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STUDY ON THE INTRAMOLECULAR MANNICH REACTION OF 4-AMINO-3-ARYL-2,3-DIHYDROGEN-5-MERCAPTO-1,2,4-TRIAZOLES

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Abstract: Seventeen novel fused heterocycles have been prepared by the intramolecular Mannich reaction of 4-amino-3-aryl-5-mercapto-1,2,4-triazole with aldehydes in the presence of acid, Yield: 32~90%. These compounds were screened for their antimicrobial activities.

The triazoles and related compounds are of biological importance. They can be used as antibiotics, anticonvulsants, dephlogisticate, plant growth regulator and anticoagulant[1~3]. 1,3,4-Thiadiazoles heterocycles also possess significant biological activities, used as herbicide, plant growth regulator, anthelmintic, dephlogisticate, prevention and control of bacterial leaf blight,

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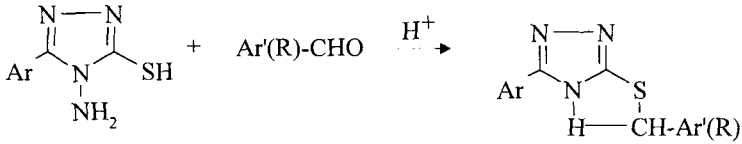
orange canker and bacterial wilt brown rot[4~6]. The encouraging biological activities of these heterocycles prompted us to synthesize the corresponding novel derivatives (2a~q) and investigate their antimicrobial activities. 17 Novel heterocycles have been prepared by the intramolecular Mannich reaction of 4-amino-3-aryl-5-mercapto-1,2,4-triazoles with aldehydes in the presence of acid (Scheme 1). All products have been characterized by elemental analysis, IR, NMR, and MS. The data confirmed the structure of the synthesized compounds as depicted in Scheme 1.



1 2a~q

Ar-: 2a~g: p-$O_2NC_6H_4$-; 2h~q: m-$O_2NC_6H_4$-.

Ar'(R)-: 2a, 2h: p-$CH_3OC_6H_4$-; 2b, 2i: p-$O_2NC_6H_4$-;

2c, 2j: p-$Me_2NC_6H_4$-; 2d, 2k: o-$CH_3OC_6H_4$-;

2e, 2l: Furyl; 2f, 2m: CH_3-CH=CH-;

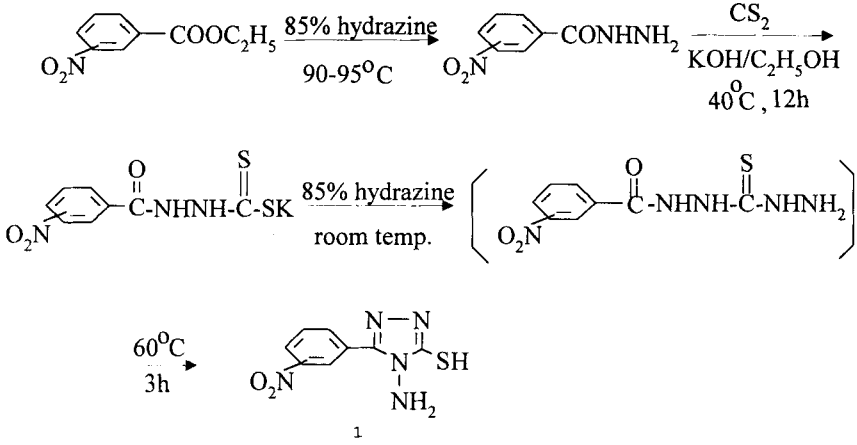
2g, 2n: -H; 2o: Ph-CH=CH-;

2p: o-HO-C_6H_4-; 2q: 4-HO-3-$CH_3OC_6H_3$-.

Scheme 1

The starting 4-amino-3-aryl-5-mercapto-1,2,4-triazoles (1) were synthesized following the method of Reid and Heindel[7]. Aromatic ester was treated with 85% hydrazine to give the corresponding aromatic acylhydrazine, then mixed with CS_2 in the presence of absolute ethanol and KOH at 40°C for 12h to give the intermediate potassium aryl acylhydrazine dithioformate. It reacted with

excess 85% hydrazine and cyclized. H_2S and water were then removed to give the products (1). (Scheme 2)

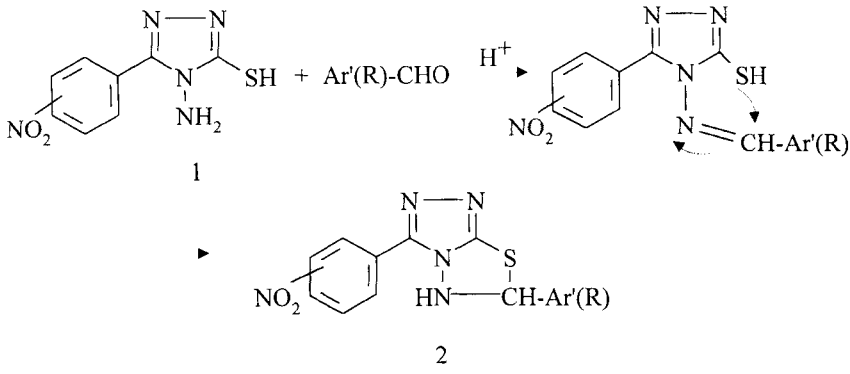


Scheme 2

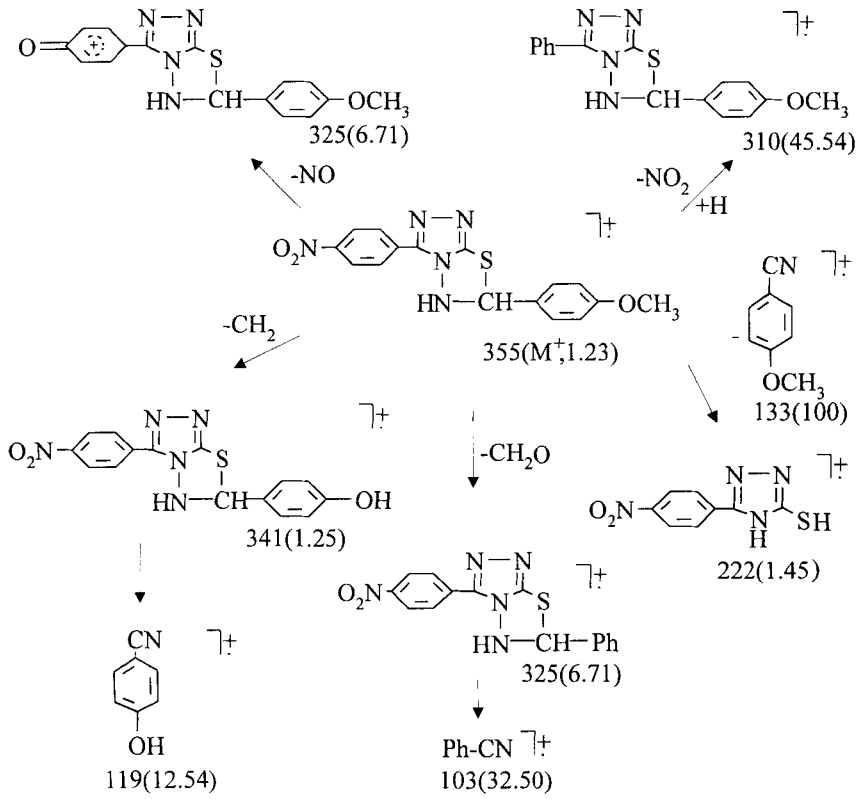
The reaction rates for the cyclization depend on the substitutes of the aromatic ring. The reaction would be stabilized by electron-donating groups of the aromatic ring at a temperature lower than 60°C. However, the cyclization occurrs fairly rapidly with the presence of electron-withdrawing substituents (such as $-NO_2$) at the same temperature. A cooler temperature is required for good yield.

Substrate (1) reacted with aldehyde to give the Schiff's base, then the mercapto group of it had nucleophilic addition with -N=CH-Ar to give title compound (2). (Scheme 3)

The first step in thiadiazole (2) synthesis is the formation of a Schiff's base. The Schiff's base is unstable in the presence of strong acid or base. The second step is that the mercapto group of the Schiff's base has intramolecular nucleophilic addition with -CH=N-, and -SH is stable under acidic condition.



Scheme 3



Scheme 4

Therefore, these two steps depend critically on the pH of the solution. At pH value less than 4, the yield of the thiadiazole may approach zero. An optimum condition is found at pH 5 ~ 6, where a buffer solution is produced and it can prevent the Schiff's base from hydralysis and contribute to the formation of the thiadiazole ring.

The structures of compounds have been confirmed by elemental analysis, IR, ^{1}HNMR, and MS. The IR spectra of these compounds revealed in each case, absorption bands in the regions 3173 ~ 3499cm^{-1}, 1585 ~ 1617cm^{-1} and 1486 ~ 1530cm^{-1} corresponding to NH, C=N and N=C-S, respectively. The ^{1}HNMR spectra of 2a for example, exhibited singlet at δ 9.51ppm and singlet at δ 6.65ppm due to NH and CH protons, respectively. The mass spectra cleavage pathways are similar. The peak of molecular ions are weak or disappear. The main reason is that there is a -NO_2 group on the ring. The -NO_2 group is easy to expell NO_2 and NO. The fragmentation pattern of 2a is shown in Scheme 4.

Experimental

All melting points were recorded on a X_4 micro melting point apparatus and are uncorrected. IR spectra were recorded from KBr pellets on FTS-40(BIO-RAD) spectrometer. ^{1}HNMR spectra were recorded on Bruker Ac-100 spectrometer. Elemental analysis were recorded on a Pekin-Elmer 2400 element analyser. Mass spectra (MS) were obtained on HP5989A apparatus. Aldehydes are analytical purity. 4-amino-3-Aryl-5-mercapto-1,2,4-triazoles were synthesized by empolying our published procedures.

A round-bottomed flask was charged with 4-amino-3-aryl-5-mercapto-1,2,4-triazole(3mmol), ethanol(5mL) and aldehyde(3.5mmol). The mixture was acidified to pH=5 ~ 6 with diluted HCl and stirred at 70°C for 8-10 hours. The

solution was allowed to stand overnight, then filtered. The precipitate was washed with 5% $NaHCO_3$ and water to neutrality and then dried. The crude material was recrystallized from ethanol, giving the pure products (2).

2a: Yellow powder, yield (51.6%); mp.152~154°C; IR (KBr) ν =3350(NH), 1600(C=N), 1510(N=C-S), 1340(-NO_2), 1270, 1030(C-O-C), 695(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ =9.51(1H, s, NH), 7.93~7.50(4H, m, Ar-H), 7.59~7.31(4H, m, Ar-H), 6.65(1H, s, CH), 3.86(3H, s, OCH_3)ppm; MS, m/z= 355(M^+,1.23), 341(1.25), 310(45.54), 222(1.45), 192(42.68), 133(100), 103(32.50); Calcd. for $C_{16}H_{13}N_5O_3S$, C, 54.07; H, 3.69; N, 19.71. Found: C, 54.38; H, 3.54; N, 19.39.

2b: Orange-red powder, yield (72.1%); mp.228~230°C; IR(KBr) ν =3360(NH), 1596(C=N), 1508(N=C-S), 1345(-NO_2), 692(C-S-C)cm^{-1}; MS, m/z= 370(M^+, 0), 340(4.81), 325(93.98), 192(37.40), 177(5.87), 148(49.70), 102(100); Calcd. for $C_{15}H_{10}N_6O_4S$, C, 48.64; H, 2.72; N, 22.70. Found: C, 48.41; H, 2.55; N, 22.42.

2c: Red powder, yield (54.3%); mp.175~177°C; IR(KBr) ν =3400(NH), 1596(C=N), 1530(N=C-S), 1355(-NO_2), 695(C-S-C)cm^{-1}; ^{1}HNMR(DMSO-d_6) δ =9.21(1H, s, NH), 8.09~7.65(4H, m, Ar-H), 7.52~6.75(4H, m, Ar-H), 6.64(1H, s, CH), 3.04(3H, s, CH_3)ppm; Calcd. for $C_{17}H_{16}N_6O_2S$, C, 55.42; H, 4.38; N, 22.81. Found: C, 55.15; H, 4.22; N, 22.95.

2d: Orange powder, yield (56.3%); mp.151~153°C; IR(KBr) ν =3440(NH), 1603(C=N), 1495(N=C-S), 1350(-NO_2), 1275, 1020(C-O-C), 755(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ =9.44(1H, s, NH), 8.12~7.75(4H, m, Ar-H), 7.58~7.38(4H, m, Ar-H), 6.65(1H, s, CH), 3.89(3H, s, OCH_3)ppm; MS, m/z= 355(M^+, 0), 325(1.60), 310(8.46), 207(3.29), 192(59.65), 177(3.17), 152(4.61), 148(3.76), 133(49.53), 121(100),

119(32.42); Calcd. for $C_{16}H_{13}N_5O_3S$, C, 54.07; H, 3.69; N, 19.71. Found: C, 53.76; H, 3.56; N, 19.35.

2e: Brown powder, yield (68.8%); mp.210°C(decomposition); IR(KBr) ν =3360(NH), 1608(C=N), 1500(N=C-S), 1400(-NO_2), 1260, 822(C-O-C), 695(C-S-C)cm^{-1}; MS, m/z= 315(M^+, 0), 285(2.17), 270(2.79), 193(34.89), 177(2.54), 93(100); Calcd. for $C_{13}H_9N_5O_3S$, C, 49.52; H, 2.88; N, 22.21. Found: C, 49.75; H, 2.71; N, 22.60.

2f: Yellowish pink powder, yield (83.0%); mp.150°C(decomposition); IR (KBr)ν=3450(NH), 1603(C=N), 1500(N=C-S), 1400(-NO_2), 700(C-S-C)cm^{-1}; MS, m/z= 289(M^+, 0), 259(1.72), 192(41.21), 164(1.52), 160(69.99), 64(100); Calcd. for $C_{12}H_{11}N_5O_2S$, C, 49.82; H, 3.83; N, 24.21. Found: C, 49.65; H, 3.66; N, 24.57.

2g: Orange powder, yield (80.3%); mp.218°C(decomposition); IR(KBr) ν =3450(NH), 1605(C=N), 1500(N=C-S), 1420(-NO_2), 695(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=13.63(1H, s, NH), 7.73~7.70(2H, d, Ar-H, J=8.59Hz), 6.62~6.60(2H, d, Ar-H, J=8.62), 5.70(2H, s, CH_2)ppm; $C_9H_7N_5O_2S$, C, 43.37; H, 2.83; N, 28.10. Found: C, 43.09; H, 2.68; N, 28.44.

2h: Yellow powder, yield (56.3%); mp.205~207°C; IR(KBr) ν=3247(NH), 1598(C=N), 1530(N=C-S), 1490(-NO_2), 1275, 1050(C-O-C), 695(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=9.96(1H, s, NH), 7.91~7.53(4H, m, Ar-H), 7.46~7.38(4H, m, Ar-H), 6.94(1H, s, CH)ppm; MS, m/z= 355(M^+, 0), 297(16.12), 240(100), 122(5.18), 118(2.96); Calcd. for $C_{16}H_{13}N_5O_3S$, C, 54.07; H, 3.69; N, 19.71. Found: C, 54.33; H, 3.51; N, 19.96.

2i: Orange powder, yield (54.1%); mp.204~205°C; IR(KBr) ν=3499(NH), 1598(C=N), 1512(-NO_2), 1496(N=C-S), 683(C-S-C)cm^{-1};

^{1}HNMR (DMSO-d_6) δ=10.08(1H, s, NH), 8.43~7.57(8H, m, Ar-H), 7.08(1H, s, CH)ppm; MS, m/z= 370(M^+, 0), 340(2.22), 325(4.85), 192(17.90), 177(4.46), 148(49.86), 102(100); Calcd. for $C_{15}H_{10}N_6O_4S$, C, 48.64; H, 2.72; N, 22.70. Found: C, 48.28; H, 2.55; N, 22.41.

2j: Drab powder, yield (54.3%); mp.197~199°C; IR(KBr) ν=3495(NH), 1595(C=N), 1526(N=C-S), 1358(-NO_2), 695(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=9.07(1H, s, NH), 7.77~7.62(8H, m, Ar-H), 6.98~6.95(1H, s, CH), 3.02(6H, s, CH_3)ppm; MS, m/z= 368(M^+, 2.45), 353(1.34), 341(1.25), 338(1.10), 324(1.56), 294(100), 222(2.94), 146(22.51), 44(14.93); Calcd. for $C_{17}H_{16}N_6O_2S$, C, 55.42; H, 4.38; N, 22.81. Found: C, 55.09; H, 4.25; N, 22.68.

2k: Pale yellow powder, yield (67.6%); mp.42~44°C; IR(KBr) ν =3200(NH), 1598(C=N), 1486(N=C-S), 1398(-NO_2), 1250,1020(C-O-C), 691(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=7.98(1H, s, NH), 7.73~7.05(8H, m, Ar-H), 7.04(1H, s, CH), 3.90(3H, s, CH_3)ppm; MS, m/z= 355(M^+, 0), 207(12.58), 193(56.90), 148(1.45), 133(24.55), 119(6.95), 93(100), 64(57.35); Calcd. for $C_{16}H_{13}N_5O_3S$, C, 54.07; H, 3.69; N, 19.71. Found: C, 54.41; H, 3.55; N, 19.46.

2l: Brown powder, yield (76.2%); mp.190°C(decomposition); IR(KBr) ν =3400(NH), 1605(C=N), 1505(N=C-S), 1411(-NO_2), 1273, 850(C-O-C), 695(C-S-C)cm^{-1}; MS, m/z= 315(M^+, 0), 285(3.60), 270(2.04), 193(62.15), 93(100), 65(32.84); Calcd. for $C_{13}H_9N_5O_3S$, C, 49.52; H, 2.88; N, 22.21. Found: C, 49.23; H, 2.69; N, 22.60.

2m: Orange powder, yield (82.1%); mp.222~224°C; IR(KBr) ν=3450(NH), 1606(C=N), 1501(N=C-S), 1323(-NO_2), 685(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=7.99(1H, s, NH), 7.06~6.99(4H, m, Ar-H), 6.75(1H, s, CH), 3.34(2H, s, CH), 1.05(3H, s, CH_3)ppm; Calcd. for $C_{12}H_{11}N_5O_2S$, C,

49.82; H, 3.83; N, 24.21. Found: C, 49.52; H, 3.66; N, 24.01.

2n: Pale yellow powder, yield (95.2%); mp.200°C(decomposition); IR (KBr)ν=3434(NH), 1606(C=N), 1497(N=C-S), 1360(-NO_2), 696(C-S-C)cm^{-1}; MS, m/z= 249(M^+, 0), 219(12.12), 222(15.55), 193(100), 192(84.05), 91(36.78); Calcd. for $C_9H_7N_5O_2S$, C, 43.37; H, 2.83; N, 28.10. Found: C, 43.06; H, 2.69; N, 27.81.

2o: Pale yellow powder, yield (90.2%); mp.178~180°C; IR(KBr) ν =3430(NH), 1585(C=N), 1506(N=C-S), 1356(-NO_2), 692(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ=9.70(1H, s, NH), 7.76~7.17(9H, m, Ar-H), 6.98(1H, s, CH), 4.35(2H, s, CH)ppm; Calcd. for $C_{17}H_{13}N_5O_2S$, C, 58.11; H, 3.73; N, 19.93. Found: C, 58.46; H, 3.55; N, 19.56.

2p: Pale yellow powder, yield (82.3%); mp.209~211°C; IR(KBr) ν =3234(NH), 1617(C=N), 1510(N=C-S), 1360(-NO_2), 695(C-S-C)cm^{-1}; ^{1}HNMR (DMSO-d_6) δ =9.80(1H, s, NH), 7.91~7.37(8H, m, Ar-H), 7.21(1H, s, OH), 6.98(1H, s, CH)ppm; MS, m/z= 341(M^+,0), 311(3.10), 296(100), 222(14.61), 192(5.14), 177(9.35), 91(21.67); Calcd. for $C_{15}H_{10}N_5O_3S$, C, 52.93; H, 2.96; N, 20.56. Found: C, 52.61; H, 2.77; N, 20.26.

2q: Yellow powder, yield (32.3%); mp.164~166°C; IR(KBr) ν =3354(OH), 3173(NH), 1585(C=N), 1510(N=C-S), 1362(-NO_2), 1262, 1032(C-O-C), 695(C-S-C)cm^{-1}; MS, m/z= 371(M^+, 0), 341(2.81), 326(11.47), 222(3.85), 207(100), 177(35.56), 149(66.61), 119(26.39), 118(32.56), 91(14.31), 65(19.47); Calcd. for $C_{16}H_{13}N_5O_4S$, C, 51.74; H, 3.53; N, 18.86. Found: C, 51.40; H, 3.37; N, 18.49.

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