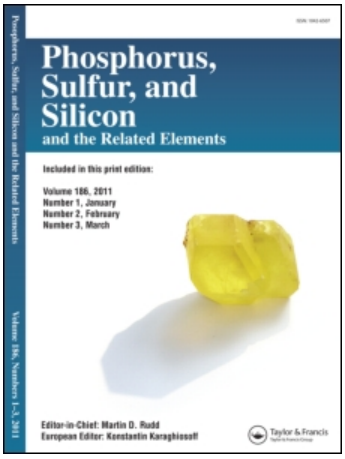

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

SYNTHESIS OF AZOLES, AZINES AND AZOLOAZINES: A VERSATILE APPROACH

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To cite this Article Ram, Vishnu J. and Nath, Mahendra(1995) 'SYNTHESIS OF AZOLES, AZINES AND AZOLOAZINES: A VERSATILE APPROACH', Phosphorus, Sulfur, and Silicon and the Related Elements, 105: 1, 11 — 15
To link to this Article: DOI: 10.1080/10426509508042040
URL: http://dx.doi.org/10.1080/10426509508042040

Phosphorus, Sulfur, and Silicon, 1995, Vol. 105, pp. 11–15
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SYNTHESIS OF AZOLES, AZINES AND AZOLOAZINES: A VERSATILE APPROACH†

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(Received February 15, 1995; in final form March 20, 1995)

A novel procedure for the synthesis of heterocycles 5, 7 have been developed from the acid catalysed condensation-cyclization of benzylidene and benzylmalononitriles with thiosemicarbazide. Base catalysed cyclization of 2 with dicyandiamide led to the formation of pyrimidine 3. Reaction of 5 and 7 with phenacyl bromide separately afforded 6 and 8 while interaction of 7 with ethyl acetoacetate gave a mixture of 9 and 10.

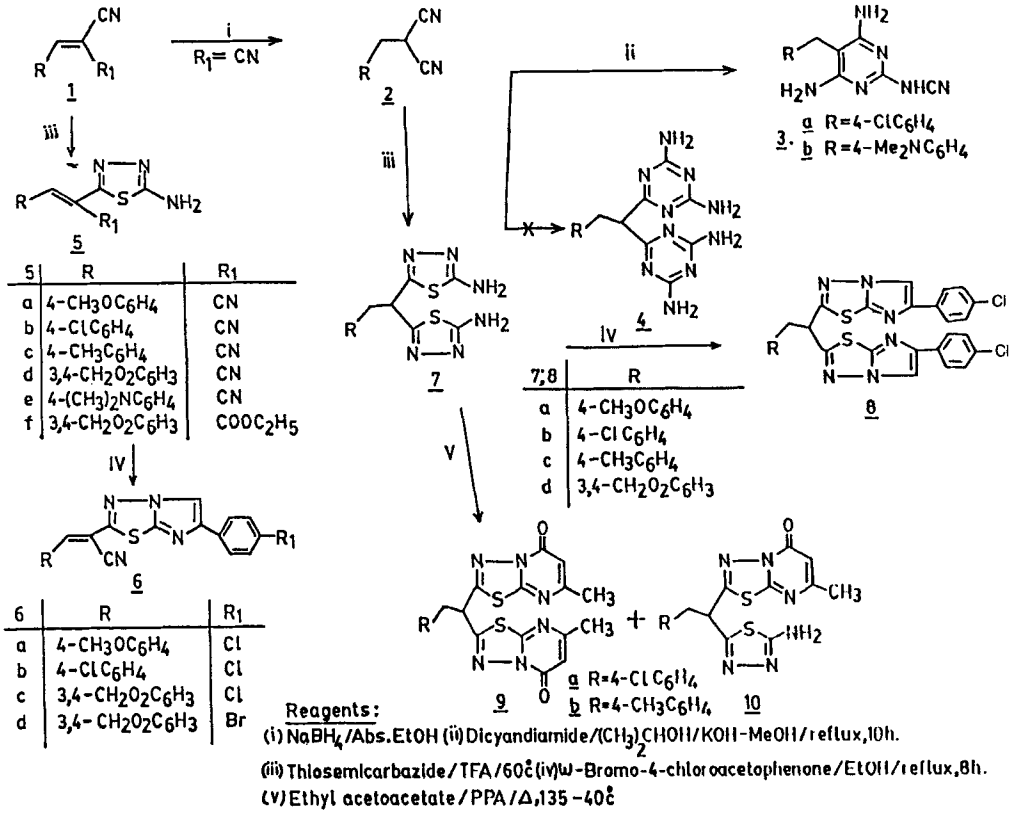
Key words: Benzylmalononitrile, 1,3,4-thiadiazolylacrylonitriles, 1,3,4-thiadiazolylacrylates, bis(1,3,4-thiadiazolyl)ethanes, bis[1,3,4-thiadiazolo[3,2-*a*]pyrimidinyl]ethanes, cyanoaminopyrimidines.

The therapeutic importance of properly substituted azoles, bis azoles, azines and bis azoloazines as antifungal,[1] amaebicidal,[2] antiviral,[3] antitumor,[4] antiinflammatory,[5] antiparasitic[6] and antiallergic[7] agents aroused considerable interest to develop novel routes for the synthesis of pharmacologically active heterocycles and drug intermediates from easily accessible precursors.

Benzylidene- and benzylmalononitriles have been previously used for the synthesis of pyrazoles,[8] isoxazoles,[9] pyrimidines[10,11] and various polynuclear heterocycles[12] but so far none had employed them as synthon for the synthesis of (thiadiazol-2-yl)acrylonitriles/acrylates (5a–f), bis(thiadiazol-2-yl)ethanes (7a–d) and cyanoaminopyrimidines (3a,b). The various syntheses of 2-amino-5-substituted-1,3,4-thiadiazoles are reported by acid catalysed cyclization of aroylthiosemicarbazides,[13,14] arylthiosemicarbazide[15] or direct condensation-cyclization of carboxylic acid or carbonitrile with thiosemicarbazide.[7,16]

In view of our continued interest in the chemistry of malononitrile,[17] benzylidene- and benzylmalononitriles have been used as synthon in the present study for the synthesis of various 2-(5-amino-1,3,4-thiadiazol-2-yl)-3-arylacrylonitriles (5a–e), acrylate (5f) and 2-aryl-1-bis(5-amino-1,3,4-thiadiazol-2-yl)ethanes (7a–d) by TFA catalysed cyclization with thiosemicarbazide (Scheme I). Attempts to synthesize 1-bis(5-amino-1,3,4-thiadiazol-2-yl)-2-aryl ethenes from the reaction of 1 with thiosemicarbazide failed and always 5a–f were isolated because of a nitrile group participation in resonance with the ring. Benzylmalononitriles under similar reaction conditions always afforded 2-aryl-1-bis(5-amino-1,3,4-thiadiazol-2-yl)ethanes (7a–d). Analogous reactions of 1 and 2 with thiocarbohydrazide, semicarbazide and aminoguanidine separately in lieu of thiosemicarbazide failed to yield corresponding 2-hydrazino-1,3,4-thiadiazoles, 2-amino-1,3,4-oxadiazoles and 2-amino-

†CDRI Communication No. 5275.



SCHEME I

1,3,4-triazoles, but always either a mixture of parent compound and dicarboxylic acid, obtained from the acid hydrolysis of nitrile was isolated.

Reaction of 5 and 7 with phenacyl bromide led to the synthesis of 3-aryl-2-[6-(4-haloaryl)imidazo[2,1-*b*]-1,3,4-thiadiazol-2-yl]acrylonitriles (6a–d) and 2-aryl-1-bis[6-(4-chlorophenyl)imidazo[2,1-*b*]-1,3,4-thiadiazol-2-yl]ethanes (8a,b). The condensation-cyclization of 7 with ethyl acetoacetate in polyphosphoric acid afforded a mixture of 2-aryl-1-bis[7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl]ethanes (9a,b) and 2-aryl-1-(5-amino-1,3,4-thiadiazol-2-yl)-1-(7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-*a*]pyrimidin-2-yl)ethanes (10a,b). Base catalysed cyclization of 2 with dicyandiamide always provided 5-benzyl-2-cyanoamino-4,6-diaminopyrimidines 3 instead of anticipated 2-aryl-1-bis[2,4-diamino-1,3,5-triazin-6-yl)ethanes (4), and provided a new avenue for an easy synthesis of cyanoaminopyrimidines (3) not reported so far (Scheme I).

EXPERIMENTAL

The melting points were obtained on an electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were obtained on Perkin-Elmer (90 MHz), EM-360 (60 MHz) and Bruker WM (400 MHz) spectrometer with TMS as internal standard. The IR spectra were recorded on a Perkin-Elmer Ac-1 spectrometer

in KBr. Mass spectra were obtained with a Jeol JMS D-300 spectrometer. The elemental analyses were performed at Regional Sophisticated Instrumentation Centre, CDRI, Lucknow.

5-(4-Chlorobenzyl)-2-cyanoamino-4,6-diaminopyrimidine 3a: To a mixture of 4-chlorobenzylmalononitrile (0.19 g, 1 mmol) and dicyandiamide (0.168 g, 2 mmol) in isopropanol (5 ml), was added a solution of KOH (0.056 g, 1 mmol) in methanol (2 ml). The reaction mixture was refluxed for 8 h. The solvent was evaporated and residue was treated with water. The solid obtained was filtered and crystallized from DMSO-water, yield 0.16 g (58%), m.p. >280°C. IR: ν 2130 (CN), 3120 (NH), 3380 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.72 (s, 2H), 5.46 (brs, 4H), 7.38 (s, 4H). MS: m/z (%) 274 (2.7, M^+). Anal. calcd. for $C_{12}H_{11}ClN_6$: C, 52.46; H, 4.04; N, 30.59. Found: C, 52.25; H, 3.96; N, 30.25.

2-Cyanoamino-4,6-diamino-5-(4-dimethylaminobenzyl)pyrimidine 3b: Yield 48%, m.p. >280°C. IR: ν 2150 (CN), 3150 (NH), 3360 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.80 (s, 6H), 3.58 (s, 2H), 6.36 (brs, 4H), 6.64 (d, 2H), 7.0 (d, 2H), 10.65 (br, 1H). MS: m/z (%) 283 (61.5, M^+). Anal. calcd. for $C_{14}H_{17}N_7$: C, 59.35; H, 6.05; N, 34.61. Found: C, 58.95; H, 6.02; N, 34.12.

2-(5-Amino-1,3,4-thiadiazol-2-yl)-3-(4-methoxyphenyl)acrylonitrile 5a: A mixture of 4-methoxybenzylidenemalononitrile (0.184 g, 1 mmol) and thiosemicarbazide (0.136 g, 1.5 mmol) in trifluoroacetic acid (2 ml) was stirred at 80°C. After 8 h, the reaction mixture was cooled and poured into ice cold water. The precipitate, obtained after neutralizing with aqueous ammonia was filtered and crystallized from methanol, yield 0.15 g (57%), m.p. 225°C. IR: ν 2200 (CN), 3440 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.65 (s, 3H), 6.70 (d, 2H), 7.31 (s, 1H), 7.52 (d, 2H). MS: m/z (%) 258 (44.3, M^+). Anal. calcd. for $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69. Found: C, 55.62; H, 3.79; N, 21.72.

2-(5-Amino-1,3,4-thiadiazol-2-yl)-3-(4-chlorophenyl)acrylonitrile 5b: Yield 42%, m.p. 262°C. IR: ν 2200 (CN), 3400 (NH_2) cm^{-1}. ^1H NMR (TFA-d): δ 7.25 (d, 2H), 7.55 (s, 1H), 7.68 (d, 2H), 9.38 (brs, 2H). MS: m/z (%) 262 (26.6, M^+). Anal. calcd. for $C_{11}H_7ClN_4S$: C, 50.29; H, 2.69; N, 21.33. Found: C, 49.89; H, 2.46; N, 21.19.

2-(5-Amino-1,3,4-thiadiazol-2-yl)-3-(4-methylphenyl)acrylonitrile 5c: Yield 58%, m.p. 240°C. IR: ν 2200 (CN), 3400 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H), 7.26 (d, 2H), 7.76 (s, 1H), 7.82 (d, 2H). MS: m/z (%) 242 (100, M^+). Anal. calcd. for $C_{12}H_{10}N_4S$: C, 59.48; H, 4.16; N, 23.12. Found: C, 59.56; H, 4.21; N, 22.86.

2-(5-Amino-[1,3,4]thiadiazol-2-yl)-3-benzo[1,3]dioxol-5-yl-acrylonitrile 5d: Yield 53%, m.p. 207°C. IR: ν 2220 (CN), 3380 (NH_2) cm^{-1}. ^1H NMR (TFA-d): δ 5.80 (s, 2H), 6.72 (s, 1H), 7.06 (d, 1H), 7.35 (d, 1H), 7.52 (s, 1H). MS: m/z (%) 272 (100, M^+). Anal. calcd. for $C_{12}H_8N_4O_2S$: C, 52.93; H, 2.96; N, 20.58. Found: C, 52.74; H, 2.89; N, 20.39.

2-(5-Amino-1,3,4-thiadiazol-2-yl)-3-(4-dimethylaminophenyl)acrylonitrile 5e: Yield 42%, m.p. 250°C. IR: ν 2200 (CN), 3360 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.0 (s, 6H), 6.76 (d, 2H), 7.49 (s, 1H), 7.82 (d, 2H). MS: m/z (%) 271 (100, M^+). Anal. calcd. for $C_{13}H_{13}N_5S$: C, 57.55; H, 4.83; N, 25.82. Found: C, 57.72; H, 4.99; N, 25.98.

Ethyl 2-(5-amino-[1,3,4]thiadiazol-2-yl)-3-benzo[1,3]dioxol-5-yl-acrylate 5f: Prepared from ethyl 2-cyano-3-(3,4-methylenedioxyphenyl)propenoate (0.245 g, 1 mmol) and thiosemicarbazide (0.136 g, 1.5 mmol) in TFA (3 ml) and purified on silica gel column using $CHCl_3$: MeOH (50:1) as eluent, yield 0.134 g (41.4%), m.p. 94°C. IR: ν 1710 (CO), 3370 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.50 (t, 3H), 4.45 (q, 2H), 6.15 (s, 2H), 7.00 (s, 1H), 7.30 (d, 1H), 7.82 (d, 1H), 8.15 (s, 1H). MS: m/z (%) 319 (5.1, M^+). Anal. calcd. for $C_{14}H_{13}N_3O_4S$: C, 52.66; H, 4.10; N, 13.16. Found: C, 52.47; H, 4.33; N, 13.35.

2-[6-(4-Chlorophenyl)imidazo[2,1-b]-1,3,4-thiadiazol-2-yl]-3-(4-methoxyphenyl)acrylonitrile 6a: A mixture of 5a (0.26 g, 1 mmol) and ω-bromo-4-chloroacetophenone (0.23 g, 1 mmol) in ethanol (10 ml) was refluxed for 8 h. The solid, obtained after cooling the reaction mixture, was filtered and crystallized from DMSO, yield 0.29 g (72%), m.p. 240°C. IR: ν 2200 (CN) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.88 (s, 3H), 7.06 (d, 2H), 7.35 (d, 2H), 7.82 (d, 2H), 7.98 (s, 2H), 8.05 (d, 2H). MS: m/z (%) 392 (100, M^+). Anal. calcd. for $C_{20}H_{13}ClN_4OS$: C, 61.15; H, 3.34; N, 14.26. Found: C, 60.92; H, 3.13; N, 13.95.

2-[6-(4-Chlorophenyl)imidazo[2,1-b]-1,3,4-thiadiazol-2-yl]-3-(4-chlorophenyl)acrylonitrile 6b: Yield 48%, m.p. 232°C. IR: ν 2200 (CN) cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.42 (d, 2H), 7.54 (d, 2H), 7.78 (d, 2H), 7.80

(s, 1H), 7.95 (d, 2H), 8.08 (s, 1H). MS: m/z (%) 397 (13.1, M^+). Anal. calcd. for $C_{19}H_{10}Cl_2N_4S$: C, 57.44; H, 2.54; N, 14.10. Found: C, 57.09; H, 2.32; N, 13.85.

3-Benzo[1,3]dioxol-5-yl-2-[6-(4-chlorophenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-acrylonitrile 6c: Yield 46%, m.p. 262°C. IR: ν 2210 (CN) cm^{-1}. ^1H NMR (TFA-d): δ 5.82 (s, 2H), 6.71 (d, 2H), 7.10–7.38 (m, 3H), 7.50 (s, 1H), 7.92 (d, 2H), 9.58 (s, 1H). MS: m/z (%) 406 (55.7, M^+). Anal. calcd. for $C_{20}H_{11}ClN_4O_2S$: C, 59.05; H, 2.73; N, 13.77. Found: C, 58.79; H, 2.86; N, 13.96.

3-Benzo[1,3]dioxol-5-yl-2-[6-(4-bromophenyl)-imidazo[2,1-b][1,3,4]thiadiazol-2-yl]-acrylonitrile 6d: Yield 42%, m.p. 264°C. IR: ν 2220 (CN) cm^{-1}. ^1H NMR ($CDCl_3$ + DMSO-d_6): δ 6.2 (s, 2H), 7.06 (d, 1H), 7.55 (d, 2H), 7.62 (d, 1H), 7.74 (s, 1H), 7.82 (d, 2H), 8.05 (s, 1H), 8.12 (s, 1H). MS: m/z (%) 451 (25.6, M^+). Anal. calcd. for $C_{20}H_{11}BrN_4O_2S$: C, 53.22; H, 2.46; N, 12.42. Found: C, 52.88; H, 2.29; N, 12.09.

1-Bis(5-amino-1,3,4-thiadiazol-2-yl)-2-(4-methoxyphenyl)ethane 7a: A mixture of 4-methoxybenzylmalononitrile (0.93 g, 5 mmol) and thiosemicarbazide (2.04 g, 15 mmol) in trifluoroacetic acid (8 ml) was heated at 60°C for 6 h. The reaction mixture was cooled, poured into ice water and neutralized with aqueous ammonia. The solid obtained was filtered and crystallized from DMSO-water, yield 0.67 g (40%), m.p. 233°C. IR: ν 3400 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.26 (d, 2H), 3.62 (s, 3H), 4.82 (t, 1H), 6.72 (d, 2H), 6.90 (d, 2H), 7.10 (brs, 4H). MS: m/z (%) 334 (9.8, M^+). Anal. calcd. for $C_{13}H_{14}N_6OS_2$: C, 46.69; H, 4.22; N, 25.13. Found: C, 46.49; H, 4.38; N, 24.89.

1-Bis(5-amino-1,3,4-thiadiazol-2-yl)-2-(4-chlorophenyl)ethane 7b: Yield 48%, m.p. 252°C. IR: ν 3420 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.32 (d, 2H), 4.91 (t, 1H), 6.90–7.15 (m, 4H), 7.26 (s, 4H). MS: m/z (%) 338 (11.6, M^+). Anal. calcd. for $C_{12}H_{11}ClN_6S_2$: C, 42.54; H, 3.27; N, 24.81. Found: C, 42.46; H, 3.49; N, 24.45.

1-Bis(5-amino-1,3,4-thiadiazol-2-yl)-2-(4-methylphenyl)ethane 7c: Yield 42%, m.p. 252°C. IR: ν 3400 (NH_2) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.21 (s, 3H), 3.32 (d, 2H), 4.88 (t, 1H), 7.06 (s, 8H). MS: m/z (%) 318 (27.7, M^+). Anal. calcd. for $C_{13}H_{14}N_6S_2$: C, 49.03; H, 4.43; N, 26.39. Found: C, 48.74; H, 4.33; N, 26.28.

1-Bis(5-amino-[1,3,4]thiadiazol-2-yl)-2-benzo[1,3]dioxol-5-yl-ethane 7d: Yield 43%, m.p. 245°C. IR: ν 3410 (NH_2) cm^{-1}. ^1H NMR (TFA-d): δ 3.22 (d, 2H), 4.78 (t, 1H), 5.75 (s, 2H), 6.41–6.69 (m, 3H), 8.02 (brs, 4H). MS: m/z (%) 348 (45.5, M^+). Anal. calcd. for $C_{13}H_{12}N_6O_2S_2$: C, 44.81; H, 3.47; N, 24.12. Found: C, 44.89; H, 3.09; N, 24.37.

1-Bis[6-(4-chlorophenyl)imidazo[2,1-b]-1,3,4-thiadiazol-2-yl]-2-(4-methoxyphenyl)ethane 8a: Prepared from 7a (0.334 g, 1 mmol) and ω-bromo-4-chloroacetophenone (0.46 g, 2 mmol) in EtOH (10 ml) and crystallized from acetone, yield 0.21 g (34%), m.p. 105°C. ^1H NMR ($CDCl_3$): δ 3.61 (d, 2H), 3.78 (s, 3H), 4.94 (t, 1H), 6.82 (d, 2H), 7.14 (d, 2H), 7.38 (d, 4H), 7.75 (d, 4H), 8.0 (s, 2H). MS: m/z (%) 603 (80, M^+). Anal. calcd. for $C_{29}H_{20}Cl_2N_6OS_2$: C, 57.71; H, 3.34; N, 13.93. Found: C, 57.52; H, 3.47; N, 13.78.

1-Bis[6-(4-chlorophenyl)imidazo[2,1-b]-1,3,4-thiadiazol-2-yl]-2-(4-chlorophenyl)ethane 8b: Yield 38%, m.p. 160°C. ^1H NMR ($CDCl_3$): δ 3.68 (d, 2H), 5.50 (t, 1H), 7.26 (d, 2H), 7.32 (d, 2H), 7.38 (d, 4H), 7.82 (d, 4H), 8.38 (s, 2H). MS: m/z (%) 607 (58, M^+). Anal. calcd. for $C_{28}H_{17}Cl_3N_6S_2$: C, 55.32; H, 2.82; N, 13.83. Found: C, 54.91; H, 2.63; N, 13.94.

1-Bis(7-methyl-5-oxo-1,3,4-thiadiazolo[3,2-a]pyrimidin-2-yl)-2-(4-chlorophenyl)ethane 9a: A suspension of 7b (3.38 g, 10 mmol) and ethyl acetoacetate (2.6 g, 20 mmol) in polyphosphoric acid was heated at 135–40°C for 1 h, cooled and poured into ice water. The precipitate obtained was filtered as a mixture of 9a and 10a. The mixture obtained was separated on silica gel column by using 1% methanol in chloroform as eluent.

9a: Yield (33%), m.p. 170°C. IR: ν 1675 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.36 (s, 6H), 3.68 (d, 2H), 5.26 (t, 1H), 6.26 (s, 2H), 7.19 (s, 4H). MS: m/z (%) 470 (10.6, M^+). Anal. calcd. for $C_{20}H_{15}ClN_6O_2S_2$: C, 51.01; H, 3.21; N, 17.85. Found: C, 51.32; H, 2.99; N, 17.70.

10a: Yield 19%, m.p. 120°C. IR: ν 1665 (CO) 3380 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.38 (s, 3H), 3.56 (d, 2H), 5.03 (t, 1H), 5.78 (brs, 2H), 6.31 (s, 1H), 7.12 (d, 2H), 7.26 (d, 2H). MS: m/z (%) 404 (21.2, M^+). Anal. calcd. for $C_{16}H_{13}ClN_6OS_2$: C, 47.46; H, 3.24; N, 20.76. Found: C, 47.29; H, 3.15; N, 20.82.

9b: Yield 34%, m.p. 155°C. IR: ν 1675 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.32 (s, 3H), 2.38 (s, 6H), 3.65 (d, 2H), 5.15 (t, 1H), 6.32 (s, 2H), 7.12 (s, 4H). MS: m/z (%) 450 (10, M^+). Anal. calcd. for $C_{21}H_{18}N_6O_2S_2$: C, 55.98; H, 4.03; N, 18.66. Found: C, 55.74; H, 4.11; N, 18.70.

10b: Yield 15%, m.p. 142°C. IR: ν 1675 (CO), 3360 (NH_2) cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.28 (s, 3H), 2.36 (s, 3H), 3.53 (d, 2H), 5.03 (t, 1H), 5.64 (brs, 2H), 6.29 (s, 1H), 7.06 (s, 4H). MS: m/z (%) 384 (10, M^+). Anal. calcd. for $C_{17}H_{16}N_6OS_2$: C, 53.10; H, 4.19; N, 21.86. Found: C, 53.33; H, 4.02; N, 21.72.

ACKNOWLEDGEMENT

Authors are thankful to ICMR for financial assistance and RSIC at CDRI, Lucknow for providing spectroscopic data and elemental analyses.

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