}N_2O_4S$[378]	63.4	3.7	7.4	8.5
				63.4	3.6	7.2	8.3
14b[b]	300	75	$C_{19}H_{12}N_2O_3S$[348]	65.5	3.5	8.0	9.2
				65.7	3.2	7.9	9.5
14c[a]	234	74	$C_{24}H_{14}N_2O_3S$[410]	70.2	3.4	6.8	7.8
				70.5	3.2	6.5	7.6
14d[a]	210	76	$C_{22}H_{12}N_2O_3S_2$[416]	63.4	2.9	6.7	15.4
				63.3	2.8	6.4	15.1
14e[a]	267	75	$C_{19}H_{11}N_2ClO_3S$[382.5]	59.6	2.9	7.3	8.4
				60.0	2.9	7.6	8.7
14f[a]	255	75	$C_{19}H_{11}N_3O_5S$[393]	58.0	2.8	10.7	8.2
				58.1	2.9	10.6	8.1
14g[a]	236	80	$C_{20}H_{13}N_2ClO_4S$[412.5]	58.2	3.2	6.8	7.8
				58.3	3.3	6.5	7.5
14h[a]	243	80	$C_{21}H_{16}N_2O_4S$[392]	64.3	4.1	7.1	8.2
				64.4	4.0	7.4	8.5
14i[b]	308	74	$C_{24}H_{13}N_2ClO_3S$[444.5]	64.8	2.9	6.3	7.2
				64.7	2.8	6.1	7.2
14j[a]	305	74	$C_{25}H_{16}N_2O_3S$[424]	70.7	3.8	6.6	7.6
				70.6	3.9	6.6	7.4
14k[b]	320	76	$C_{23}H_{14}N_2O_3S_2$[430]	64.2	3.3	6.5	14.9
				64.1	3.2	6.2	14.6
19a[b]	280	70	$C_{26}H_{18}N_2O_3S$[438]	71.2	4.1	6.4	7.3
				71.3	4.4	6.4	7.4
19b[b]	227	76	$C_{31}H_{19}NO_3S$[485]	76.7	3.9	2.9	6.6
				76.6	3.8	2.8	6.5
19c[a]	299	74	$C_{22}H_{17}NO_4S$[391]	67.5	4.3	3.6	8.2
				67.4	4.2	3.7	8.3
19d[b]	270	65	$C_{24}H_{15}NO_2S$[381]	75.6	4.0	3.7	8.4
				75.8	3.8	3.6	8.3

[a]AcOH is the solvent used for the synthesis of these compounds.
[b]DMF is the solvent used for the synthesis of these compounds.

NMR, MS) of all compounds are in agreement with the suggested structure **19**. For example, the IR spectrum of compound **19c** revealed three absorption bands at 1718, 1690, and 1636 cm^{-1} assignable to ester carbonyl and indane-1,3-dione carbonyl groups, respectively. Its ^1H NMR spectrum showed typical ethyl pattern signals, a triplet at δ1.4 and a quartet at δ 4.4. Also, it showed a singlet signal at δ 2.3 (3H) in addition to a multiplet signal at δ 7.1–7.7 (9H) assignable to methyl and aromatic protons, respectively. An intense molecular ion peak at m^+/z 391 characterized the mass spectrum of **19c**.

EXPERIMENTAL

Melting points were determined on a Gallenkamp electrothermal apparatus and are uncorrected. Infrared spectra (KBr) were recorded on a Pye Unican SP-300 IR spectrophotometer and Testscan Shimadzu FT-IR 8000 series. The ^1H NMR spectra in $CDCl_3$ were recorded on Varian Gemini 200 and Varian EM 390 spectrometers with TMS as the internal standard. Mass spectra were recorded on a GCMS-QP 1000-EX Shimadzu, Japan instrument. Elemental analyses were carried out at the Microanalytical Center, University of Cairo, Giza, Egypt. Hydrazonoyl halides **1,2** [11–18] and **15b** [19] were prepared as previously reported.

Indane-1,3-dione-2-thiocarboxanilides **5a–d**

General Procedure. To a stirred suspension of potassium hydroxide (0.28 g, 5 mmoles) in dimethylformamide (20 ml), indane-1,3-dione (**4**) (0.73 g, 5 mmoles) was added. To the resulting solution, the appropriate aryl isothiocyanate (**3**) (5 mmoles) was added and the reaction mixture was stirred for 24 h at room temperature. The solution was acidified with dilute hydrochloric acid (30 ml, 10%). The solid that formed was collected, washed with water, and crystallized from a suitable solvent to give the corresponding thioanilides **5a–d** (Tables 1 and 2).

2,3-Dihydro-1,3,4-thiadiazoles **12a–c**

Method A. Equimolecular quantities of thioanilides **5**, hydrazonoyl halides **1** and triethylamine (5 mmoles each) were dissolved in chloroform (30 ml). The reaction mixture was refluxed for 6 h. The excess solvent was evaporated under reduced pressure, and the residue was treated with methanol

TABLE 2 Spectral Data of the Newly Synthesized Compounds

Comp. No.	ν_{max} *(cm^{-1})*	δ_H *(ppm)*	*m/z*
5a	3217 (NH), 1697 (CO), 1664 (CO)	7.0–7.4 (m, 9H, Ar-H), 11.7 (s, 1H, NH), 14.1 (s, 1H, SH)	281
5b	3239 (NH), 1680 (CO), 1660 (CO)	2.4 (s, 3H, CH_3), 7.2–7.6 (m, 8H, Ar-H), 11.7 (s, 1H, NH), 14.1 (s, 1H, SH)	295
5c	3242 (NH), 1705 (CO), 1678 (CO)	7.0–7.6 (m, 8H, Ar-H), 11.8 (s, 1H, NH), 14.2 (s, 1H, SH)	315
5d	3243(NH), 1705 (CO), 1678 (CO)	7.1–7.8 (m, 8H, Ar-H), 11.6 (s, 1H, NH), 14.0 (s, 1H, SH)	360
12a	1688 (CO), 1641 (CO)		382
12b	1695 (CO), 1649 (CO)	7.2–7.7 (m, Ar-H)	408
12c	1687(CO), 1647 (CO)	7.3–8.5 (m, Ar-H)	427
14a	1742 (CO), 1697 (CO), 1645 (CO)	1.5 (t, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.3–7.6 (m, 9H, Ar-H)	378
14b	1697 (CO), 1645 (CO)	2.6 (s, 3H, CH_3), 7.7–7.9 (m, 9H, Ar-H)	348
14c	1697 (CO), 1647 (CO), 1628 (CO)	7.3–8.4 (m, Ar-H)	410
14d	1699 (CO), 1645 (CO), 1624 (CO)	7.3–8.5 (m, Ar-H)	416
14e	1701 (CO), 1644 (CO)	2.7 (s, 3H, CH_3), 7.2–7.7 (m, 8H, Ar-H)	382
14f	1688 (CO), 1641 (CO)		393
14g	1739 (CO), 1700 (CO), 1645 (CO)	1.4 (t, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.3–7.8 (m, 8H, Ar-H)	412
14h	1739 (CO), 1696 (CO), 1645 (CO)	1.4 (t, 3H, CH_3), 2.5 (s, 3H, CH_3), 4.5 (q, 2H, CH_2), 7.0–7.8 (m, 8H, Ar-H)	392
14i	1697 (CO), 1631 (CO)		444
14j	1696 (CO), 1647 (CO)	2.5 (s, 3H, CH_3), 7.1–8.4 (m, 13H, Ar-H)	424
14k	1698 (CO), 1646 (CO)	2.6 (s, 3H, CH_3), 7.2–8.4 (m, 11H, Ar-H)	430
19a	3308 (NH), 1684(CO), 1670, 1628 (CO)	2.1 (s, 3H, CH_3), 7.1–7.7 (m, 14H, Ar-H), 8.3 (s, 1H)	438
19b	1712 (CO), 1672(CO), 1663 (CO)	7.2–7.8 (m, Ar-H)	485
19c	1718 (CO), 1690(CO), 1636 (CO)	1.4 (t, 3H, CH_3), 2.3 (s, 3H, CH_3), 4.4 (q, 2H, CH_2), 7.1–7.7 (m, 9H, Ar-H)	391
19d	1677 (CO), 1630 (CO)		381

(10 ml). The solid that formed was collected, washed with water, and finally crystallized from a suitable solvent to give the corresponding 1,3,4-thiadiazoles (**12a–c**).

Method B. Equimolecular quantities of potassium hydroxide in dimethylformamide (20 ml), thioanilides (5 mmoles), and hydrazonoyl halides (5 mmoles) were stirred for 30 min, then left at room temperature for 24 h. The reaction mixture was treated with ethanol (10 ml), and the solid that formed was collected, washed with water, and crystallized from a suitable solvent to give **12a–c** (Tables 1 and 2).

*2,3-Dihydro-1,3,4-thiadiazole (**14a–k**)*

These compounds were prepared by the same procedures (method A and B) described for the preparation of **12** using hydrazonoyl halides of type **2** in place of **1** (Tables 1 and 2).

*4,5-Diaryl-2,3-dihydro-1,3-thiazole derivatives (**19a–d**)*

Equimolecular quantities of a thioanilide **5a** and an active chloromethylene compound **15a–d** (5 mmoles each) were dissolved in ethanol (50 ml). The reaction mixture was refluxed for 3 h. The solvent was evaporated and the solid that formed was collected, washed with water, and finally crystallized from a suitable solvent to give the corresponding 1,3-thiazole derivatives **19a–d** (Tables 1 and 2).

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