Synthesis and tautomeric structure of 2-arylazo-4*H*-imidazo[2,1-*b*][1,3,4] thiadiazines

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Two series of the title compounds were prepared *via* reaction of *N*-aryl 2-oxohydrazonoyl halides with 1-amino-4-phenylimidazoline-2-thione. Their tautomeric structure was elucidated by spectral analysis, and the correlation of their acid dissociation constants with the Hammett equation, to be as the hydrazone form.

Keywords: imidazoles, fused imidazoles, 1,3,4-thiadiazines, azo-hydrazone tautomerism, hydrazonoyl halides, thiohydrazonates

Hydrazonoyl halides (**1**) have demonstrated their potential for the synthesis of various types of fused heterocycles. Considerable effort has been made therefore during the past three decades to study their synthesis and reactions.[1-5] Furthermore, a literature search revealed that although several imidazo[2,1-*b*][1,3,4]thiadiazine derivatives have been prepared by the action of α-halocarbonyl compounds upon either 2-amino-1,3,4-thiadiazines[6-8] or 1-amino-2-imidazolinethione derivatives,[7-9] the 2-arylazo derivatives of this fused-ring system have not been reported previously.[5] In continuation of our recent studies on the reactions of hydrazonoyl halides with heterocyclic thiones,[10-17] we now describe a new one-pot method for the preparation of 3-substituted 2-arylazo-7-phenyl-4*H*-imidazo[2,1-*b*][1,3,4]thiadiazines **4**. Our interest in the synthesis of these compounds is owing to the increasing utility of arylazo heterocycles in various sectors of industry including hair dyeing, thermal transfer printing, nonlinear optics, disperse dyes, pigments and ink-jet inks.[18] Furthermore, as compounds **4** can exist in one or more of the three tautomeric forms **I–III** (Fig. 1), it was thought worthwhile to elucidate their actual tautomeric structure. This is a necessary preliminary to an intended exploration of their nonlinear optical properties.

Results and discussion

Treatment of the hydrazonoyl halides **1A** and **1B** with 1-amino-4-phenylimidazole-2-thiol (1-amino-4-phenyl-1,3-dihydro-2*H*-imidazole-2-thione, **2**) in ethanol in the presence of sodium ethoxide at room temperature afforded, in each case, only one isolable material as evidenced by TLC analysis of the crude products. Both microanalysis and spectral data (MS, IR and ^{1}H and ^{13}C NMR) indicated that the isolated products are the respective 3,7-disubstituted 2-arylhydrazono-imidazo[2,1-*b*][1,3,4]thiadiazines **4A** and **4B**, respectively (Scheme 1). This finding indicates that the initially formed thiohydrazonate esters **3A** and **3B** undergo *in situ* dehydrative cyclisation as soon as they are formed to give the respective **4** directly as end products. The involvement of intermediates **3** was evidenced by their isolation in two cases. Thus, reaction of **2** with the hydrazonoyl halides **1Bc** and **1Cd**, respectively, yielded the thiohydrazonates **3Bc** and **3Cd**.

The assigned structures of the thiohydrazonates **3Bc** and **3Cd** were supported by their mass spectra. Characteristic peaks were observed corresponding to the fragments (M^+ – RCOC=NNHAr). This finding supports the thiohydrazonate structure **3**, because the mass spectra of both aryl and heteroaryl thiohydrazonates have been reported to be characterised by elimination of the elements of the corresponding arenethiol and heteroaryl thiol from their molecular ions, respectively.[10] Further evidence in support of structure **3** for the isolated products was provided by the ^{13}C NMR spectra which revealed the presence of a signal near δ 147 attributable to the carbon atom of the S-C=N-NH group.[10] Refluxing the esters **3Bc** and **3Cd** in acetic acid for 24 h resulted in dehydrative cyclisation and the formation of products that proved identical with compounds **4Bc** and **4Cd**, respectively (Scheme 1).

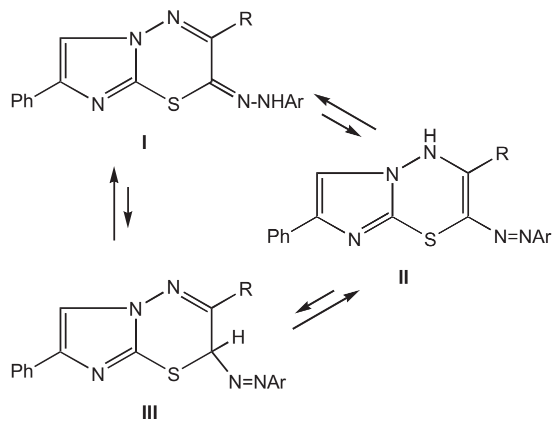
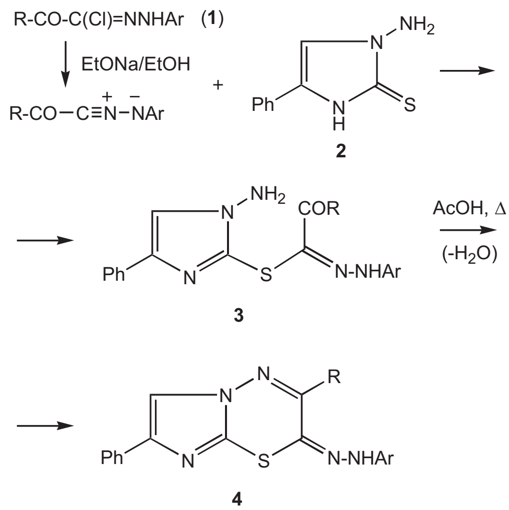


Fig. 1

The assignment of structure **4** for the isolated products was further confirmed by alternative syntheses of **4Ac**, **4Bb** and **4Bc** as typical examples of the two series prepared. Thus, treatment of **2** with phenacyl bromide in ethanol in the presence of triethylamine afforded 3,7-diphenylimidazo[2,1-*b*][1,3,4] thiadiazine (**6**, Scheme 2). Similarly, treatment of **2** with 3-chloro-2,4-pentanedione in ethanolic potassium hydroxide



R = **A**, CH_3; **B**, Ph; **C**, 2-thienyl

Ar = C_6H_4X; X: **a**, 4-OMe; **b**, 4-Me; **c**, H; **d**, 4-Cl, **e**, 3-Cl; **f**, 3-NO_2; **g**, 4-NO_2; **h**, 4-CO_2Et; **i**, 4-$COCH_3$; **j**, 4-CN

Scheme 1

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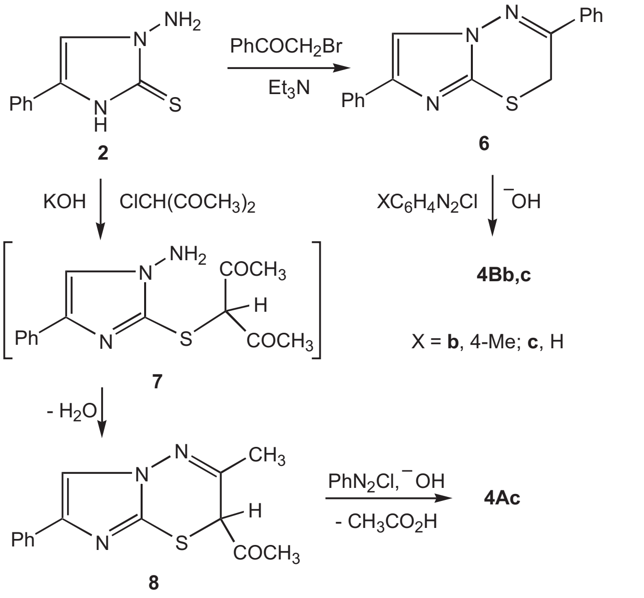

Scheme 2

yielded 2-acetyl-3-methyl-7-phenylimidazo[2,1-*b*][1,3,4]thiadiazine (**8**), probably *via* cyclisation of the initially formed substitution intermediate, 3-[(1-amino-4-phenyl-imidazol-2-yl)thio]-2,4-pentanedione (**7**, Scheme 2). The structures of the isolated products **6** and **8** were assigned on the basis of their spectral data (mass, IR, ^{1}H NMR) and microanalyses. For example, the PMR spectrum of **8** revealed characteristic signals at δ 2.26 (s, 3H), 2.33 (s, 3H), 4.99 (s, 1H), 7.35 – 7.75 (m, 5H), 8.08 (s, 1H); whereas the pmr spectrum of **6** showed signals at δ 4.40 (s, 2H), 7.73 – 7.99 (m, 10H), 8.24 (s, 1H). Reaction of **8** with diazotised aniline in ethanol in the presence of sodium acetate yielded a product in overall good yield that was identified as the phenylhydrazone **4Ac**, formed *via* a Japp-Klingemann reaction[19] (Scheme 2). The latter product proved identical with that obtained above from **1Ac** and **2**. Similar coupling of **6** with diazotised *p*-toluidine and aniline in pyridine yielded products that were found to be identical with compounds **4Bb** and **4Bc**, respectively.

Next, the tautomerism of **4** was studied. As shown in Fig. 1, the products **4** can exist in one or more of three possible tautomeric structures, *viz.* the iminohydrazone, the azo-enamine and the CH-azo forms, **I** – **III**, respectively. Of these forms, structure **I** seems to be the form of choice, as it is consistent with the electronic absorption and ^{1}H NMR spectra. For example, like typical hydrazones,[20,21] the electronic absorption spectra of **4** in dioxan revealed in each case two characteristic absorption bands in the regions 429–389 and 286–234 nm (Table 1), and the spectra of the unsubstituted derivatives **4Ac** and **4Bc**, taken as representative examples of the series prepared, each in different solvents, exhibit little if any solvent dependence (Table 1). On the basis of such absorption patterns, it can be concluded that the studied compounds **4** have in solution one tautomeric form, namely the hydrazone tautomer **I**.

This conclusion was confirmed by the ^{1}H NMR spectra of the studied compounds **4**. Thus, their spectra showed hydrazone NH proton signals in the region δ 9.85–10.89 (see Experimental), and the absence of signals at δ 11.7 and 5.3 which would be characteristic for the NH and CH protons of the azo-enamine and CH-azo forms **II** and **III**, respectively.[22,23]

To obtain further evidence for the assignment of structure I for the products **4**, their acid dissociation constants were determined and their correlation by the Hammett equation was tested.[20-24] The pK_a values for the series **4Aa-j** and **4Ba-j** were determined potentiometrically at 27°C in 80% dioxan-water mixture (v/v). In all determinations the ionic strength was kept constant at 0.1. From the pH – titrant volume data, the acid dissociation constants of the compounds studied were calculated (see Experimental) and the results are summarised in Table 2.

When the pK_a values for each series were plotted *vs.* Hammett substituent constants σ_X,[25] all the substituents fall on the correlation line except the substituents with –R effect, namely the *p*-Ac, *p*-CN, *p*-NO_2 and *p*-CO_2Et groups, which are capable of direct interaction with the negatively charged reaction site. When the pK_a data were plotted versus σ_X^- constants,[25] better correlations were obtained. The equations of the regression lines obtained are:

$$pK_a\ (\mathbf{4A}) = 7.49 - 2.51\ \sigma_X^-;\ r = 0.993;\ s = \pm 0.10$$

$$pK_a\ (\mathbf{4B}) = 8.56 - 2.31\ \sigma_X^-;\ r = 0.992;\ s = \pm 0.10$$

These excellent correlations indicate that the parameter r^- in the Yukawa–Tsuno equation: $pK_a = pK_a^o + \rho[\sigma_X + r^-(\sigma_X^- - \sigma_X)]$, which gives the contribution of the resonance effect of the substituent varied, is close to unity for the two series **4Aa–j** and **4Ba–j** studied.[26]

The linear correlation between pK_a values and σ_X^- constants, and the determined values of ρ and r^-, provide further evidence that the studied compounds **4** exist predominantly in the hydrazone form **I**. This is because the values of ρ (2.51 and 2.31) and r^- = 1.00 are similar to those reported for the ionisation of phenols (ρ = 2.67; r^- = 1.00) and anilinium ions (ρ = 2.77; r^- = 1.00) in 50% ethanol–water mixture.[27-29] If either **II** or **III** were the predominant form for the studied compounds, the ρ values would be expected to be less than 2.0 and to be similar to that reported for the ionisation of 2-arylazophenols (ρ = 1.223; r^- = 0.286),[27] since the bridge between the substituent and the (deprotonation) reaction site in forms **II** and **III** is longer than in **I**. Thus, it is reasonable

Table 1 Electronic absorption spectra of imidazo[2,1-*b*][1,3,4]thiadiazines **4Aa–j** and **4Ba–j** in dioxan

Cpd no	λ_{max} (log ε)
4Aa	414 (3.98), 324 (4.03), 244 (4.22)
4Ab	404 (4.08), 379 (4.18), 268 (4.30)
4Ac[a]	390 (4.08), 270 (4.35)
4Ad	392 (4.15), 271 (4.27)
4Ae	389 (4.00), 272 (4.21)
4Af	393 (4.07), 310 (4.37), 241 (4.34)
4Ag	414 (4.30), 270 (4.24)
4Ah	394 (4.24), 286 (4.22)
4Ai	396 (4.15), 286 (4.19)
4Aj	393 (4.15), 286 (4.19)
4Ba	415 (3.81), 282 (3.97)
4Bb	429 (3.70), 251 (4.00)
4Bc[b]	406 (3.80), 279 (4.02), 234 (4.04)
4Bd	409 (3.72), 252 (4.28)
4Be	424 (3.77), 321 (4.15), 245 (4.02)
4Bf	406 (3.80), 279 (4.02), 246 (4.04)
4Bg	418 (3.87), 305 (3.80)
4Bh	408 (4.14), 321 (4.17)
4Bi	407 (3.89), 325 (3.96)
4Bj	406 (4.25), 288 (4.48)

[a]Solvent, λ_{max} (log ε): EtOH 392 (4.05), 270 (4.13); acetone 389 (4.07); chloroform 383 (4.22); cyclohexane 394 (4.23); acetic acid 382 (4.27); DMSO 398 (4.10); acetonitrile 387 (4.49); dichloromethane 390 (4.35); DMF 393 (4.24); toluene 392 (4.51).
[b]Solvent, λ_{max} (log ε): EtOH 408 (3.59), 279 (3.80), 230 (3.84); acetone 405 (3.80); chloroform 407 (3.76); cyclohexane 410 (3.80); acetic acid 405 (3.63); DMSO 413 (3.86); acetonitrile 404 (3.99); dichloromethane 407 (3.71), DMF 409 (3.90), toluene 408 (3.80).

Table 2 Acid dissociation constants[a] of **4Aa–j** and **4Ba–j**

Cpd No.	pKa (±s)	Cpd No.	pKa (±s)	σ_X	σ_X^-
4Aa	8.30 (0.05)	**4Ba**	9.20 (0.03)	–0.27	–0.27
4Ab	7.91 (0.03)	**4Bb**	8.90 (0.03)	–0.17	–0.17
4Ac	7.42 (0.02)	**4Bc**	8.50 (0.04)	0.00	0.00
4Ad	6.80 (0.02)	**4Bd**	8.10 (0.03)	0.23	0.23
4Ae	6.50 (0.02)	**4Be**	7.60 (0.03)	0.37	0.37
4Af	5.76 (0.04)	**4Bf**	7.05 (0.04)	0.71	0.71
4Ag	4.30 (0.03)	**4Bg**	5.50 (0.03)	0.78	1.28
4Ah	5.90 (0.01)	**4Bh**	7.17 (0.02)	0.45	0.68
4Ai	5.50 (0.03)	**4Bi**	6.70 (0.02)	0.50	0.84
4Aj	5.10 (0.02)	**4Bj**	6.40 (0.04	0.66	0.88

[a]In dioxan–water (4:1 v/v) at 27°C and μ = 0.10.

to conclude that the observed linear correlation of the dissociation constants with the Hammett equation indicates that the hydrazone tautomeric form **I** prevails under the conditions of the pK_a measurement.

Experimental

All melting points were determined on a Gallenkamp Electrothermal apparatus. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^1H and 75 MHz for ^{13}C) and the chemical shifts were related to that of the solvent (DMSO-d_6 throughout). Mass spectra were recorded on a GCMS-Q1000-EX Shimadzu and GCMS 5988-A HP spectrometers; the ionising voltage was 70 eV. Electronic absorption spectra were recorded on a Perkin-Elmer Lambada 40 spectrophotometer. Elemental analyses were carried out by the Microanalytical Centre of Cairo University, Giza, Egypt. The hydrazonoyl halides **1Aa–j**, **1Ba–j**[14,30-34] and **1Cd**,[35a] and 1-amino-4-phenylimidazole-2-thiol **2**,[35b] were prepared by literature methods.

Synthesis of 3,7-disubstituted 2-arylhydrazonoimidazo[2,1-b][1,3,4] thiadiazines (**4**)

To sodium ethoxide solution, prepared from sodium metal (0.06 g, 2.5 mmole) and absolute ethanol (15 ml) was added compound **2** (0.48 g, 2.5 mmole) and the mixture was stirred for 10 min. To the resulting solution was added the appropriate hydrazonoyl chloride **1A** (2.5 mmole) and the reaction mixture was stirred overnight at room temperature. The solid that precipitated was filtered off, washed with water, dried and finally crystallised from an appropriate solvent to give the respective 3,7-disubstituted 2-arylhydrazonoimidazo[2,1-*b*][1,3,4]thiadiazine **4A**.

Repetition of the above procedure using **1B** and **1Cd** each in place of **1A** gave in all cases the respective fused system **4** except in the cases of **1Bc** and **1Cd,** where the isolated products were the thiohydrazonates **3Bc** and **3Cd**, respectively.

(1-Amino-4-phenylimidazol-2-yl) N-phenyl-2-oxo-2-phenylethane-thiohydrazonate (**3Bc**): Pale yellow solid (0.74 g, 72%), m.p. 160–162°C (EtOH-dioxan). IR: ν_{max} 3317, 3186, 1643 cm^{-1}. NMR: δ_H 6.35 (s, 2H, NH_2), 7.23-7.80 (m, 15H, ArH), 8.30 (s, 1H, ArH), 11.0 (s, 1H, NH). MS: *m/z* (%) 413 (M^+, 3), 250 (15), 234 (30), 191 (39), 176 (13), 131 (18), 118 (21), 117 (29), 105 (100), 103 (24), 77 (80). Anal. Calcd. for $C_{23}H_{19}N_5OS$ (413.44): C, 66.81; H, 4.63; N, 16.94. Found: C, 66.41; H, 4.53; N, 16.60%.

(1-Amino-4-phenyl-imidazol-2-yl) N-(4-chlorophenyl)-2-oxo-2-thienyl-ethane-thiohydrazonate (**3Cd**): Yellow solid (0.62 g, 55%), m.p. 182–184°C (EtOH-dioxan). IR: ν_{max} 3277, 3181, 1630 cm^{-1}. NMR: δ_H 5.74 (s, 2H, NH_2), 6.76 (d, J = 9 Hz, 2H, ArH), 7.20–7.65 (m, 8H, ArH), 7.67 (d, J = 9 Hz, 2H, ArH), 8.23 (s,1H, ArH), 10.82 (s, 1H, NH); δ_C 113.9, 115.3, 123.6, 123.8, 125.0, 126.1, 127.4, 128.2, 128.6, 128.8, 129.0, 137.2, 139.0, 147.4, 159.0, 161.3, 189.0. MS: *m/z* (%) 456 (M^+ + 3, 1), 455 (M^+ + 2, 2), 453 (M^+, 2), 286 (3), 191 (55), 174 (5), 171 (8), 137 (16), 117 (19), 111 (100), 104 (11), 78 (27). Anal. Calcd. for $C_{21}H_{16}ClN_5OS_2$ (453.98): C, 55.56; H, 3.55; N, 15.43. Found: C, 55.40; H, 3.77; N, 15.25%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-methoxyphenyl)hydrazone) (**4Aa**): Pale yellow solid (0.64 g, 70%), m.p. 220–222°C (EtOH-dioxan). IR: ν_{max} 3150 cm^{-1}. NMR: δ_H 2.44 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 6.91 (d, J = 9 Hz, 2H, ArH), 7.28–7.39 (m, 5H, ArH), 7.79 (d, J = 9 Hz, 2H, ArH), 8.17 (s,1H, ArH), 9.85 (s, 1H, NH). MS: *m/z* (%) 365 (M^+ + 2, 4), 364 (M^+ + 1, 14), 363 (M^+, 45), 228 (9), 187 (19), 174 (7), 142 (2), 135 (35), 122 (100), 116 (10), 107 (97), 103 (14), 95 (20), 77 (20). Anal. Calcd. for $C_{19}H_{17}N_5OS$ (363.44): C, 62.79; H, 4.71; N, 19.27. Found: C, 62.80; H, 4.57; N, 19.00%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-methylphenyl)hydrazone (**4Ab**): Yellow solid (0.65 g, 75%), m.p. 236–238°C (EtOH-dioxan). IR: ν_{max} 3163. NMR: δ_H 2.08 (s, 3H, CH_3), 2.39 (s, 3H, CH_3), 7.24–7.31 (m, 5H, ArH), 7.33 (d, J = 8 Hz, 2H, ArH), 7.73 (d, J = 8 Hz, 2H, ArH), 8.08 (s,1H, ArH), 10.06 (s, 1H, NH). MS *m/z* (%) 349 (M^+ + 2, 6), 348 (M^+ + 1, 22), 347 (M^+, 82), 346 (61), 228 (7), 187 (31), 183 (16), 174 (21), 119 (11), 116 (17), 106 (17), 103 (27), 91 (100), 77 (27). Anal. Calcd. for $C_{19}H_{17}N_5S$ (347.44): C, 65.68; H, 4.93; N, 20.16. Found: C, 65.70; H, 4.53; N, 20.32%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-phenylhydrazone (**4Ac**): Pale yellow crystals (0.67 g, 80%), m.p. 218–220°C (EtOH-dioxan). IR: ν_{max} 3425 cm^{-1}. NMR: δ_H 2.45 (s, 3H, CH_3), 6.93–7.81 (m, 10H, ArH), 8.16 (s, 1H, ArH), 10.10 (s, 1H, NH). MS: *m/z* (%) 335 (M^+ + 2, 9), 334 (M^+ + 1, 22), 333 (M^+, 100), 228 (9), 187 (64), 183 (64), 174 (24), 147 (14), 142 (9), 116 (27), 105 (22), 103 (56), 92 (20), 77 (95). Anal. Calcd. for $C_{18}H_{15}N_5S$ (333.42): C, 64.84; H, 4.53; N, 21.00. Found: C, 64.77; H, 4.47; N, 21.02%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-chlorophenyl)hydrazone (**4Ad**): Yellow solid (0.72 g, 78%), m.p. 260–262°C (EtOH-dioxan). IR: ν_{max} 3440 cm^{-1}. NMR: δ_H 2.45 (s, 3H, CH_3), 7.20–7.35 (m, 5H, ArH), 7.39 (d, J = 8 Hz, 2H, ArH), 7.79 (d, J = 8 Hz, 2H, ArH), 8.17 (s,1H, ArH), 10.06 (s, 1H, NH): δ_C 20.4, 115.8, 116.7, 120.9, 124.4, 125.3, 127.1, 127.3, 128.5, 128.9, 132.8, 139.1, 143.2, 149.1. MS: *m/z* (%) 370 (M^+ + 2, 11), 369 (M^+ + 1, 30), 368 (M^+, 26), 367 (100), 188 (14), 187 (89), 183 (44), 174 (31), 147 (16), 142 (12), 139 (24), 126 (23), 117 (13), 113 (20), 111 (68), 103 (87), 77 (18), 76 (25). Anal. Calcd. for $C_{18}H_{14}ClN_5S$ (367.86): C, 58.77; H, 3.84; N, 19.04. Found: C, 58.83; H, 3.74; N, 19.32%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(3-chlorophenyl)hydrazone (**4Ae**): Yellow solid (0.67 g, 73%), m.p. 256–258°C (EtOH–dioxan). IR: ν_{max} 3417 cm^{-1}. NMR: δ_H 2.43 (s, 3H, CH_3), 6.95–7.81 (m, 8H, ArH), 8.18 (s, 1H, ArH), 10.11 (s, 1H, NH). MS: *m/z* (%) 370 (M^+ + 2, 5), 369 (M^+ + 1, 22), 368 (M^+, 13), 367 (55), 210 (18), 188 (14),187 (100), 174 (35), 142 (16), 117 (13), 113 (18), 111 (57), 102 (21), 91 (11), 77 (19). Anal. Calcd. for $C_{18}H_{14}ClN_5S$ (367.86): C, 58.77; H, 3.84; N, 19.04. Found: C, 58.70; H, 3.62; N, 19.00%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(3-nitrophenyl)hydrazone (**4Af**): Yellow solid (0.64 g, 68%), m.p. 244–246°C (EtOH-dioxan). IR: ν_{max} 3417 cm^{-1}. NMR: δ_H 2.39 (s, 3H, CH_3), 7.24 (m, 9H, ArH), 8.20 (s, 1H, ArH), 10.41 (s, 1H, NH). MS: *m/z* (%) 380 (M^+ + 2, 7), 379 (M^+ + 1, 22), 378 (M^+, 100), 187 (37), 183 (17), 174 (18), 147 (10), 116 (20), 103 (31), 76 (8). Anal. Calcd. for $C_{18}H_{14}N_6O_2S$ (378.42): C, 57.13; H, 3.73; N, 22.21. Found: C, 56.73; H, 3.77; N, 22.10%.

3-Methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-nitrophenyl)hydrazone (**4Ag**): Orange solid, (0.68 g, 72%), m.p. 272–274°C (EtOH-dioxan). IR: ν_{max} 3247 cm^{-1}. NMR: δ_H 2.49 (s, 3H, CH_3), 7.08 (d, J = 9 Hz, 2H, ArH), 7.10–7.67 (m, 5H, ArH), 7.68 (d, J = 9 Hz, 2H, ArH), 8.01 (s, 1H, ArH), 10.02 (s, 1H, NH). MS: *m/z* (%) 380 (M^+ + 2, 9), 379 (M^+ + 1, 30), 378 (M^+, 100), 348 (13), 228 (12), 210 (19), 189 (13), 187 (60), 174 (35), 147 (20), 142 (16), 122 (12), 116 (38), 107 (32), 104 (19), 92 (18), 77 (13), 76 (24). Anal. Calcd. for $C_{18}H_{14}N_6O_2S$ (378.42): C, 57.13; H, 3.73; N, 22.21. Found: C, 57.11; H, 3.51; N, 21.92%.

2-[(4-Ethoxycarbonylphenyl)hydrazono]-3-methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazine (**4Ah**): Yellow solid (0.70 g, 70%), m.p. 240–242°C (EtOH-dioxan). IR: ν_{max} 3386, 1701 cm^{-1}. NMR: δ_H 1.30 (t, J = 7 Hz, 3H, CH$_3$), 2.45 (s, 3H, CH$_3$), 4.27 (q, J = 7 Hz, 2H, CH$_2$), 7.26–7.41 (m, 5H, ArH), 7.79 (d, J = 7 Hz, 2H, ArH), 7.88 (d, J = 7 Hz, 2H, ArH), 8.18 (s,1H, ArH), 10.40 (s, 1H, NH). MS: *m/z* (%) 406 (M$^+$ + 1, 20), 405 (M$^+$, 76), 189 (11), 187 (100), 174 (37), 149 (74), 121 (39), 103 (82), 91 (29), 77 (19), 73 (44). Anal. Calcd. for $C_{21}H_{19}N_5O_2S$ (405.48): C, 62.21; H, 4.72; N, 17.27. Found: C, 62.01; H, 4.55; N, 17.10%.

2-[(4-Acetylphenyl)hydrazono]-3-methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazine (**4Ai**): Dark red solid (0.62 g, 66%), m.p. 268–269°C (EtOH). IR: ν_{max} 3244, 1658 cm^{-1}. NMR: δ_H 2.46 (s, 3H, CH$_3$), 2.50 (s, 3H, COCH$_3$), 7.26–7.43 (m, 5H, ArH), 7.79 (d, J = 8 Hz, 2H, ArH), 7.91 (d, J = 8 Hz, 2H, ArH), 8.2 (s, 1H, ArH), 10.40 (s, 1H, NH). MS: *m/z* (%) 377 (M$^+$ + 2, 10), 376 (M$^+$ + 1, 29), 375 (M$^+$, 100), 256 (11), 228 (15), 187 (61), 183 (17), 174 (18), 147 (14), 119 (42), 103 (31), 77 (15). Anal. Calcd. for $C_{20}H_{17}N_5OS$ (375.46): C, 63.98; H, 4.56; N, 18.65. Found: C, 64.21; H, 4.32; N, 18.75%.

2-[(4-Cyanophenylhydrazono]-3-methyl-7-phenyl-2H-imidazo[2,1-b][1,3,4]thiadiazine (**4Aj**): Yellow solid (0.63 g, 70%), m.p. 260–262°C (EtOH). IR: ν_{max} 3386, 2218 cm^{-1}. ^{1}H NMR (DMSO-d$_6$) δ 2.44 (s, 3H, CH$_3$), 7.23–7.44 (m, 5H, ArH), 7.71 (d, J = 8 Hz, 2H, ArH),, 7.78 (d, J = 8 Hz, 2H, ArH), 8.19 (s, 1H, ArH), 10.46 (s, 1H, NH). MS: *m/z* (%) 360 (M$^+$ + 2, 7), 359 (M$^+$ + 1, 24), 358 (M$^+$, 100), 187 (65), 177 (26), 147 (18), 142 (12), 116 (37), 103 (67), 90 (39), 77 (10). Anal. Calcd. for $C_{19}H_{14}N_6S$ (358.43): C, 63.67; H, 3.94; N, 23.45. Found: C, 63.54; H, 3.65; N, 23.20%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-methoxyphenyl)hydrazone (**4Ba**): Dark red solid, (Yield 0.64 g, 60%), m.p.108–110°C (EtOH). IR: ν_{max} 3140 cm^{-1}. NMR: δ_H 3.68 (s, 3H, OCH$_3$), 6.82 (d, J = 9 Hz, 2H, ArH), 7.02 (d, J = 9 Hz, 2H, ArH), 7.27–7.85 (m, 10H, ArH), 8.27 (s, 1H, ArH), 10.08 (s, 1H, NH). MS: *m/z* (%) 427 (M$^+$ + 2, 16), 426 (M$^+$ + 1, 20), 425 (M$^+$, 73), 365 (11), 290 (28), 268 (4), 236 (3), 213 (6), 187 (45), 160 (7), 147 (6), 135 (43), 122 (73), 107 (100), 77 (35), 76 (13). Anal. Calcd. for $C_{24}H_{19}N_5OS$ (425.52): C, 67.75; H, 4.50; N, 16.46. Found: C, 67.42; H, 4.23; N, 16.32%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-methylphenyl)hydrazone (**4Bb**): Dark red solid (0.66 g, 65%), m.p. 110–112°C (EtOH). IR: ν_{max} 3218 cm^{-1}. NMR: δ_H 2.21 (s, 3H, CH$_3$), 6.97 (d, J = 9 Hz, 2H, ArH), 7.02 (d, J = 9 Hz, 2H, ArH), 7.28–7.85 (m, 10H, ArH), 8.28 (s, 1H, ArH), 10.13 (s, 1H, NH). MS: *m/z* (%) 411 (M$^+$ + 2, 8), 410 (M$^+$ + 1, 21), 409 (M$^+$, 58), 290 (19), 245 (11), 244 (21), 187 (60), 137 (6), 119 (20), 116 (27), 103 (35), 91 (100), 77 (25). Anal. Calcd. for $C_{24}H_{19}N_5S$ (409.52): C, 70.39; H, 4.68; N, 17.10. Found: C, 70.34; H, 4.52; N, 17.40%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-chlorophenyl)hydrazone (**4Bd**): Yellow solid (0.77 g, 72%), m.p.158–160°C (EtOH). IR: ν_{max} 3417 cm^{-1}. NMR: δ_H 7.06–7.55 (m, 10H, ArH), 7.74 (d, J = 9 Hz, 2H, ArH), 7.82 (d, J = 9 Hz, 2H, ArH), 8.30 (s, 1H, ArH), 10.33 (s, 1H, NH); δ_C 113.7, 115.3, 118.1, 122.5, 123.5, 125.3, 125.9, 126.1, 126.7, 127.0, 127.7, 128.1, 130.7, 132.8, 137.5, 140.9, 148.5. MS: *m/z* (%) 432 (M$^+$ + 3, 13) 431 (M$^+$ + 2, 39), 430 (M$^+$ + 1, 33), 429 (M$^+$, 100), 290 (46), 244 (27), 187 (96), 173 (16), 139 (16), 116 (26), 111 (30), 103 (41), 89 (12), 77 (15). Anal. Calcd. for $C_{23}H_{16}ClN_5S$ (429.93): C, 64.26; H, 3.75; N, 16.29. Found: C, 64.42; H, 3.58; N, 16.13%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(3-chlorophenyl)hydrazone (**4Be**): Dark red solid (0.73 g, 68%), m.p.120–122°C (EtOH). IR: ν_{max} 3358 cm^{-1}. NMR: δ_H 6.92-7.85 (m, 14H, ArH), 8.32 (s, 1H, ArH), 10.38 (s, 1H, NH). MS: *m/z* (%) 432 (M$^+$ + 3, 12), 431 (M$^+$ + 2, 39), 430 (M$^+$ + 1, 31), 429 (M$^+$, 74), 290 (31), 272 (19), 244 (22), 187 (100), 173 (16), 147 (12), 139 (11), 116 (28), 111 (25), 103 (42), 89 (15), 77 (19). Anal. Calcd. for $C_{23}H_{16}ClN_5S$ (429.93): C, 64.26; H, 3.75; N, 16.29. Found: C, 64.09; H, 3.58; N, 16.14%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(3-nitrophenyl)hydrazone (**4Bf**): Dark red solid (0.72 g, 65%), m.p.160°C (EtOH). IR: ν_{max} 3293 cm^{-1}. NMR: δ_H 7.28–7.91 (m, 14H, ArH), 8.33 (s, 1H, ArH), 10.62 (s, 1H, NH). MS: *m/z* (%) 442 (M$^+$ + 2, 10), 441(M$^+$ + 1, 35), 440 (M$^+$, 100), 290 (28), 277 (18), 245 (27), 174 (15), 118 (32), 103 (44), 89 (12), 77 (21). Anal. Calcd. for $C_{23}H_{16}N_6O_2S$ (440.49): C, 62.72; H, 3.66; N, 19.08. Found: C, 62.53; H, 3.80; N, 19.00%.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-nitrophenyl)hydrazone (**4Bg**): Orange solid (0.74 g, 67%), m.p. 250–252°C (EtOH). IR: ν_{max} 3375 cm^{-1}. NMR: δ_H 7.18 (d, J = 9 Hz, 2H, ArH), 7.26–7.85 (m, 10H, ArH), 8.12 (d, J = 9 Hz, 2H, ArH), 8.34 (s, 1H, ArH), 10.89 (s, 1H, NH). MS: *m/z* (%) 441(M$^+$ + 1, 2), 440 (M$^+$, 8), 186 (20), 122 (12), 116 (19), 105 (100), 103 (33), 91 (15), 76 (34). Anal. Calcd. for $C_{23}H_{16}N_6O_2S$ (440.49): C, 62.72; H, 3.66; N, 19.08. Found: C, 62.97; H, 3.68; N, 19.20%.

2-[(4-Ethoxycarbonylphenyl)hydrazono]-3,7-diphenyl-2H-imidazo[2,1-b][1,3,4]-thiadiazine (**4Bh**): Orange solid (0.81 g, 69%), m.p. 180°C (EtOH-dioxan). IR: ν_{max} 3155, 1708 cm^{-1}. NMR: δ_H 1.29 (t, J = 7 Hz, 3H, CH$_3$), 4.25 (q, J = 7 Hz, 2H, CH$_2$), 7.26–7.85 (m, 14H, ArH), 8.31 (s, 1H, ArH), 10.57 (s, 1H, NH). MS: *m/z* (%) 468 (M$^+$ + 1, 9), 467 (M$^+$, 27), 439 (23), 295 (5), 291 (25), 205 (6), 187 (88), 174 (17), 161 (11), 150 (12), 137 (35), 121 (25), 116 (80), 103 (100), 77 (99), 74 (10). Anal. Calcd. for $C_{26}H_{21}N_5O_2S$ (467.55): C, 66.79; H, 4.53; N, 14.98. Found: C, 66.64; H, 4.30; N, 14.90%.

2-[(4-Acetylphenyl)hydrazono]-3,7-diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazine (**4Bi**): Yellow solid (0.76 g, 70%), m.p. 224°C (EtOH-dioxan). IR: ν_{max} 3220, 1662 cm^{-1}. ^{1}H NMR (DMSO-d$_6$) δ 2.47 (s, 3H, COCH$_3$), 7.13 (d, J = 8 Hz, 2H, ArH), 7.25-7.86 (m, 10H, ArH), 7.77 (d, J = 8 Hz, 2H, ArH), 8.32 (s, 1H, ArH), 10.59 (s, 1H, NH). MS: *m/z* (%) 439 (M$^+$ + 2, 6), 438 (M$^+$ + 1, 17), 437 (M$^+$, 53), 409 (12), 290 (24), 245 (19), 244 (32), 211 (12), 187 (100), 173 (21), 147 (29), 129 (13), 119 (61), 116 (56), 105 (33), 103 (86), 91 (37), 77 (67). Anal. Calcd. for $C_{25}H_{19}N_5OS$ (437.53): C, 68.63; H, 4.38; N, 16.01. Found: C, 69.00; H, 4.70; N, 16.40%.

2-[(4-Cyanophenyl)hydrazono]-3,7-diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazine (**4Bj**): Orange solid (0.77 g, 73%), m.p. 272°C (dioxan). IR: ν_{max} 3236, 2221 cm^{-1}. NMR: δ_H 7.15 (d, J = 7 Hz, 2H, ArH), 7.28–7.76 (m, 10H, ArH), 7.83 (d, J = 7 Hz, 2H, ArH), 8.33 (s, 1H, ArH), 10.65 (s, 1H, NH). MS: *m/z* (%) 422 (M$^+$ + 2, 6), 421 (M$^+$ + 1, 18), 420 (M$^+$, 62), 290 (22), 244 (27), 187 (100), 173 (21), 146 (17), 117 (32), 115 (52), 105 (28), 103 (85), 91 (35), 77 (52). Anal. Calcd. for $C_{24}H_{16}N_6S$ (420.50): C, 68.55; H, 3.84; N, 19.99. Found: C, 68.45; H, 4.12; N, 19.81%.

Cyclisation of the open-chain intermediates **3Bc** *and* **3Cd**

A solution of **3Bc** or **3Cd** (0.0025 mole) in glacial acetic acid (30 ml) was refluxed for 5 hours, then poured onto ice with stirring. The solid that precipitated was filtered off, dried and crystallised from the ethanol to give the respective **4Bc** or **4Cd**.

3,7-Diphenyl-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-phenylhydrazone (**4Bc**): Yellow solid (0.68 g, 69%), m.p.100°C (EtOH). IR: ν_{max} 3417 cm^{-1}. NMR: δ_H 6.48-8.14 (m, 15H, ArH), 8.17 (s, 1H, ArH), 10.00 (s, 1H, NH). MS: *m/z* (%) 397 (M$^+$ + 2, 6), 396 (M$^+$ + 1, 24), 395 (M$^+$, 71), 290 (19), 244 (20), 187 (63), 173 (16), 147 (12), 116 (27), 105 (24),103 (48), 77 (100), 76 (16). Anal. Calcd. for $C_{23}H_{17}N_5S$ (395.49): C, 69.85; H, 4.33; N, 17.71. Found: C, 69.62; H, 4.35; N, 17.35%.

7-Phenyl-3-(2-thienyl)-2H-imidazo[2,1-b][1,3,4]thiadiazin-2-one 2-(4-chlorophenyl)hydrazone (**4Cd**): Dark red solid (0.65 g, 60%), m.p.140°C (EtOH). IR: ν_{max} 3150 cm^{-1}. NMR: δ_H 7.25–7.38 (m, 8H, ArH), 7.41 (d, J = 7 Hz, 2H, ArH), 7.83 (d, J = 7 Hz, 2H, ArH), 8.32 (s, 1H, ArH), 10.39 (s, 1H, NH). MS: *m/z* (%) 439 (M$^+$ + 3, 4), 438 (M$^+$ + 2, 5), 437 (M$^+$ + 1, 26), 436 (M$^+$, 17), 269 (13), 250 (15), 178 (100), 174 (11), 139 (23), 116 (49), 113 (11), 103 (37), 99 (21), 89 (18), 77 (16), 76 (18). Anal. Calcd. for $C_{21}H_{14}ClN_5S_2$ (435.96): C, 57.86; H, 3.24; N, 16.06. Found: C, 57.52; H, 3.10; N, 15.94%.

Synthesis of 2-acetyl-3-methyl-7-phenyl-2H-imidazo-[2,1-b][1,3,4]thiadiazine (**8**)

To a solution of **2** (0.96 g, 5 mmole) in ethanol was added an aqueous solution of potassium hydroxide (0.4 ml, 75%) and the mixture was warmed for 10 min. at 80°C and then cooled. To the resulting clear solution was added 3-chloro-2,4-pentanedione (0.6 ml, 5 mmol) dropwise with stirring. After the addition was complete the mixture was stirred for a further 18 h at room temperature. Petroleum ether was added and the mixture was left in a refrigerator over night. A solid which separated was filtered off and crystallised from petroleum ether to give pure **8** as a pale yellow solid (0.75 g, 55%), m.p.128–130°C. IR: ν_{max} 1712 cm^{-1}. NMR: δ_H 2.26 (s, 3H, CH$_3$), 2.33 (s, 3H, COCH$_3$), 4.99 (s, 1H, CH), 7.35–7.75 (m, 5H, ArH), 8.08 (s,1H, ArH). MS: *m/z* (%) 272 (M$^+$ + 1, 10), 271 (M$^+$, 49), 228 (100), 201 (34), 188 (77), 116 (97), 102 (93), 89 (56), 76 (76). Anal. Calcd. for $C_{14}H_{13}N_3OS$ (271): C, 61.99; H, 4.80; N, 15.50. Found: C, 62.10; H, 4.63; N, 15.32%.

Alternative synthesis of **4Ac**

To a solution of **8** (0.68 g, 2.5 mmol) in ethanol (20 ml) was added sodium acetate trihydrate (0.34 g, 2.5 mmol) and the mixture was cooled to 0–5°C in an ice-bath. A solution of benzenediazonium chloride, prepared as usual by diazotising (2.5 mmol) in hydrochloric acid (6 M, 1.5 ml) with sodium nitrite (1M, 2.5 ml) was added dropwise over a period of 20 min. The whole was then left in a refrigerator overnight. The precipitated solid was collected, washed with water and finally crystallised from ethanol to give **4Ac** The isolated product **4Ac** was found to be identical with that obtained above from the reaction of **2** with **1Ac**.

Synthesis of 3,7-diphenyl-imidazo[2,1-b][1,3,4]thiadiazine (**6**)
Triethylamine (0.35 ml, 2.5 mmole) was added to a mixture of 1-amino-4-phenylimidazole-2-thiol (**2**) (0.48 g, 2.5 mmole) and phenacyl bromide (0.50 g, 2.5 mmole) in ethanol (20 ml). The whole was refluxed for 5 hours. Excess of solvent was evaporated off and the residue was cooled and poured into cold water. The precipitated solid was filtered off and recrystallised from methanol to give 3,7-diphenylimidazo[2,1-*b*][1,3,4]thiadiazine (**6**) as a yellow solid (0.44 g, 60%), m.p.146°C (MeOH) (Lit.[35b] m.p. 140°C). NMR: δ_H 4.40 (s, 2H, CH_2), 7.73-7.99 (m, 10H, ArH), 8.24 (s,1H, ArH). MS: *m/z* (%) 293 (M^+ + 2, 5), 292 (M^+ + 1, 17), 291 (M^+, 82), 188 (77), 186 (64), 160 (18), 149 (11), 130 (11), 117 (26), 116 (45), 103 (69), 89 (22), 77 (100). Anal. Calcd. for $C_{17}H_{13}N_3S$ (291.38): C, 70.08; H, 4.50; N, 14.42. Found: C, 70.40; H, 4.23; N, 14.52%.

Preparation of authentic samples of **4Bb** *and* **4Bc**
A solution of *p*-methylbenzenediazonium chloride, prepared by diazotising *p*-toluidine (2.5 mmol) in hydrochloric acid (6M, 1.5 ml) with sodium nitrite (1M, 2.5 ml) was added dropwise over a period of 20 min to a cold stirred solution of **6** (0.73 g, 2.5 mmol) in pyridine (10 ml), cooling in an ice bath. The whole was then left in a refrigerator overnight. The solution was poured onto ice and hydrochloric acid. The precipitated solid was collected, washed with water and finally crystallised from ethanol to give **4Bb**. Repetition using diazotised aniline in lieu of the diazotised *p*-toluidine gave **4Bc.** The isolated products **4Bb** and **4Bc** were found to be identical with those obtained *via* cyclisation of **3Bc** as described above.

pKa determination of compounds **4Aa–j** *and* **4Ba–j**
The acid dissociation constants of the compound series **4A** and **4B** were determined potentiometrically in 80% dioxan–water mixture at 25 + 0.1°C and ionic strength (KNO_3) of 0.1. A Meetrohm 686 titroprocessor equipped with 665 Dosimat was employed. The electrode and the titroprocessor were calibrated with standard Beckman buffer solutions of pH 4.01 and 7.00. The pH meter reading B recorded in dioxan–water solution was converted to hydrogen ion concentration [H^+] by means of the widely relation of van Uitert and Hass[36], namely:

$$-\log [H^+] = B + \log U_H$$

where log U_H is the correction factor for the solvent composition and ionic strength used for which B is read. The value of log U_H was found to be 0.48. A carbonate-free sodium hydroxide titrant was prepared and standardised against potassium hydrogen phthalate solution.

The experimental procedure followed in the determination of pK_a values and their calculations, by the method of least squares, from the titrant volume-pH data using the relation:

$$pK_a = pH_i - \log V_i/(V_e - V_i)$$

where pH_i is the corrected pH value of the solution when the volume of the added titrant is V_i and V_e is the volume of the titrant at the equivalence point as previously described.[37] The calculations of the pK_a values were carried out using the computer program MINIQUAD-75.[38] The pK_a values obtained were reproducible to within ± 0.02 pK_a unit. The results are recorded in Table 2.

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References

1 A.S. Shawali, *Chem. Rev.*, 1993, **93**, 2731.
2 A.S. Shawali and M.A. Abdallah, *Adv. Heterocyclic Chem.*, 1995, **63**, 277.
3 A.S. Shawali, *Heterocycles,* 1983, **20**, 2239.
4 A.S. Shawali and C. Parkanyi, *J. Heterocyclic Chem.*, 1980, **17**, 833.
5 A.S. Shawali and S.M. Elsheikh, *J. Heterocyclic Chem.*, 2001, **38**, 541.
6 D.L. Trepanier and P.E. Krieger, *J. Heterocyclic Chem.*, 1972, **9**, 1385.
7 E. Bulka.and W.D. Pfeiffer, *Z. Chem.*, 1975, **15**, 482.
8 I.V. Smolanka, T.A. Krasnitskaya and M.M. Tsitsika, *Ukr. Khim. Zh.*, 1972, **38**, 587; *Chem. Abstr.*, 1973, **78**: 29 733n.
9 H.R. Snyder Jr. and L.E. Benjamin, *J. Med. Chem.*, 1970, **13**, 164.
10 A.S. Shawali, M.A. Abdallah, I.M. Abbas and G.M. Eid, *J. Chin. Chem. Soc.,* 2004, **51**, 351 and references cited therein.
11 A.S. Shawali, S. Elsheikh and C. Parkanyi, *J. Heterocyclic Chem.*, 2003, **40**, 207.
12 A.S. Shawali, M.A. Abdallah, M.A.N. Mosselhi and Y.F. Mohammed, *Z. Naturforsch.*, 2002, **57b**, 552.
13 A.S. Shawali, M.A. Abdallah and M.M. Zayed, *J. Heterocyclic Chem.,* 2002, **39**, 45.
14 M.A.N. Mosselhi, M.A. Abdallah, Y.F. Mohamed and A.S. Shawali, *Phosphorus, Sulfur, Silicon Rel. Elements,* 2002. **177**, 487.
15 A.S. Shawali, I.F. Zeied, M.M. Abdelkader, A.A. Elsherbini and F.M.A. Altalbawy, *J. Chinese Chem. Soc.*, 2002, **48**, 65.
16 A.S. Shawali, A.A. Elghandour and S.M. Elsheikh, *Heteroatom Chem.*, 2000, **11**, 87.
17 A.S. Shawali, A.A. Elghandour and S.M. Elsheikh, *J. Prakt. Chem.*, 2000, **142**, 96.
18 A.S. Shawali and M.A.N. Mosselhi, *J. Heterocyclic Chem.,* 2003, **40**, 725.
19 R.R. Phillip, *Organic Reactions*, Adams, R., ed., John Wiley & Sons, New York, 1959, Vol. 10, Chap. pp. 143.
20 A.S. Shawali, N.M.S. Harb and K.O. Badahdah, *J. Heterocyclic Chem.*, 1985, **22**, 1397.
21 R. Jones, A.J. Ryan, S. Sternhell and S.E. Wright, *Tetrahedron*, 1963, **19**, 1497.
22 Y. Kurasawa, R. Miyashita, A. Takada, H.S. Kim and Y. Okamoto, *J. Heterocyclic Chem.*, 1995, **32**, 671.
23 J.G. Schantl and P. Hebeisen, *Tetrahedron*, 1990, **46**, 393.
24 D.A. Charistos, G.V. Vagenas, I.C. Tzavellas, C.A. Tsderidis and N.A. Rodios, *J. Heterocyclic Chem.*, 1994, **31**, 1593.
25 C.D. Johnson, *The Hammett Equation*, Cambridge University Press, 1973.
26 A.S. Shawali, I.M. Abbas, M.A. Abdallah and A.A. Fahmi, *Indian J. Chem.*, 1990, **29B**, 1012.
27 A.S. Shawali, MS. Rizk, A.O. Abdelhamid, M.A. Abdallah, C. Parkanyi and M.E. Wojciechowska, *Heterocycles,* 1983, **20**, 2211.
28 A.S. Shawali, H.M. Hassaneen and M.A. Hanna, *Heterocycles,* 1981, **15**, 697.
29 A.E. Elhilaly, A.S. Shawali and M.A. Madkour, *Inorg. Chim. Acta*, 1979, **36**, 179.
30 N.F. Eweiss and A. Osman, *J. Heterocyclic Chem.,* 1980, **17**, 1713.
31 M.M. El-Abadela, A.Q. Hussein and B.A. Thaher, *Heterocycles,* 1991, **32**. 1829.
32 A.S. Shawali and A.O. Abdelhamid, *Bull. Chem. Soc. Jpn.*, 1976, **49**, 321.
33 A.S. Shawali, M.H. Abdel Kader and M.A. Eltalbawy, *Tetrahedron*, 2002, **58**, 2875.
34 D.B. Sharp, *J. Am. Chem. Soc.*, 1949, **71**, 1106.
35 (a) A.M. Farag and M.S. Algharib, *Org. Prep. Proc. Int.*, 1988, **20**, 521; (b) T. Pyl, F. Waschk and H. Beyer, *Liebigs Ann. Chem.*, 1963, **663***,* 113.
36 L.G. Van Uitert and C.G. Haas, *J. Am. Chem. Soc*. 1953, **75**, 451.
37 A. Albert and E.P. Serjeant, *The Determination of Ionisation Constants,* Chapman and Hall Ltd., London, 1971, pp. 9 – 39.
38 P. Gans, A. Sabatini and A. Vacca, *Inorg. Chim. Acta*, 1976, **18**, 237.