Monatshefte für Chemie 127, 557–568 (1996)

Monatshefte für Chemie
Chemical Monthly

A Convenient Synthesis of Polyfunctionally Substituted 2-(Aroyl-(arylsulfonyl)-methylene)-2,3-dihydrothiazoles and -thiazolidin-4-ones and their Fused Derivatives

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Summary. The reaction of phenyl isothiocyanate with arylsulfonylacetophenones **1a–d** in alkaline medium afforded the non-isolable intermediates **2a–d**. Upon reaction with some bromo compounds, the latter underwent *in situ* heterocyclization to afford the corresponding polyfunctionally substituted 2-(aroyl-(arylsulfonyl)-methylene)-2,3-dihydrothiazoles and -thiazolidin-4-ones. The structures of the newly synthesized compounds were assigned and confirmed on the basis of their elemental analyses, spectroscopic data, and alternative syntheses whenever possible.

Keywords. 2,3-Dihydrothiazoles; Thiazolidin-4-ones; Thiazolo[4,5-*d*]pyrimidines; Pyrano[2,3-*d*]-thiazoles.

Eine einfache Synthese von polyfunktionell substituierten 2-(Aroyl-(arylsulfonyl)-methylen)-2,3-dihydrothiazolen und -thiazolidin-4-onen und ihrer kondensierten Derivate

Zusammenfassung. Die Reaktion von Phenylisothiocyanat mit den Arylsulfonylacetophenonen **1a–d** in alkalischem Medium führt zu den nicht isolierbaren Zwischenprodukten **2a–d**. Diese cyclisieren mit einigen Bromverbindungen *in situ* zu den entsprechenden polyfunktionell substituierten 2-(Aroyl-(arylsulfonyl)-methylen-2,3-dihydrothiazolen und -thiazolidin-4-onen. Die Strukturen der neuen Verbindungen wurden aufgrund ihrer Elementaranalysen und ihrer spektroskopischen Daten aufgeklärt und, wenn möglich, durch alternative Synthesen bestätigt.

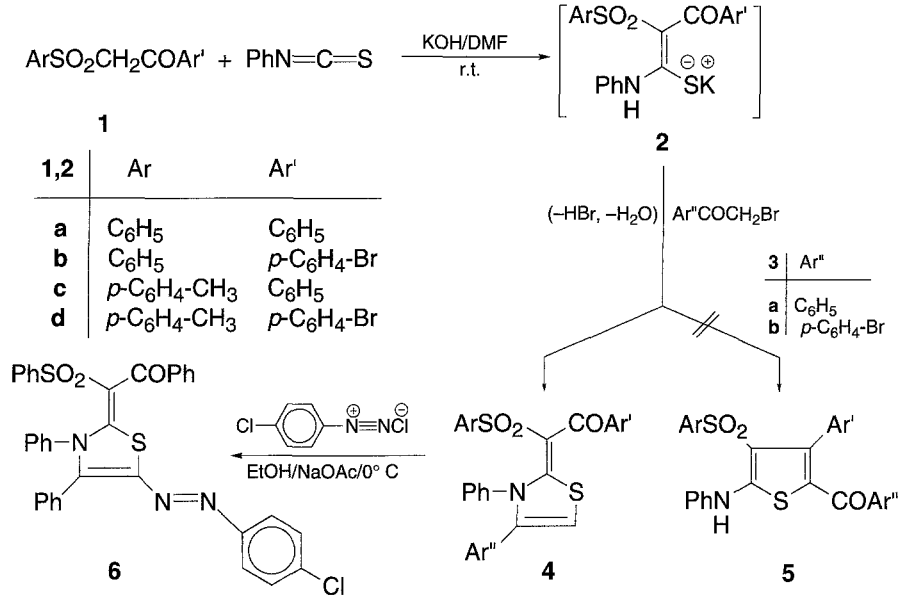
Introduction

Hantzsch and *Weber* [1] have reported that a great variety of reactants bearing the N=C=S fragment undergo *in situ* heterocyclization upon reaction with some α-halocarbonyl compounds [2, 3]. This synthetic route proved to be an easy, facile, and sole approach for the synthesis of hitherto unreported derivatives of polyfunctionally substituted thiophenes [4], 2,3-dihydrothiazoles, and thiazolidines [5, 6]. As an extension of our previous work, we wish to report the reaction of phenyl isothiocyanate with arylsulfonylacetophenones, followed by heterocyclization of the resulting adducts with some α-halo compounds. The work has resulted in the formation of several new polyfunctionally substituted 2-(aroyl-(arylsulfonyl)-

methylene)-2,3-dihydrothiazoles and -thiazolidines which proved to be convenient candidates for the annelation to fused heterocyclic ring systems of an expected wide spectrum of biological activities [7–9].

Results and Discussion

The base-promoted nucleophilic addition of the acidic arylsulfonylacetophenones **1a–d** to equimolar amounts of phenyl isothiocyanate in dry *DMF* at room temperature afforded the non-isolable potassium sulfide salts **2a–d**. Upon treatment with the appropriate substituted phenacyl bromides **3a, b**, the latter underwent *in situ* heterocyclization to yield products that could be formulated as the thiazole **4** and not its isomeric thiophene **5** on the basis of their elemental microanalyses and their spectroscopic data. Thus, the ^{1}H NMR spectrum (*DMSO*-d_6) of **4a**, as an example, revealed the presence of a singlet at $\delta = 6.65$ ppm characteristic for the 2,3-dihydrothiazole H-5 together with the expected multiplet signal attributed to the aromatic protons. Coupling of **4a** with equimolar amounts of *p*-chlorobenzenediazonium chloride in EtOH/AcONa solution at 0–5 °C afforded the corresponding 5-(4-chlorophenylazo)-2,3-dihydrothiazole derivative **6** in reasonable yield (Scheme 1). To our knowledge, formation of 5-arylazothiazole derivatives is rarely reported in the literature [10, 11].

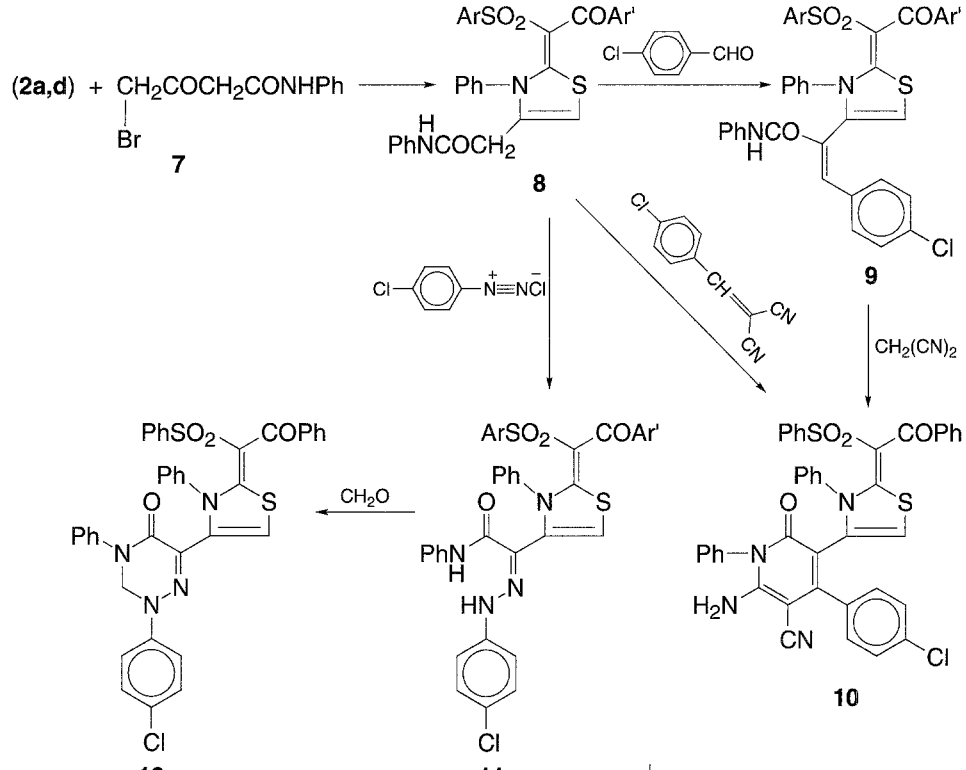


1,2	Ar	Ar'
a	C_6H_5	C_6H_5
b	C_6H_5	*p*-C_6H_4-Br
c	*p*-C_6H_4-CH_3	C_6H_5
d	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br

4	Ar	Ar'	Ar''
a	C_6H_5	C_6H_5	C_6H_5
b	C_6H_5	*p*-C_6H_4-Br	C_6H_5
c	C_6H_5	*p*-C_6H_4-Br	*p*-C_6H_4-Br
d	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br	*p*-C_6H_4-Br

Scheme 1

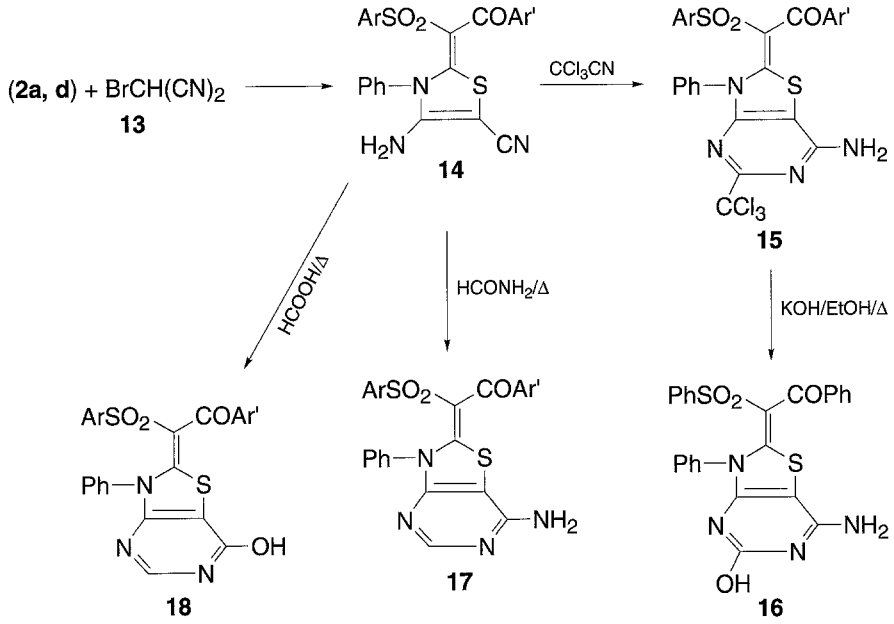
Subsequent treatment of the intermediate salts **2a, d** with γ-bromoacetoacetanilide (**7**) [12] yielded exclusively the corresponding 2,3-dihydrothiazole derivatives **8a, b**. The identity of the product was established in each case on the basis of analytical and spectroscopic data as well as by investigation of its chemical behaviour. Thus, condensation of **8a, b** with equimolar proportions of *p*-chlorobenzaldehyde in refluxing glacial AcOH/AcONa solution afforded the corresponding 6-amino-4-(4-chlorobenzalacetanilido-α-yl)-2,3-dihydrothiazole derivatives **9a, b**. (Scheme 2). Compound **9a** could be cyclized to the corresponding 4-(4-chlorophenyl)-1,2-dihydro-3-(2′,3′-dihydro-3′-phenyl-1′,3′-thiazol-4′-yl)-2-oxo-pyridine-5-carbonitrile derivative **10** upon refluxing with malononitrile and a trace of piperidine in ethanolic solution. Formation of **10** was assumed to proceed *via* anticipated *Michael* addition of malononitrile to the benzylidene moiety of **9**, intramolecular cyclization, and autoxidation. Similar autoxidations have been reported previously [13, 14]. Alternatively, compound **8a** reacted with an equimolar amount of *p*-chlorobenzylidenemalononitrile to afford a single product which was found to be identical in all aspects (m.p., mixed m.p., and IR spectrum) with **10**. Coupling of **8a, b** with equimolar amounts of *p*-chlorobenzenediazonium chloride in EtOH/AcONa at 0–5 °C afforded the corresponding 4-(4-chlorophenylhydrazonoacetanilido-α-yl)-



Scheme 2

2,3-dihydrothiazole derivatives **11a, b** (Scheme 2). The isomeric 5-(4-chlorophenylhydrazono)-2,3-dihydrothiazole coupling products were excluded by spectroscopic data. Thus, the ^{1}H NMR spectrum *(DMSO*-d_6) of **11a**, as an example, revealed the presence of thiazole H-5 at $\delta = 6.53$ ppm. Refluxing compound **10a** with ethanolic formaldehyde solution resulted in cyclization to the corresponding 1,2,4-triazine derivative **12**, a synthetic route well documented for the preparation of *as*-triazine ring systems [15].

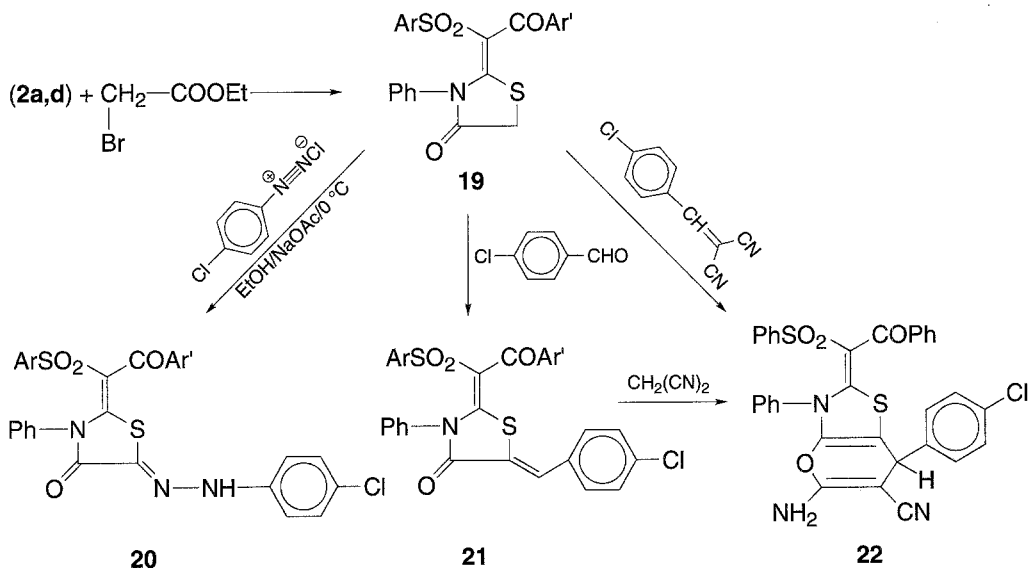
Cyclization of the intermediate salts **2a, d** with equimolar amounts of bromomalononitrile (**13**) afforded the corresponding 4-amino-2,3-dihydro-1,3-thiazole-5-carbonitrile derivatives **14a, b**. The *β*-enaminonitrile moiety in **14** proved to be highly reactive towards a variety of chemical reagents. Thus, compounds **14a, b** reacted with equimolar amounts of trichloroacetonitrile in dioxane/Et_3N to yield 1:1 adducts to which the thiazolo[4,5-*d*]pyrimidine structure **15** was assigned. The trichloromethyl moiety in **15** was readily attacked by nucleophilic reagents. Thus, compound **15a**, upon refluxing in EtOH/KOH, afforded the corresponding 5-hydroxythiazolo[4,5-*d*]pyrimidine derivative **16**. A similar observation has been reported previously [16, 17]. Compounds **14a, b** reacted with formamide in the presence of formic acid and dimethylformamide to yield the corresponding 7-aminothiazolo[4,5-*d*]pyrimidines **17a, b**, respectively. Similarly, prolonged heating of compounds **14a, b** with formic acid afforded the 7-hydroxythiazolo[4,5-*d*]pyrimidines **18a, b** (Scheme 3).



14, 15 / 17, 18	Ar	Ar'
a	C_6H_5	C_6H_5
b	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br

Scheme 3

When the intermediate salts **2a, d** were treated with an equimolar amount of ethyl bromoacetate, the corresponding thiazolidin-4-ones **19a, b** were exclusively isolated in good yields *via* a similar procedure. Compounds **19a, b** coupled with equimolar amounts of *p*-chlorobenzenediazonium chloride in EtOH in the presence of AcONa ($pH = 8$) at 0–5 °C to afford the corresponding 5-(4-chlorophenylhydrazono)-thiazolidin-4-one derivatives **20a, b**. As expected, compounds **19a, b** condensed with equimolar amounts of *p*-chlorobenzaldehyde in EtOH in the presence of a catalytic amount of piperidine to the corresponding 5-(4-chlorobenzal)-1,3-thiazolidin-4-one derivatives **21a, b** (Scheme 4). The reaction of **21a** with equimolar amounts of malononitrile in refluxing EtOH/Et_3N furnished a 1:1 adduct of molecular formula $C_{33}H_{22}ClN_3O_4S_2$ ($m/z = 624$, 34%). The pyrano[2,3-*d*]thiazole structure **22** was assigned to this product based on its spectroscopic data. Alternatively, the reaction of **19a** with *p*-chlorobenzylidenemalonitrile in refluxing pyridine furnished a single product identical in all aspects (m.p., mixed m.p., and IR spectrum) with **22**.



19–21	Ar	Ar'
a	C_6H_5	C_6H_5
b	*p*-C_6H_4-CH_3	*p*-C_6H_4-Br

Scheme 4

Experimental

Melting points are uncorrected; IR spectra (KBr): Pye Unicam SP-1000, cm^{-1}; ^1H NMR spectra (*DMSO*-d_6): Varian Gemini 200 MHz spectrometer, *TMS* as internal standard, chemical shifts in

δ (ppm); mass spectra: AEI MS 30 mass spectrometer operating at 70 eV; microanalytical data: Microanalytical Data Unit at Cairo University.

2-(Aroyl-(arylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-1,3-thiazoles (**4a–d**, **8a, b**, **14a, b**, and **19a, b**); *general procedure*

To a cooled suspension of finely grounded KOH (0.57 g, 0.01 mol) in dry *DMF* (40 ml), the appropriate arylsulfonylacetophenone **1a–d** and subsequently phenyl isothiocyanate (1.3 g, 0.01 mol) were added. The reaction mixture was stirred overnight at room temperature, then treated with the appropriate bromo compound (0.01 mol), and left at room temperature for an additional 24 h. The reaction mixture was then triturated with cold H_2O (50 ml) and neutralized with dilute HCl ($pH = 7$). The resulting precipitated solid was collected by filtration, washed with water, dried, and crystallized from an appropriate solvent.

2-(Benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3,4-diphenyl-1,3-thiazole (**4a**)

Yield: 3.1 g (64%); m.p.: 305 °C (dilute dioxane); $C_{29}H_{21}NO_3S_2$ (495.60); calc.: C 70.28, H 4.27, N 2.82, S 12.93; found: C 70.0, H 4.1, N 2.7, S 12.7; IR: 1709 (C=O); ^{1}H NMR: 6.65 (s, 1H, thiazole H-5), 6.93–7.63 (m, 20H, arom. protons); MS: m/z (%) = 495 (M^+, 22%).

2-(4-Bromobenzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3,4-diphenyl-1,3-thiazole (**4b**)

Yield: 3.9 g (69%); m.p.: 288 °C (dilute *DMF*); $C_{29}H_{20}BrNO_3S_2$ (574.50); calc.: C 60.62, H 3.50, Br 13.90, N 2.43, S 11.16; found: C 60.5, H 3.5, Br 13.9, N 2.4, S 11.0; IR: 1695 (C=O); ^{1}H NMR: 6.51 (s, 1H, thiazole H-5), 6.99–7.69 (m, 19H, arom. protons).

2-(4-Bromobenzoyl-(phenylsulfonyl)-methylene)-4-(4-bromophenyl)-2,3-dihydro-3-phenyl-1,3-thiazole (**4c**)

Yield: 4.0 (62%); m.p.: 293 °C (dioxane); $C_{29}H_{19}Br_2NO_3S_2$ (653.39); calc.: C 53.30, H 2.93, Br 24.45, N 2.14, S 9.81; found: C 53.0, H 3.0, Br 24.4; N 2.0, S 9.7; IR: 1700 (C=O); ^{1}H NMR: 6.60 (s, 1H,thiazole H-5), 7.01–7.61 (m, 18H, arom. protons).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-4-(4-bromophenyl)-2,3-dihydro-3-phenyl-1,3-thiazole (**4d**)

Yield: 4.0 g (60%); m.p.: 279 °C (dilute *DMF*); $C_{30}H_{21}Br_2NO_3S_2$ (667.42); calc.: C 53.98, H 3.17, Br 23.94, N 2.09, S 9.60; found: C 53.9, H 3.0, Br 23.9, N 2.0, S 9.6; IR: 1695 (C=O).

α-(2-(Benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-1,3-thiazol-4-yl)-acetanilide (**8a**)

Yield: 3.4 g (62%); m.p.: 299 °C (dilute *DMF*); $C_{31}H_{24}N_2O_4S_2$ (552.67); calc.: C 67.37, H 4.37, N 5.06, S 11.60; found: C 67.3, H 4.1, N 5.0, S 11.4; IR: 3450–3300 (NH), 1680, 1669 (2 CO); ^{1}H NMR: 3.81 (s, 2H, CH_2), 6.32 (s, 1H, thiazole H-5), 6.83–7.85 (m, 20H, arom. protons), 9.33 (s, 1H, NH, D_2O-exchangeable); MS: m/z (%) = 552 (M^+, 32%).

α-(2-4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-1,3-thiazol-4-yl)-acetanilide (**8b**)

Yield: 3.5 g (55%); m.p.: 315 °C (*DMF*); $C_{32}H_{25}BrN_2O_4S_2$ (645.59); calc.: C 59.53, H 3.90, Br 12.37, N 4.33, S 9.93; found: C 59.5, H 3.7, Br 12.2, N 4.1, S 9.8; IR: 3445–3309 (NH), 1688, 1665 (2 CO);

^{1}H NMR: 1.9 (s, 3H, CH_3), 3.79 (s, 2H, CH_2), 6.45 (s, 1H, thiazole H-5), 6.89–7.55 (m, 18H, arom. protons.), 9.91 (s, 1H, NH, D_2O-exchangeable).

4-Amino-2-(benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-1,3-thiazole-5-carbonitrile (**14a**)

Yield: 2.8 g (61%); m.p.: 285 °C (dilute dioxane); $C_{24}H_{17}N_3O_3S_2$ (459.54); calc.: C 62.72, H 3.72, N 9.14, S 13.95; found: C 62.7; H 3.5, N 9.0, S 13.9; IR: 3450–3300 (NH_2), 2208 (CN), 1690 (C=O); ^{1}H NMR: 6.91–7.82 (m, 15H, arom. protons), 8.51 (s, 2H, NH_2, D_2O-exchangeable); MS: m/z (%) = 459 (M^+, 28%).

4-Amino-2-(4-bromobenzoyl-(p-tolylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-1,3-thiazole-5-carbonitrile (**14b**)

Yield: 3.0 g (55%); m.p.: 294 °C; $C_{25}H_{18}BrN_3O_3S_2$ (552.47); calc.: C 54.35, H 3.28, Br 14.46, N 7.60, S 11.60; found: C 54.2, H 3.0, Br 14.4, N 7.5, S 11.6; IR: 3445–3311 (NH_2), 2210 (CN), 1693 (C=O); ^{1}H NMR: 2.11 (s, 3H, CH_3), 6.93–7.66 (m, 13H, arom. protons), 7.99 (s, 2H, NH_2, D_2O-exchangeable).

2-(Benzoyl-(phenylsulfonyl)-methylene)-3-phenyl-1,3-thiazolidin-4-one (**19a**)

Yield: 2.7 g (63%); m.p.: 276 °C (dilute *DMF*); $C_{23}H_{17}NO_4S_2$ (435.52); calc.: C 63.43, H 3.93, N 3.21, S 14.72; found: C 63.4, H 3.9, N 3.0, S 14.7; IR: 1740, 1690 (2 CO); ^{1}H NMR: 3.21 (s, 2H, CH_2), 7.01–7.58 (m, 15H, arom. protons); MS: m/z (%) = 435 (M^+, 27%).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-3-phenyl-1,3-thiazolidin-4-one (**19b**)

Yield: 3.1 g (59%); m.p.: 281 °C (dilute *DMF*); $C_{24}H_{18}BrNO_4S_2$ (528.44); calc.: C 54.54, H 3.43, Br 15.12, N 2.65, S 12.13; found: C 54.4, H 3.3, Br 15.0, N 2.6, S 12.0; IR: 1742, 1688 (2 CO); ^{1}H NMR: 2.11 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 6.95–7.51 (m, 13H, arom. protons).

2-(Benzoyl-(phenylsulfonyl)-methylene)-5-(4-chlorophenylazo)-2,3-dihydro-3,4-diphenyl-1,3-thiazole (**6**)

To a stirred solution of **4a** (0.005 mol) in EtOH (50 ml) containing AcONa (3 g), *p*-chlorobenzenediazonium chloride (prepared by adding $NaNO_2$ (0.005 mol) to *p*-chloroaniline (0.005 mol) in concentrated HCl (2 ml) at 0–5 °C under stirring) was added dropwise while cooling to 0–5 °C and stirring. The reaction mixture was then left at room temperature for 2 h and the solid product formed was collected by filtration and crystallized from dilute dioxane. Yield: 1.8 g (57%); m.p.: 319 °C; $C_{35}H_{24}ClN_3O_3S_2$ (634.17); calc.: C 66.28, H 3.81, Cl 5.59, N 6.62, S 10.11; found: C 66.0, H 3.8, Cl 5.3, N 6.8, S 9.8; IR: 1705 (C=O); ^{1}H NMR: 6.98–7.83 (m, 24H, arom. protons); MS: m/z (%) = 634 (M^+, 21%).

4-(4-Chlorobenzalacetanilido-α-yl)-1,3-thiazole derivatives (**9a, b**); *General procedure*

A mixture of each of **8a, b** (0.002 mol) and *p*-chlorobenzaldehyde (0.002 mol) in glacial AcOH (30 ml) containing anhydrous AcONa (1 g) was heated under reflux for 4 h. The reaction mixture was poured into cold H_2O; the solid product that separated was filtered off and crystallized from an appropriate solvent.

2-(Benzoyl-(phenylsulfonyl)-methylene)-4-(4-chlorobenzalacetanilido-α-yl)-2,3-dihydro-3-phenyl-1,3-thiazole (**9a**)

Yield: 0.8 g (59%); m.p. > 320 °C (dilute *DMF*); $C_{38}H_{27}ClN_2O_4S_2$ (675.22); calc.: C 67.59, H 4.03, Cl 5.25, N 4.14, S 9.49; found: C 67.5; H 3.8, Cl 5.1, N 4.0, S 9.3; IR: 3452–3312 (NH), 1680 (C=O); ^{1}H NMR: 6.52 (s, 1H, thiazole H-5), 6.59 (s, 1H, ylidene CH), 7.02–7.53 (m, 24H, arom. protons), 9.31 (s, 1H, NH, D_2O-exchangeable); MS: m/z (%) = 675 (M^+, 19%).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-4-(4-chlorobenzalacetanilido-α-yl)-2,3-dihydro-3-phenyl-1,3-thiazole (**9b**)

Yield: 0.85 g (55%); m.p. > 320 °C (dilute *DMF*); $C_{39}H_{28}BrClN_2O_4S_2$ (768.14); calc.: C 60.98, H 3.67, Br 10.40, Cl 4.61, N 3.64, S 8.34; found: C 60.8, H 3.5, Br 10.2, Cl 4.4, N 3.5, S 8.3; IR: 3448–3305 (NH), 1684 (C=O); ^{1}H NMR: 2.10 (s, 3H, CH_3), 6.39 (s, 1H, thiazole H-5), 6.71 (s, 1H, ylidene CH), 6.89–7.59 (m, 22H, arom. protons), 9.89 (s, 1H, NH, D_2O-exchangeable).

6-Amino-3-(2'-(benzoyl-(phenylsulfonyl)-methylene)-2',3'-dihydro-3'-phenyl-1',3'-thiazol-4'-yl)-4-(4-chlorophenyl)-1,2-dihydro-2-oxo-1-phenylpyridine-5-carbonitrile (**10**)

Method A. A suspension of **9a** (0.002 mol) was refluxed with malononitrile (0.002 mol) in EtOH (20 ml) catalyzed by 3 drops of piperidine for 2 h. The reaction mixture was poured into H_2O and neutralized with dilute HCl ($pH = 7$). The solid product which precipitated was collected by filtration and crystallized from dioxane. Yield: 0.76 g (52%); m.p. > 320 °C; $C_{41}H_{27}ClN_4O_4S_2$ (739.27); calc.: C 66.61, H 3.68, Cl 4.79, N 7.57, S 8.67; found: C 66.4; H 3.5, Cl 4.6, N 7.57, S 8.5, IR: 3450–3320 (NH_2), 2212 (CN), 1710. 1685 (2 CO); ^{1}H NMR: 6.53 (s, 1H, thiazole H-5), 6.95–7.42 (m, 24H, arom. protons), 9.93 (s, 2H, NH_2, D_2O-exchangeable).

Method B. To a solution of **8a** (0.002 mol) in dioxane (20 ml) containing piperidine (5 drops), *p*-chlorobenzylidenemalononitrile (0.002 mol) was added. The reaction mixture was heated under reflux for 3 h. The solid product precipitating upon dilution with H_2O was collected by filtration and crystallized from dioxane (yield 0.8 g (55%). It was found to be identical (m.p., mixed m.p., and IR spectrum) with an authentic sample prepared according to Method A.

Coupling of **8a, b** *with p-chlorobenzenediazonium chloride; general procedure*

The same experimental procedure described above for the synthesis of **6** has been followed except for using **8a, b** (0.005 mol) instead of **4a**.

2-(Benzoyl-(phenylsulfonyl)-methylene)-4-(4-chlorophenylhydrazonoacetanilido-α-yl)-2,3-dihydro-3-phenyl-1,3-thiazole (**11a**)

Yield: 1.7 g (50%); m.p.: 315 °C (AcOH); $C_{37}H_{27}ClN_4O_4S_2$ (691.22); calc.: C 64.29, H 3.93, Cl 5.12, N 8.10, S 9.27; found: C 64.0, H 3.8, Cl 5.0, N 8.1, S 9.0; IR: 3450–3320 (NH), 1693, 1685 (2 CO); ^{1}H NMR: 6.53 (s, 1H, thiazole H-5), 6.95–7.41 (m, 24H, arom. protons), 8.33 (s, 1H, NH, D_2O-exchangeable), 9.51 (s, 1H, NH, D_2O-exchangeable).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-4-(4-chlorophenylhydrazonoacetanilido-α-yl)-2,3-dihydro-3-phenyl-1,3-thiazole (**11b**)

Yield: 2 g (52%); m.p. > 320 °C (AcOH); $C_{38}H_{28}BrClN_4O_4S_2$ (784.15); calc.: C 58.20, H 3.59, Br 10.18, Cl 4.52, N 7.14, S 8.17; found: C 58.0, H 3.5, Br 10.0, Cl 4.3, N 7.1, S 7.9; IR: 3455–3318 (NH), 1690, 1682 (2 CO).

6-(2'-(Benzoyl-(phenylsulfonyl)-methylene)-2',3'-dihydro-3'-phenyl-1',3'-thiazol-4'-yl-)-2-(4-chlorophenyl)-4-phenyl-2,3,4,5-tetrahydro-1,2,4-triazine-5-one (**12**)

To a suspension of **11a** (0.002 mol) in EtOH (20 ml), formaldehyde solution (4 ml, 40%) was added. The mixture was refluxed for 1 h; the solid product which precipitated on standing at room temperature was filtered off, washed thoroughly with H_2O, and crystallized from dilute *DMF*. Yield: 0.7 g (50%); m.p.: >320 °C; $C_{37}H_{27}ClN_4O_4S_2$ (691.22); calc.: C 64.29, H 3.93, Cl 5.12, N 8.10, S 9.27; found: C 64.0, H 3.9, Cl 5.0, N 8.1, S 9.2; IR: 1715, 1695 (2 CO); ^{1}H NMR: 4.31 (s, 2H, CH_2), 6.51 (s, 1H, thiazole H-5), 6.96–7.49 (m, 24H, arom. protons); MS: *m/z* (%) = 691 (M^+, 16%).

7-Amino-5-trichloromethylthiazolo[4,5-d]pyrimidines (**15a, b**); *general procedure*

A mixture of each of **14a, b** (0.002 mol) and trichloroacetonitrile (0.002 mol) in dioxane (30 ml) containing a catalytic amount of Et_3N (5 drops) was heated under reflux for 5 h and then left overnight at room temperature. The mixture was then poured onto ice/H_2O and neutralized with dilute HCl. The product formed was filtered off, dried, and crystallized from an appropriate solvent.

7-Amino-2-(benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-5-trichloromethylthiazolo-[4,5-d]pyrimidine (**15a**)

Yield: 0.7 g (60%); m.p.: 312 °C; $C_{26}H_{17}Cl_3N_4O_3S_2$ (603.93); calc.: C 51.70, H 2.83, Cl 17.61, N 9.27, S 10.61; found: C 51.6, H 2.8, Cl 17.5, N 9.0, S 10.6; IR: 3445–3307 (NH_2), 1694 (C=O); ^{1}H NMR: 6.88–7.53 (m, 15H, arom. protons), 9.13 (s, 2H, NH_2, D_2O-exchangeable).

7-Amino-2-(4-bromophenyl-(p-tolylsulfonyl)-methylene)-2,3-dihydro-3-phenyl-5-trichloromethylthiazolo[4,5-d]pyrimidine (**15b**)

Yield: 0.8 g (58%); m.p. >320 °C; $C_{27}H_{18}BrCl_3N_4O_3S_2$ (696.85); calc.: C 46.53, H 2.60, Br 11.46, Cl 15.26, N 8.04, S 9.20; found: C 46.5, H 2.4, Br 11.2, Cl 15.0, N 7.7, S 9.1; IR: 3450–3310 (NH_2), 1688 (C=O); ^{1}H NMR: 2.13 (s, 3H, CH_3), 6.81–7.61 (m, 13H, arom. protons), 9.22 (s, 2H, NH_2, D_2O-exchangeable).

7-Amino-2-(benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-5-hydroxy-3-phenylthiazolo[4,5-d]pyrimidine (**16**)

A mixture of **15a** (0.002 mol) and KOH (0.002 mol) in EtOH (30 ml) was heated under reflux for 2 h. The reaction mixture was poured into cold H_2O and neutralized with dilute HCl. The solid product formed was filtered off and crystallized from dilute dioxane. Yield: 0.46 g (46%); m.p.: >320 °C; $C_{25}H_{18}N_4O_4S_2$ (502.57); calc. C 59.74, H 3.60, N 11.14, S 12.76; found C 59.6, H 3.6, N 11.0, S 12.7; IR: 3540–3020 (OH, NH_2), 1695 (C=O); MS: *m/z* (%) = 502 (M^+, 18%).

7-Amino-2-(aroyl-(arylsulfonyl)-methylene)-2,3-dihydro-3-phenylthiazolo[4,5-d]pyrimidines (**17a, b**); *general procedure*

Each of **14a, b** (0.002 mol) was heated under reflux with a ternary mixture of formic acid (5 ml), formamide (5 ml), and dimethylformamide (5 ml) for 10 h. The reaction mixture was then allowed to stand at room temperature overnight. The solid product precipitated was filtered off and crystallized from an appropriate solvent.

7-Amino-2-(benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-3-phenylthiazolo[4,5-d]pyrimidine (**17a**)

Yield: 0.5 g (54%); m.p.: >320 °C; $C_{25}H_{18}N_4O_3S_2$ (486.57); calc.: C 61.71, H 3.72, N 11.51, S 13.18; found: C 61.5, H 3.6, N 11.5, S 13.0; IR: 3455–3311 (NH_2), 1695 (C=O); ^{1}H NMR: 6.31 (s, 1H, pyrimidine

H-2), 7.00–7.71 (m, 15H, arom. protons), 9.13 (s, 2H, NH_2, D_2O-exchangeable); MS: m/z (%) = 486 (M^+, 26%).

7-Amino-2-(4-bromobenzoyl-(p-tolylsulfonyl)-methylene)-2,3-dihydro-3-phenylthiazolo-[4,5-d]pyrimidine (**17b**)

Yield: 0.56 g (49%); m.p.: > 320 °C; $C_{26}H_{19}BrN_4O_3S_2$ (579.49); calc.: C 53.88, H 3.30, Br 13.78, N 9.66, S 11.06; found: C 53.7, H 3.3, Br 13.6, N 9.5, S 11.0; IR: 3450–3312 (NH_2), 1690 (C=O); ^{1}H NMR: 1.99 (s, 3H, CH_3), 6.12 (s, 1H, pyrimidine H-2), 6.95–7.63 (m, 13H, arom. protons), 8.95 (s, 2H, NH_2, D_2O-exchangeable).

2-(Aroyl-(arylsulfonyl)-methylene)-2,3-dihydro-7-hydroxy-3-phenylthiazolo[4,5-d]pyrimidines (**18a, b**)

Each of **14a, b** (0.002 mol) was heated under reflux in formic acid (85%, 10 ml) for 10 h. The solid product formed upon cooling to room temperature was filtered off and crystallized from an appropriate solvent.

2-(Benzoyl-(phenylsulfonyl)-methylene)-2,3-dihydro-7-hydroxy-3-phenylthiazolo[4,5-d]pyrimidine (**18a**)

Yield: 0.5 g (55%); m.p.: > 320 °C; $C_{25}H_{17}N_3O_4S_2$ (487.55); calc.: C 61.58, H 3.51, N 8.61, S 13.15; found: C 61.5, H 3.3, N 8.6, S 13.0; IR: 3612–3430 (OH), 1695 (C=O); ^{1}H NMR: 6.31 (s, 1H, pyrimidine H-2), 6.91–7.51 (m, 15H, arom. protons), 8.93 (s, 1H, OH, D_2O-exchangeable); MS: m/z (%) = 487 (M^+, 23%).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-2,3-dihydro-7-hydroxy-3-phenylthiazolo[4,5-d]-pyrimidine (**18b**)

Yield: 0.6 g (52%); m.p.: > 320 °C; $C_{26}H_{18}BrN_3O_4S_2$ (580.48); calc.: C 53.79, H 3.12, Br 13.76, N 7.23, S 11.04; found: C 53.7, H 3.0, Br 13.6, N 7.1, S 10.9; IR: 3620–3435 (OH), 1690 (C=O); ^{1}H NMR: 2.10 (s, 3H, CH_3), 6.56 (s, 1H, pyrimidine H-2), 7.01–7.63 (m, 13H, arom. protons), 8.33 (s, 1H, OH, D_2O-exchangeable).

Coupling of **19a, b** *with p-chlorobenzenediazonium chloride*

The same experimental procedure described above for the synthesis of **6** has been followed except for using **19a, b** (0.005 mol) instead of **4a**.

2-(Benzoyl-(phenylsulfonyl)-methylene)-5-(4-chlorophenylhydrazono)-3-phenyl-1,3-thiazolidin-4-one (**20a**)

Yield: 1.7 g (61%); m.p.: 288 °C; $C_{29}H_{20}ClN_3O_4S_2$ (574.07); calc.: C 60.67, H 3.51, Cl 6.17, N 7.31, S 11.17; found: C 60.6, H 3.3, Cl 6.0, N 7.3, S 11.1; IR: 3455–3310 (NH), 1695 (C=O); ^{1}H NMR: 6.96–7.53 (m, 19H, arom. protons), 9.93 (s, 1H, NH, D_2O-exchangeable).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-5-(4-chlorophenylhydrazono)-3-phenyl-1,3-thiazolidin-4-one (**20b**)

Yield: 1.8 g (56%); m.p.: 296 °C; $C_{30}H_{21}BrClN_3O_4S_2$ (667.00); calc.: C 54.02, H 3.17, Br 11.97, Cl 5.31, N 6.29, S 9.61; found: C 54.0, H 2.9, Br 11.8, Cl 5.2, N 6.1, S 9.4; IR: 3452–3308 (NH), 1697 (C=O).

2-(Aroyl-(arylsulfonyl)-methylene)-5-(4-chlorobenzal)-3-phenyl-1,3-thiazolidin-4-ones (**21a, b**); *general procedure*

A mixture of each of **19a, b** (0.002 mol) and *p*-chlorobenzaldehyde (0.002 mol) in EtOH (30 ml) containing a catalytic amount of piperidine (3 drops) was refluxed for 3 h. The reaction mixture was then poured into cold H_2O. The solid product formed was filtered off and crystallized from an appropriate solvent.

2-(Benzoyl-(phenylsulfonyl)-methylene)-5-(4-chlorobenzal)-3-phenyl-1,3-thiazolidin-4-one (**21a**)

Yield: 0.65 g (59%); m.p.: >320 °C; $C_{30}H_{20}ClNO_4S_2$ (558.07); calc.: C 64.56, H 3.61, Cl 6.35, N 2.50, S 11.49; found C 64.4, H 3.6, Cl 6.2, N 2.3, S 11.4; IR: 1710, 1693 (2 CO); ^{1}H NMR: 6.71 (s, 1H, ylidene CH), 6.95–7.43 (m, 19H, arom. protons).

2-(4-Bromobenzoyl-(p-tolylsulfonyl)-methylene)-5-(4-chlorobenzal)-3-phenyl-1,3-thiazolidin-4-one (**21b**)

Yield: 0.8 g (62%); m.p. >320 °C; $C_{31}H_{21}BrClNO_4S_2$ (650.99); calc.: C 57.19, H 3.25, Br 12.27, Cl 5.44, N 2.15, S 9.85; found: C 57.0, H 3.1, Br 12.0, Cl 5.3, N 2.0, S 9.8; IR: 1712, 1690 (2 CO); ^{1}H NMR: 2.13 (s, 3H, CH_3), 6.59 (s, 1H, ylidene CH), 6.83–7.49 (m, 17H, arom. protons).

5-Amino-2-(benzoyl-(phenylsulfonyl)-methylene)-7-(4-chlorophenyl)-3-phenyl-2,3,7-trihydropyrano[2,3-d]thiazole-6-carbonitrile (**22**)

Method A. A mixture of **21a** (0.002 mol) and malononitrile (0.002 mol) in EtOH (30 ml) containing a catalytic amount of Et_3N (3 drops) was refluxed for 3 h. The reaction mixture was then poured into H_2O and neutralized with dilute HCl. The solid product formed was filtered off and crystallized from dioxane. Yield: 0.6 g (60%); m.p.: >320 °C; $C_{33}H_{22}ClN_3O_4S_2$ (624.13); calc.: C 63.50, H 3.55, Cl 5.68, N 6.73, S 10.27; found: C 63.4, H 3.3, Cl 5.4, N 6.7, S 10.0; IR: 3452–3320 (NH_2), 2210 (CN), 1695 (C=O); ^{1}H NMR: 6.72 (s, 1H, pyran H-4), 6.91–7.63 (m, 19H, arom. protons), 8.99 (s, 2H, NH_2, D_2O-exchangeable); MS: $m/z = 624$ (M^+, 34%).

Method B. A mixture of **19a** (0.002 mol) and *p*-chlorobenzylidenemalononitrile (0.002 mol) was refluxed in pyridine (30 ml) for 12 h. The reaction mixture was then poured into cold H_2O and neutralized with dilute HCl. The solid product formed was collected by filtration, crystallized from dioxan, and found to be identical in all aspects (m.p., mixed m.p., and IR spectrum) with an authentic sample prepared according to Method A.

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Received November 15, 1995. Accepted November 17, 1995