Reactions with Hydrazidoyl Halides. IV. [1]

Synthesis of Thiazolo[3,2-*a*]benzimidazoles, Imidazo[2,1-*b*]thiazoles and Pyrazolo[4,3-*b*]thiazines

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Hydrazidoyl halides were condensed with 2-mercaptobenzimidazole yielding **4a-c** and **7a,b** which were cyclized to the corresponding 2-arylhydrazonothiazolo[3,2-*a*]benzimidazol-3-ones **5a,b** and 3-substituted 2-arylazo thiazolo[3,2-*a*]benzimidazoles **8a,b** respectively. Imidazo[2,1-*b*]thiazoles were obtained by the reaction of hydrazidoyl halides with 2-mercapto-4,5-dihydroimidazole. Also, hydrazidoyl halides **6a,b** were reacted with 3-amino-4-mercapto-5-phenylpyrazole to give pyrazolo[4,3-*b*]thiazines **15a,b**. The structures of the products were assigned on the basis of their elemental analysis and spectral data.

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Hydrazidoyl halides have been widely used as important tools for the synthesis of heterocyclic compounds, both through condensation reactions and as precursors of nitrile imines, which undergo cycloaddition with several dipolarophiles [2-15].

In this work we report new syntheses of potentially herbicidal thiazolo[3,2-*a*]benzimidazoles, imidazo[2,1-*b*]thiazoles and pyrazolo[4,3-*b*]thiazine derivatives, which have been developed starting from 2-mercaptobenzimidazole, 2-mercapto-4,5-dihydroimidazole or 3-amino-4-mercapto-5-phenylpyrazole and readily accessible hydrazidoyl halides.

2-Mercaptobenzimidazole **1** was easily condensed with hydrazidoyl halides, **2**, **3**, and **6** in presence of a base, such as triethylamine, as hydrogen halide acceptor in ethanol (Chart 1). Treatment of hydrazidoyl halides **2**, **3**, and **6** with **1** gave the single products **4** and **7** respectively, isolated by recrystallization of the crude reaction material. The intermediates **4a-c** and **7a,b** were readily identified through elemental analyses and through their ir spectra (NH stretching in the 3420-3280 region and CO stretching in the 1670-1720 region).

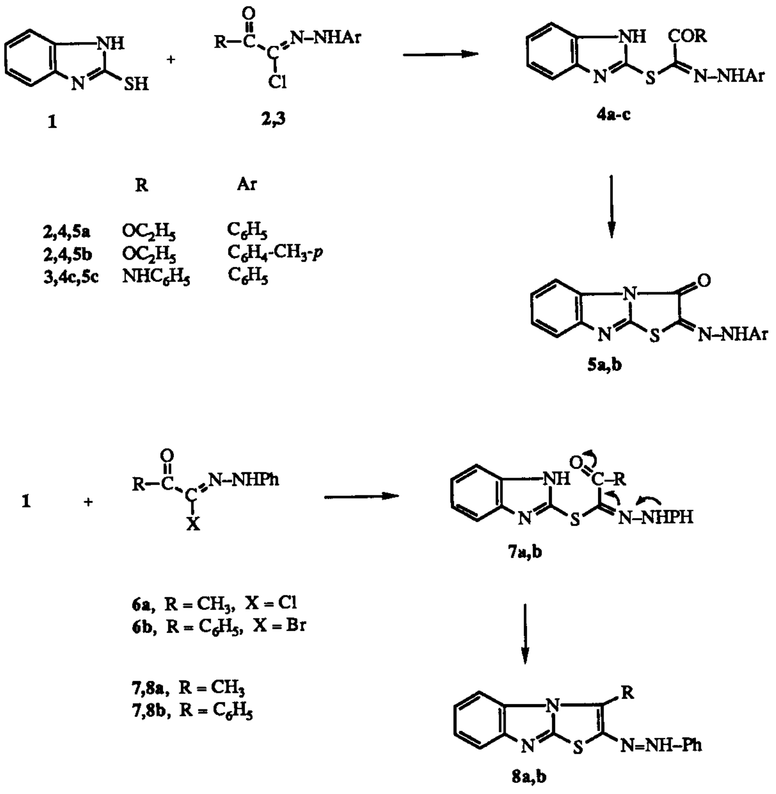
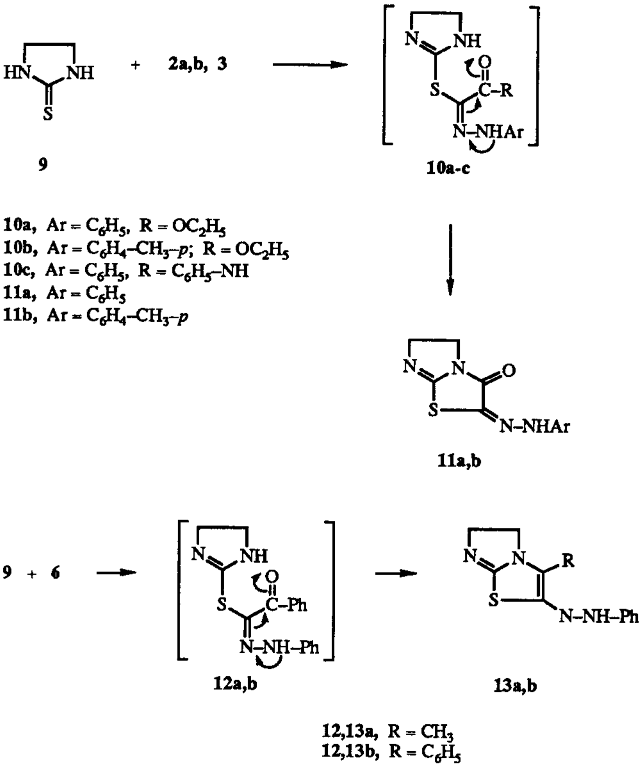


Chart 1

The cyclization of the intermediates **4a,b** was achieved or effected by treating the substrate (i) with hydrogen chloride in ethanol solution, (ii) *p*-toluenesulfonic acid in ethanol solution, (iii) thermal heating above melting point. Method (iii) yielded the best results. The cyclization of intermediates **7a,b** was achieved by refluxing the substrates with ethanol for 2 hours.

The cyclization products **5a,b** and **8a,b** were identified as 2-(arylhydrazono)thiazolo[3,2-*a*]benzimidazol-3-ones and 3-substituted 2-(arylazo)thiazolo[3,2-*a*]benzimidazoles, respectively, on the basis of their analytical and spectral data. The ir spectra of 5 revealed a CO bands at 1680 cm^{-1} and in the ^1H-nmr spectra the NH resonances are found in the 9.5-11.1 ppm region. The ir spectra of **8a,b** showed no CO and NH absorption bands.

Reaction of hydrazidoyl chlorides **2**, **3** or hydrazidoyl halide **6** with 2-mercapto-4,5-dihydroimidazole (**9**) in ethanolic triethylamine solution under reflux yielded the corresponding 2-(arylhydrazono)-5,6-dihydroimidazo[2,1-*b*]thiazol-3-ones **11** and 2-(arylazo)-5,6-dihydroimidazo[2,1-*b*]thiazole **13**, respectively, in good yields through the intermediates **10** and **12**. The structures of these products were elucidated by analytical and spectral data (*cf.* Chart 2).

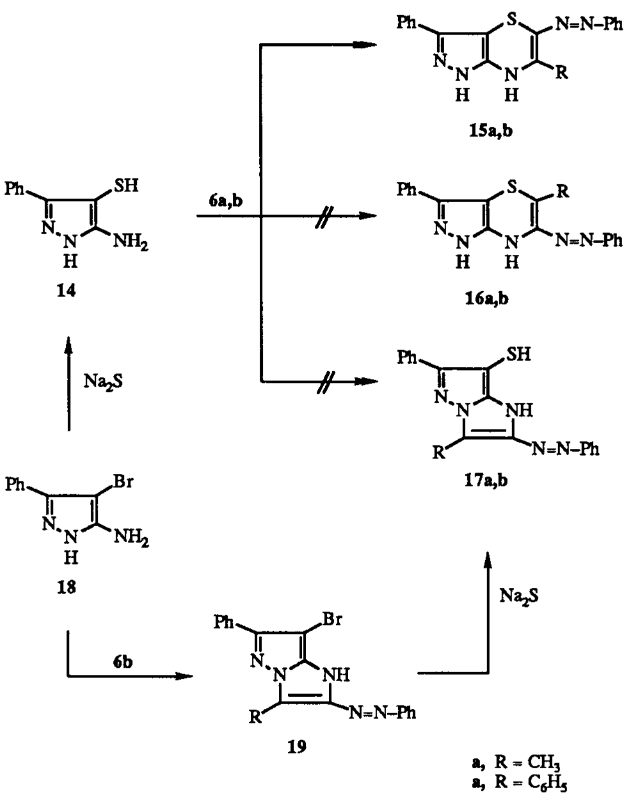


10a, Ar = C_6H_5, R = OC_2H_5
10b, Ar = C_6H_4-CH_3-*p*; R = OC_2H_5
10c, Ar = C_6H_5, R = C_6H_5-NH
11a, Ar = C_6H_5
11b, Ar = C_6H_4-CH_3-*p*

12,13a, R = CH_3
12,13b, R = C_6H_5

Chart 2

Reaction of hydrazidoyl halide **6** with 3-amino-4-mercapto-5-phenylpyrazole **14** in ethanol solution under reflux afforded a product which could be represented by one of the formulas **15-17**. Structure **17** could be easily ruled out by comparison with a sample prepared by the reaction of **6** with 3-amino-4-bromo-5-phenylpyrazole (**18**) followed by treatment with sodium sulfide. Structure **16** could be eliminated on the basis of the reaction of hydrazidoyl halide **6** with aminothiophenol (**9**). Compounds **15** were thus identified as 3-substituted-2-(arylazo)pyrazolo[4,3-*b*]thiazines on the basis of analytical and spectral data. The ir spectra lacked a CO-band between 1660-2000 cm^{-1} and revealed a band at 3280-3250 assigned to NH groups. The ^1H-nmr spectra revealed the NH resonances at 10.4-10.6 ppm region (*cf.* Chart 3). The tautomeric hydrazone structure of **15** was excluded based on the fact that the electronic absorption spectra of **15a,b** in chloroform showed a maximum in the 450-500 nm region [11].



a, R = CH_3
a, R = C_6H_5

Chart 3

EXPERIMENTAL

Melting points are uncorrected. The ir spectra were recorded with a Pye Unicam SP-1100 spectrophotometer. The ^1H-nmr spectra were obtained on a Varian 360-A spectrometer. Values are expressed relative to TMS as internal standard. The electronic absorption spectra were obtained in chloroform using Cary 17 and Cary 118 spectrophotometers. Elemental analyses were carried out by Microanalytical Centre of Cairo University, Giza, Egypt. The hydrazidoyl chlorides, **2**, **3**, **6a** were prepared by a standard procedure [16-21] through coupling of diazotized arylamines ethyl α-chloroacetoacetate, α-chloroacetoacetanilide and 3-chloro-2,4-pentanedione, respectively. Hydrazidoyl bromide **6b** was prepared by literature procedure [13] through coupling of *N*-nitrosoacetanilide with phenacyldimethylsulfonium bromide. 3-Amino-4-mercapto-5-phenylpyrazole [14] was prepared by a previously described method [22].

Reaction of Hydrazidoyl Halides **2a,b**, **3** and **6a,b** with 2-Mercaptobenzimidazole (**1**).

Equivalent amounts of a hydrazidoyl halides (0.005 mole), 2-mercaptobenzimidazole (0.75 g, 0.005 mole) and triethylamine (0.5 g, 0.005 mole) in ethanol were refluxed for 3 hours and then cooled. The precipitated solid was collected, washed with water and recrystallized from the proper solvent.

Ethyl 2-(2′-Mercaptobenzimidazolyl)-2-phenylhydrazonoglyoxalate (**4a**).

This compound was obtained as yellow crystals (dimethylformamide), (90%); mp 170°; ir: ν NH (3280), CO (1705) cm^{-1}; pmr: δ 1.3 (t, 3H, CH_3CH_2), 4.2 (q, 2H, CH_3CH_2), 7.0-8.1 (m, 9H, ArH's), 9.4 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{17}H_{16}N_4SO_2$: C, 59.98; H, 4.75; N, 16.45; S, 9.41. Found: C, 60.23; H, 4.92; N, 16.25; S, 9.23.

Ethyl 2-(2′-Mercaptobenzimidazolyl)-2-*p*-tolylhydrazonoglyoxalate (**4b**).

This compound was obtained as yellow crystals (dimethylformamide), (85%), mp 205°; ir: ν NH (3260), CO (1705) cm^{-1}; pmr: δ 1.3 (t, 3H, CH_3CH_2), 2.3 (s, 3H, $CH_3C_6H_4$), 4.2 (q, 2H, CH_3CH_2), 7.1-8.0 (m, 8H, ArH's), 9.3 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{18}H_{18}N_4SO_2$: C, 60.99; H, 5.11; N, 15.80; S, 9.04. Found: C, 61.11; H, 5.14; N, 15.45; S, 9.23.

2-(2′-Mercaptobenzimidazolyl-1-anilinoglyoxal-2-phenylhydrazone (**4c**).

This compound was obtained as yellow crystals (dimethylformamide), (95%), mp 230°; ir: ν NH (3250), CO (1680) cm^{-1}; pmr: δ 7.1-7.9 (m, 14H, ArH's), 9.5-9.7 (s, br, 3H, 3NH) ppm.

Anal. Calcd. for $C_{21}H_{17}N_5SO$: C, 65.09; H, 4.42; N, 18.07; S, 8.27. Found: C, 65.25; H, 4.52; N, 18.11; S, 8.35.

Methyl-2-(2′-mercaptobenzimidazolyl)-2-phenylhydrazonoglyoxal (**7a**).

The compound was obtained as yellow crystals (ethyl alcohol), (78%), mp 135°; ir: ν NH (3200), CO (1660) cm^{-1}; pmr: δ 2.5 (s, 3H, CH_3CO), 7.0-7.8 (m, 9H, ArH's), 10.2 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{16}H_{14}N_4SO$: C, 61.91; H, 4.54; N, 18.05; S, 10.33. Found: C, 61.78; H, 4.33; N, 18.22; S, 10.55.

Phenyl-2-(2′-mercaptobenzimidazolyl)-2-phenylhydrazonoglyoxal (**7b**).

This compound was obtained as yellow crystals (dimethylformamide), (75%), mp 220°; ir: ν NH (3150), CO (1650); pmr: δ 7.0-7.8 (m, 14H, ArH's), 10.1 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{21}H_{16}N_4SO$: C, 67.72; H, 4.33; N, 15.04; S, 8.60. Found: C, 67.87; H, 4.55; N, 10.22; S, 8.45.

2-Arylhydrazono-3-oxothiazolo[3,2-*a*]benzimidazoles **5a,b**.

(i) The open-chain precursors **4a,b** were dissolved in ethanol, which had been previously saturated with anhydrous hydrogen chloride. Alternatively (ii) an equimolecular amount of *p*-toluenesulfonic acid was added to the solution of starting compound. The ethanol solution was refluxed until cyclization was complete (tlc) (3 hours). Then the solvent was evaporated, the residue taken up with water and neutralized with sodium hydrogen carbonate solution. The solid was collected and crystallized from dimethylformamide yielding pure products **5a,b**.

(iii) Compounds **4a,b** (1 g) were heated in a test tube above the melting point for 5 minutes. The reaction mixture was boiled in ethanol (20 ml). The solid was collected and crystallized from dimethylformamide to afford **5a,b** which were found identical (mp, mixed mp and spectral data) with **5a,b** previously obtained.

2-Phenylhydrazono-3-oxothiazolo[3,2-*a*]benzimidazole (**5a**).

This compound was obtained as yellow crystals (dimethylformamide) (72%), mp 305°; ir: ν NH (3150), CO (1680) cm^{-1}; pmr: δ 7.1-7.8 (m, 9H, ArH's), 10.7 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{15}H_{10}N_4SO$: C, 61.21; H, 3.42; N, 19.03; S, 10.89. Found: C, 61.31; H, 3.48; N, 19.18; S, 10.55.

2-*p*-Tolylhydrazono-3-oxothiazolo[3,2-*a*]benzimidazole (**5b**).

This compound was obtained as yellow crystals (dimethylformamide), (80%), mp 297°; ir: ν NH (3150), CO (1670) cm^{-1}; pmr: δ 2.3 (s, 3H, $CH_3C_6H_4$-p); 7.1-7.9 (m, 8H, ArH's), 10.8 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{16}H_{12}N_4SO$: C, 62.30; H, 3.92; N, 18.16; S, 10.39. Found: C, 62.20; H, 3.82; N, 18.33; S, 10.45.

3-Substituted-2-phenylazothiazolo[3,2-*a*]benzimidazoles **8a,b**.

Compounds **7a,b** (1 g) were dissolved in ethanol (20 ml) which had been previously saturated with anhydrous hydrogen chloride and refluxed for 2 hours by which time cyclization was complete (tlc). The solid so formed after cooling was collected, washed with water and crystallized from the proper solvents.

2-Phenylazo-3-methylthiazo[3,2-*a*]benzimidazole (**8a**).

This compound was obtained as orange crystals (ethyl alcohol), 65%), mp and mixed mp [23] 180°; ir: ν C=N (1620), C=C (1600) cm^{-1}; pmr: δ 2.3 (s, 3H, CH_3), 7.0-7.9 (m, 9H, ArH's ppm.

Anal. Calcd. for $C_{16}H_{12}N_4S$: C, 65.73; H, 4.13; N, 19.16; S, 10.96. Found: C, 65.65; H, 4.27; N, 19.32; S, 10.85.

2-Phenylazo-3-phenylthiazolo[3,2-*a*]benzimidazole (**8b**).

This compound was obtained as orange crystals (dimethylformamide) (62%), mp >300°; ir: ν C=N (1620), C=C (1600) cm^{-1}; pmr: δ 7.1-7.8 (m, ArH's) ppm.

Anal. Calcd. for $C_{21}H_{14}N_4S$: C, 71.16; H, 3.98; N, 15.80; S, 9.04. Found: C, 71.31; H, 4.03; N, 15.75; S, 9.13.

Reaction of 2-Mercapto-4,5-dihydroimidazole (**9**) with Hydrazidoyl Halides.

Equimolar amounts of the appropriate hydrazidoyl halides **2**, **3** and **6** and 2-mercapto-4,5-dihydroimidazole **9** (0.005 mole) in ethanolic solution (20 ml) containing triethylamine (0.5 ml, 0.005 mole) were refluxed for 2 hours. The reaction mixture was evaporated under reduced pressure. The solid so formed was collected, washed with water and crystallized from the proper solvent.

2-Phenylhydrazono-3-oxo-5,6-dihydroimidazo[2,1-*b*]thiazole (**11a**).

This compound was obtained as yellow crystals (ethyl alcohol)

(75%); mp 220°; ir: ν NH (3200), CO (1675) cm^{-1}; pmr: δ 3.7 (s, br, 4H, $2CH_2$), 7.1-7.4 (m, 5H, ArH's), 10.6 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{11}H_{10}N_4SO$: C, 53.64; H, 4.09; N, 22.74; S, 13.01. Found: C, 53.75; H, 4.15; N, 22.55; S, 13.12.

2-*p*-Tolylhydrazono-3-oxo-5,6-dihydroimidazo[2,1-*b*]thiazole (**11b**).

This compound was obtained as yellow crystals; mp 160° (ethyl alcohol) (65%), mp 160°; ir: ν NH (3150), CO (1670); pmr: δ 2.3 (s, 3H, $CH_3C_6H_4$-*p*), 3.6 (s, br, 4H, $2CH_2$), 7.1-7.6 (m, 4H, ArH's), 10.4 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{12}H_{12}N_4SO$: C, 55.36; H, 4.64; N, 21.52; S, 12.31. Found: C, 55.42; H, 4.52; N, 21.57; S, 12.39.

2-(2'-Mercapto-4,5-dihydroimidazolyl)-1-anilinoglyoxal-2-phenylhydrazone (**10c**).

This compound was obtained as yellow crystals (dimethylformamide) (71%), mp 225°; ir: ν NH (3400), CO (1690) cm^{-1}; pmr: δ 3.6 (s, br, 4H, $2CH_2$), 7.1-7.6 (m, 10 H, ArH's), 9.6 (s, br, 3H, 3NH) ppm.

Anal. Calcd. for $C_{17}H_{17}N_5SO$: C, 60.15; H, 5.04; N, 20.63; S, 9.44. Found: C, 60.25; H, 5.12; N, 20.69; S, 9.54.

2-Phenylazo-3-methyl-4,5-dihydroimidazo[2,1-*b*]thiazole (**13a**).

This compound was obtained as orange crystals; mp >320° (acetic acid) (72%); ir: ν C=N (1620), C=C (1600) cm^{-1}; pmr: δ 2.4 (s, 3H, CH_3), 3.7 (s, br, 4H, $2CH_2$), 7.1-7.5 (m, 5H, ArH's) ppm.

Anal. Calcd. for $C_{12}H_{12}N_4S$: C, 58.99; H, 4.95; N, 22.94; S, 13.12. Found: C, 59.11; H, 4.87; N, 23.11; S, 13.18.

2-Phenylazo-3-phenyl-4,5-dihydroimidazo[2,1-*b*]thiazole (**13b**).

This compound was obtained as orange crystals, mp 195° (acetic acid) (60%); ir: ν C=N (1625), C=C (1600) cm^{-1}; pmr: δ 3.6 (s, br, 4H, $2CH_2$), 7.1-7.7 (m, 10 H, ArH's) ppm.

Anal. Calcd. for $C_{17}H_{14}N_4S$: C, 66.64; H, 4.60; N, 18.28; S, 10.46. Found: C, 66.71; H, 4.58; N, 18.35; S, 10.54.

Synthesis of Pyrazolo[3,4-*b*]thiazines **15a,b**.

A mixture of 3-amino-4-mercapto-5-phenylpyrazole (**14**) (1.9 g, 0.01 mole) and the appropriate hydrazidoyl halides **6a,b** (0.005 mole) in ethanol (25 ml) was refluxed for 2 hours. The reaction mixture was cooled, washed with water and crystallized from dimethylformamide.

2-Phenylazo-3-methyl-7-phenylpyrazolo[4,3-*a*]thiazine (**15a**).

This compound was obtained as red crystals, mp 205° (dimethylformamide) (82%); ir: ν NH (3200), C=N (1620), C=C (1600); pmr: δ 2.5 (s, 3H, CH_3), 7.1-7.8 (m, 10 H, ArH's), 10.4 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{18}H_{15}N_5S$: C, 64.84; H, 4.53; N, 21.00; S, 9.61. Found: C, 64.75; H, 4.61; N, 20.92; S, 9.33.

2-Phenylazo-3,7-diphenylpyrazolo[4,3-*a*]thiazine (**15b**).

This compound was obtained as red crystals, mp 210° (dimethylformamide) (85%); ir: ν NH (3150), C=N (1620), C=C (1600) cm^{-1}; pmr: δ 7.1-7.7 (m, 15H, ArH's), 10.6 (s, br, 2H, 2NH) ppm.

Anal. Calcd. for $C_{23}H_{17}N_5S$: C, 69.85; H, 4.37; N, 17.70; S, 8.10. Found: C, 70.11; H, 4.42; N, 17.62; S, 8.17.

Synthesis of 1*H*-Pyrazolo[1,5-*b*]imidazole Derivative **19**.

Equivalent amounts of 3-amino-4-bromo-5-phenylpyrazole (**18**) and hydrazidoyl bromide **6b** were refluxed in ethanol for 3 hours and then cooled. The crude red coloured product was collected and crystallized from dimethylformamide.

2-Phenylazo-3,5-diphenyl-6-bromoimidazo[1,2-*b*]pyrazole (**19**).

This compound was obtained as red crystals (dimethylformamide) (55%), mp 226°; ir: ν NH (3200), C=N (1620), C=C (1600) cm^{-1}; pmr: δ 7.1-7.6 (m, 15H, ArH's), 10.4 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{23}H_{16}BrN_5S$: C, 58.23; H, 3.40; N, 14.76; S, 6.75. Found: C, 58.42; H, 3.31; N, 14.52; S, 6.61.

Synthesis of **17b**.

The method described for the preparation of 3-amino-4-mercapto-5-phenylpyrazole (**14**) was followed [22]. The product was isolated and crystallized from ethanol.

2-Phenylazo-3,5-diphenyl-6-mercaptoimidazo[1,2-*b*]pyrazole (**17b**).

This compound was obtained as brown crystals, (ethyl alcohol), (75%), mp 218°; ir: ν NH (3150), SH (2600), C=N (1620), C=C (1600) cm^{-1}; pmr: δ 7.1-7.7 (m, 15H, ArH's), 12.2 (s, 1H, H-5), 10.4 (s, br, 1H, NH) ppm.

Anal. Calcd. for $C_{23}H_{17}N_5S$: C, 69.85; H, 4.37; N, 17.70; S, 8.10. Found: C, 69.61; H, 4.21; N, 17.51; S, 8.21.

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