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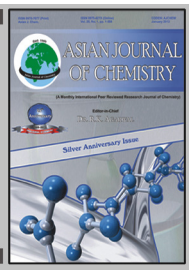

Synthesis of New 1,3,4-Thiadiazole Derivatives Containing of Morpholine Ring

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The synthesis of new of 1,3,4-thiadiazole derivatives containing of morpholine ring are investigated. In this study, the derivatives of naphthol, amine and phenol are reacted with 4-morpholine carbonyl chloride. Then, prepared solutions are added to diazotized 2-amino-5-mercapto-1,3,4-thiadiazole to give 2-amino-5-mercapto-1,3,4-thiadiazole products. These dyes were characterized by elemental analysis and spectral analyses (IR, ^{1}H NMR, ^{13}C NMR and mass spectra).

Key Words: 1,3,4-Thiadiazole, Azo dyes, Sulfur, Synthesis, Morpholine.

INTRODUCTION

Recently, synthesis of thiadiazoles has attracted widespread attention due to their diverse applications as antibacterial, antimycobacterial, antimycotic, antifungal and antimicrobial effects[1-4].

Heterocyclic azo dyes are extensively used for textile or non-textile applications including their application in reprography, functional dye and non-linear optical systems, photodynamic therapy and lasers. Azo dyes containing heterocyclic rings lead to brighter and often deeper shades than their benzene analogues and they are still very important for applications such as disperse dyes for polyester fibers[5-7].

Dyes derived from 2-amino-5-mercapto-1,3,4-thiadiazole are of technical interest for the production of brilliant red shades. Comparatively less research work has been done regarding this class compared to the other categories of dyes derived from five-membered sulphur-containing heterocycles. In addition, the level of recent patent activity has been low, although papers focusing exclusively on dyes derived from 1,3,4-thiadiazole have appeared.

As no report seems to be available in the literature on the use of 2-amino-1,3,4-thiadiazole and morpholine in the synthesis of new 1,3,4-thiadiazole derivatives by coupling with naphthol, amine and phenol. Herein, we wish to report synthesis of some new 2-amino-5-mercapto-1,3,4-thiadiazole products.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. IR spectra were recorded with the MATTSON 1000 FT-IR Spectrophotometer. Nuclear magnetic resonance spectra were recorded on the BRUKER 400 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra were obtained by SHIMADZU QP 1100EX. Elemental analyses were performed by Heracus CHN-O-Rapid analyzer. UV spectra were recorded using a GBC scientific equipment (CINTRA 5) UV visible spectrometer.

2-Amino-5-mercapto-1,3,5-thiadiazole (0.01 mol) was added to 2.5 % sodium carbonate solution (35 mL) until it was dissolved by boiling. The solution was then cooled and sodium nitrite (0.01 mol) was added, with stirring, until it was dissolved. The solution was cooled by placing it in an ice bath and then concentrated hydrochloric acid (3 mL) and water (5 mL) were added. By acidifying the solution, a powdery yellow precipitate of the diazonium salt was separated.

Appropriate aromatic compounds (**2**) (0.01 mol) was added to morpholine carbonyl chloride (0.01 mol) and was refluxed for 20 min on the water bath. The residue was mixed with water (15 mL) to give yellow solution. The solution was added to suspension of 1,3,4-thiadiazole diazonum salt and a powdery precipitate was separated after 1 h. The crud product was recrystallized from appropriate solvent.

***N*^{4}-{4-[2-(5-Sulfanyl-1,3,4-thiadiazol-2-yl)-1-diazenyl] phenyl}-4-morpholine carboxamide (4a):** Recrystallization in 2-propanol. Yellow powder. m.p. 135-136 ºC. IR (KBr, ν_{max}, cm^{-1}): 3266, 1635. ^{1}H NMR (400 MHz, DMSO-d_6): 3.49 (t, J = 4.8, 4H, 2CH$_2$); 3.60 (t, J = 4.6, 4H, 2CH$_2$); 6.92 (s, 1H, NH); 7.22 (d, J = 8.0, 2H, ArH); 7.44 (d, J = 7.6, 2H, ArH); 8.54 (s, 1H, NH). ^{13}CNMR (400 MHz, DMSO-d_6): 44.65, 66.48, 118.46, 120.13, 128.75, 129.21, 140.85, 155.68 ppm. $C_{13}H_{14}N_6O_2S_2$ calcd: C 44.57, H 4.00, N 24.00; found: C 44.66,

H 3.81, N 23.80. MS *m/z*: 203 (70 %), 114 (86 %), 86 (46 %), 76 (31 %), 70 (100 %).

***N*[4]-{3-Nitro-4-[2-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1-diazenyl] phenyl}-4-morpholine carboxamide (4b):** Recrystallization in DMF and water (4:1). Yellow powder. m.p: 163-164 ºC. IR (KBr, ν_{max}, cm^{-1}): 3280, 1663, 1530, 1349. ^{1}H NMR (400 MHz, DMSO-d_6): 2.88 (t, *J* = 4.8, 4H, $2CH_2$); 3.35 (t, *J* = 4.6, 4H, $2CH_2$); 7.69-8.13 (m, 5H, ArH and 2NH). ^{13}C NMR (400 MHz, DMSO-d_6): ppm. 45.78, 67.91, 115.21, 124.64, 128.12, 134,97, 138.37, 141.83, 146.47, 152.33, 159.71. $C_{13}H_{13}N_7O_4S_2$ calcd.: C 39.49, H 3.29, N 24.81; found: C 39.57, H 3.11, N 24.96. MS *m/z*: 149 (60 %), 121 (100 %), 112 (49 %), 90 (68 %), 75 (98 %).

3-Hydroxy-4-[2-(5-sulfanyl-1,3,4-thiadiazol-2-yl)-1-diazenyl]phenyl}-4-morpholine carboxylate (4c): Recrystallization in 2-propanol. Orange powder. m.p.: 89-90 ºC. IR (KBr, ν_{max}, cm^{-1}): 3267, 3101, 1696. ^{1}H NMR (400 MHz, DMSO-d_6): 3.39 (t, *J* = 4.8, 4H, $2CH_2$); 3.62 (t, *J* = 4.7, 4H, $2CH_2$); 6.47-7.83 (m, 5H, ArH, 2NH); 9.29 (s, 1H, OH). ^{13}CNMR (400 MHz, DMSO-d_6): 43.33, 63.63, 103.77, 109.52, 112.82, 129.99, 137.7, 152.44, 158.62, 159.99, 169.64. ppm. $C_{13}H_{13}N_5O_4S_2$ calcd.: C 42.51, H 3.54, N 19.07; found: C 42.33, H 3.61, N 19.24. MS *m/z*: 149 (11 %), 114 (26 %), 84 (20 %), 58 (42 %), 42 (100 %).

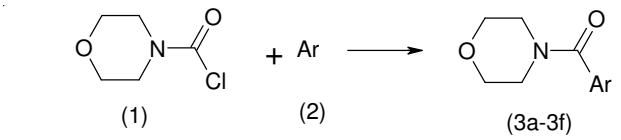
4-[2-(5-Sulfanyl-1,3,4-thiadiazol-2-yl)-1-diazenyl]-1-naphthyl-4-morpholine carboxylate (4d): Recrystallization in 2-propanol. Red powder. m.p: 52-53 ºC. IR (KBr, ν_{max}, cm^{-1}): 3055, 2358, 1697. ^{1}H NMR (400 MHz, DMSO-d_6): 3.36 (t, *J* = 4.8, 4H, $2CH_2$); 3.66 (t, *J* = 4.6, 4H, $2CH_2$); 7.06-7.94 (m, 7H, Ar, NH); 9.74 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 43.20, 63.69, 118.83, 119.06, 122.35, 124.07, 126.03, 127.87, 128.17, 129.73, 133.78, 135.06, 149.25, 155.77, 162.78 ppm. $C_{17}H_{15}N_5O_3S_2$ calcd: C 50.87, H 3.74, N 17.46; found: C 50.58, H 3.59, N 17.33. MS *m/z*: 256 (30 %), 144 (100 %), 114 (76 %), 70 (19 %).

3-Hydroxy-4-[(morpholinocarbonyl)amino]-2-[(5-sulfanyl-1-diazenyl]-1-naphthalene sulfonic acid (4e): Recrystallization in ethanol. Brown powder. m.p: 57-59 ºC. IR (KBr, ν_{max}, cm^{-1}): 3417, 3292, 2457, 1622. ^{1}H NMR (400 MHz, DMSO-d_6): 3.47 (t, *J* = 4.7, 4H, $2CH_2$); 3.76 (t, *J* = 4.5, 4H, $2CH_2$); 6.91-7.79 (m, 7H, Ar, OH, SO_3H, NH); 8.54 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): 43.05, 63.62, 109.11, 119.08, 122.35, 124.07, 126.43, 127.03, 128.17, 129.73, 131.18, 133.78, 149.25, 155.77, 162.78 pm. $C_{17}H_{16}N_6O_6S_3$ calcd: C 41.13, H 3.23, N 16.94; found: C 40.98, H 3.12, N 17.04. MS *m/z*: 463 (6 %), 158 (12 %), 105 (14 %), 86 (63 %), 56 (100 %).

4-Hydroxy-5- [(morpholinocarbonyl)amino]-3-[2-(5-sulfanyl-1,3,4-thiadiazole-2-yl)-1-diazenyl]-2,7-naphthalene disulfonic acid (4f): Recrystallization in ethanol. Purple powder. m.p.: 117-119 ºC. IR (KBr, ν_{max}, cm^{-1}): 3417, 3310, 2356, 1619. ^{1}H NMR (400 MHz, DMSO-d_6): 3.43 (t, *J* = 4.8, 4H, $2CH_2$); 3.77 (t, *J* = 4.6, 4H, $2CH_2$), 7.24-7.83 (m, 5H, Ar, OH, NH); 9.54 (broad, 3H, NH, $2SO_3H$). ^{13}CNMR (400 MHz, DMSO-d_6): 46.53, 65.92, 107.13, 111.23, 112.78, 115.26, 121.68, 124.55, 129.33, 134.61, 137.34, 141.29, 148.79, 159.11, 164.83 ppm. $C_{17}H_{16}N_6O_9S_4$ calcd.: C 35.42, H 2.78, N 14.58; found: C 35.51, H 2.61, N 14.40. MS *m/z*: 330 (7 %), 114 (24 %), 86 (54 %), 56 (100 %).

RESULTS AND DISCUSSION

Morpholine carbonyl chloride (**1**) reacted with appropriate aromatic compounds (**2**) and are produced morpholine derivatives (**3a-3f**) (Fig. 1).



Ar= Aniline, 3-Nitroaniline, 1-Naphthole, Resorcinol, 1-Amino-2-hydroxy-4-naphthalene sulfonic acid, 4-Amino-5-hydroxy naphthalene-2,7-disulfonic acid

Fig. 1. Reaction of Morpholine carbonyl chloride with appropriate aromatic compounds

2-Amino-5-mercapto-1,3,4-thiadiazole (**4**) was diazotized satisfactorily at 0 ºC by adding to nitrosyl hydrochloric acid (Fig. 2).

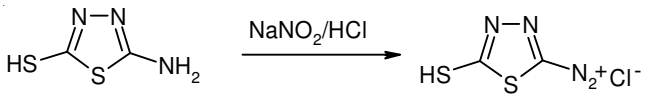


Fig. 2. Diazotation of 2-amino-5-mercapto-1,3,4-thiadiazole

In order to determine the end point of diazotization, it was found useful to check for the presence of unreacted diazo component on TLC by sampling the diazotization mixture. Thus, when unreacted diazo component no longer persisted on TLC, the diazotization was ended. Coupling compounds (**3a-3f**) was added to diazonum salt of 2-amino-5-mercapto-1,3,5-thiadiazole (**5**) to give 2-amino-5-mercapto-1,3,4-thiadiazole products (Fig. 3).

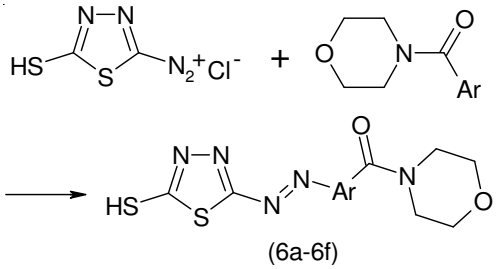
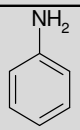
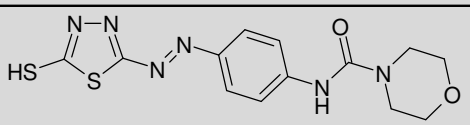
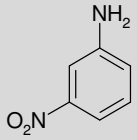
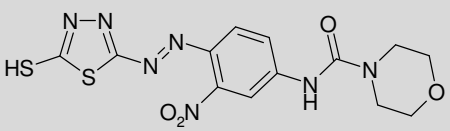
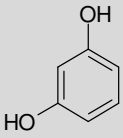
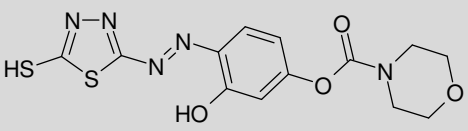
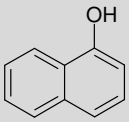
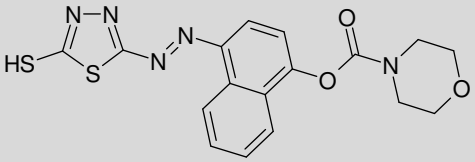
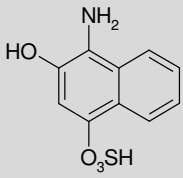
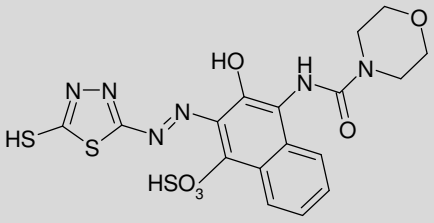
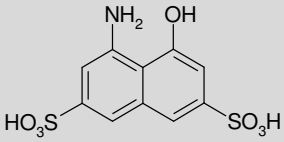
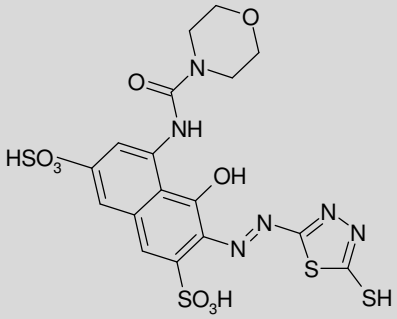


Fig. 3. Reaction of diazonum salt of 2-amino-5-mercapto-1,3,5-thiadiazole with morpholine derivatives

All the recrystallized products exhibited well-defined melting points characteristics of pure compounds. It would be unwise to attempt to explain in detail their relative values, because of the complex dependence of the melting points on a number of factor like polarity, size, geometry, interaction, *etc*. the purity of the dyes were checked by TLC using ethyl acetate-benzene (1:4) as the solvent system. When adsorbed onto silica chromatography plates, the dyes produced a single colour spot.

Generally, variation in colour of these dyes results from the alternation in coupling components. Since the synthesized dyes obtained varied in colour from yellow to brown, a

TABLE-1
YIELDS AND λ_{max} OF PREPARED 1,3,4-THIADIAZOLE DERIVATIVES

Entry	Ar	Product		λ_{max}[a] (nm)	Yield[b] (%)
1			**6a**	423	72
2			**6b**	384	78
3			**6c**	447	74
4			**6d**	542	66
5			**6e**	495	64
6			**6f**	623	58

[a]λ_{max} was determined in DMSO; [b]Isolated product

convenient method of measuring the colour of the compound was to study the absorption spectra of their solutions. The visible absorption maxima for the synthesized dyes were measured in Me_2SO at the concentration of 10^{-5} M and are listed in Table-1. The absorption maxima of the synthesized dyes ranged from 384 to 623 nm (Table-1).

In this work, 2-amino-5-mercapto-1,3,4-thiadiazole derivatives in DMSO were tautomerized. (Fig 4).

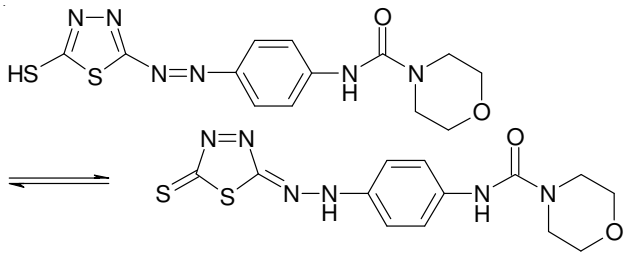


Fig. 4. Tautomerism of new 1,3,4-thiadiazole compounds

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