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Research Article

SYNTHESIS OF NOVEL B-DIKETONES FROM DIAZONIUM SALT OF 3-AMINO 1, 2, 4-TRIAZOLE AND ITS DERIVATIVES

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ABSTRACT

A series of novel β-diketones(5a-e) of 3-Amino 1, 2, 4-triazole (2) and N-[4-(3-Amino-[1, 2, 4] triazole-1-sulfonyl)-phenyl]-acetamide (3) have been synthesized by reacting with different 1,3-diketones viz: acetylacetone, benzoylacetone, dibenzoylmethane via diazotination in the presence of sodium methoxide in methanol. Newly synthesized compounds were characterized on the basis of elemental analysis and spectral studies viz. IR, ^{1}HNMR, ^{13}CNMR, and Mass.

Keywords: β-diketones, 3-amino 1, 2, 4-triazole, N-[4-(3-Amino-[1, 2, 4] triazole-1-sulfonyl)-phenyl]-acetamide, Sodium methoxide.

INTRODUCTION

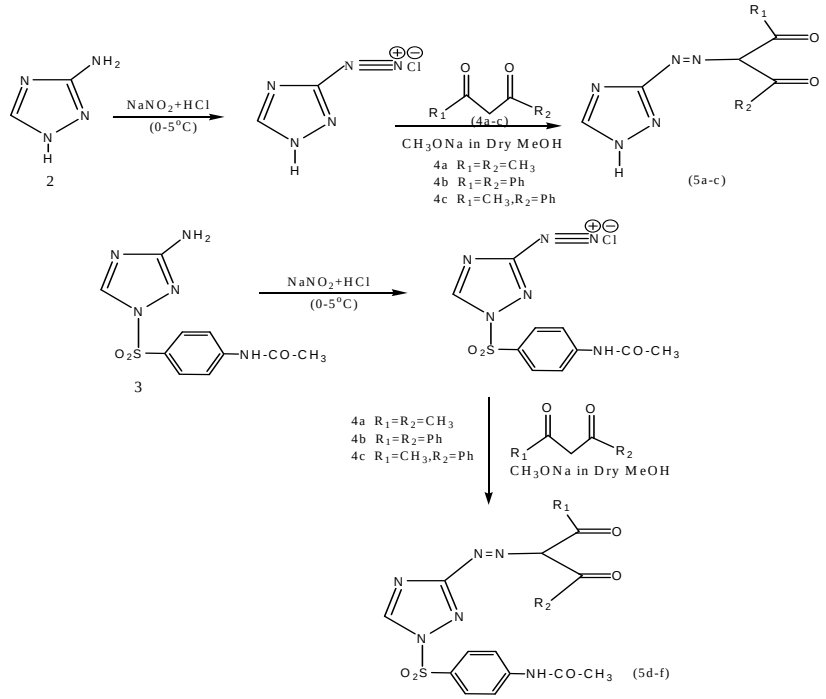
Development of simple synthetic routes to widely used organic compounds using readily available reagents is one of the most objectives of organic synthesis. Nitrogen heterocycles have constituted an important class of natural and synthetic products and well recognized for their pharmacological properties. 1, 2, 4-Triazoles and its derivatives find a unique place in drugs research because of their diverse bioactivities[1] for example, Fluconazole is used as an antimicrobial, while Vorozole, Letrozole, and Anastrozole are nonsteroidal drugs used for treatment of cancer and Loreclezole is used as an anticonvulsant.[2] Some other derivatives of 1, 2,4-Triazole have also been found to exhibit, antibacterial[3], antifungal[4], antimicrobial[5,6] antimycobacterial[7], anticonvulsant activity.[8,9]

Sulfonamide derivatives have possessed pharmacological properties such as antibacterial & antifungal[10], antitumor[11] and antiviral[12,13] activities and other benzene sulfonamide derivative such as sildenafil 1-[4-ethoxy-3-(6,7-dihydro-1-methyl-7-oxo-3-propyl-1H-pyrazolo[4,3-d]pyrimidin-5-yl)phenylsulfonyl]-4-methylpiperazine is used for the treatment of sexual dysfunction.

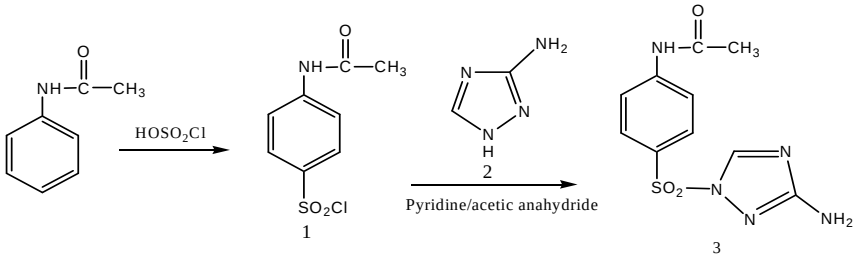
β-diketones have attracted considerable interest in medicinal chemistry. They serve as precursors for the synthesis of large number of biologically active heterocyclic compounds[14,15] such as diazepines, benzodiazepines pyrazoles, isoxazoles, and, imidazole, benzimidazole.

β-diketones have also been shown to have a wide assortment of pharmacological activities like antibacterial[16], antiviral[17], systematic insecticidal[18], antioxidant[19] and prophylactic antitumor[20]. In addition, β-diketones have also been used as an antisunscreen agent that filters U.V rays to protect skin[21]. Nevertheless, β-diketones have examined as breast cancer chemopreventive blocking agent[22], antiestrogenic[23] and anticarcinogenic[24] agent. Further β-diketones are well known to have a keto-enol tautomerism[25] and recently it is reported that β-keto-enols are the important pharmacophore for the HIV-I integrase (IN) inhibitor[26].

In continuation to our earlier research work done on β-diketones[27,28] and potential biological activities associated with β-diketones, 3-amino 1,2,4 triazole and sulfonamide derivatives encourage us to synthesized novel β-diketones.(5a-f) of 3-amino 1,2,4-triazole and 3-amino 1,2,4-triazole derivative having 4-acetyl amino benzene sulfonyl chloride moiety to get better biological active compounds.



Scheme II: Synthesis of Novel 1,3-Diketones via diazotination



Scheme I: Synthesis of 3-Amino-1, 2, 4-triazole derivative

MATERIAL AND METHOD

The melting point of the compound was determined in open capillaries and is uncorrected. The IR spectra were recorded on a Nicolet Megna-FT-IR 550 spectrometer in KBr pellets; ^{1}H NMR and ^{13}C NMR were run on model DRX 300 at 300.13Hz and 75Mz in $CDCl_3$ using TMS as internal standard. The mass spectra were obtained on an LCMS instrument. Elemental analyses were done using Perkin Elmer CHNS/O analyzer 2400. The purity of the newly synthesized compounds was checked through TLC on aluminium oxide 60 F254 plates (Merck) and spots were visualized by iodine vapors or by irradiation with ultraviolet lights (254 nm).

General procedure for synthesis of N-[4-(3-Amino-[1,2,4]triazole-1-sulfonyl)-phenyl]-acetamide (3): 3-Amino-1, 2, 4-triazole (0.02 mol, 1.68 g) was taken in pyridine (4ml) and acetic anhydride (20ml) was added. To this 4-Acetylamino-benzenesulfonyl chloride (2.5g, 0.01mol) was added and the mixture was kept on a water bath for two hours. The progress of the reaction was monitored through TLC. After completion of the reaction, reaction mixture was poured to ice cold water, the solid obtained was filtered and crystallized from ethanol-water (50:50) mixture to obtain pure compound.

General procedure for synthesis of diazonioum salt of 3-Amino-1,2,4-Triazole (2) and N-[4-(3-Amino-[1, 2, 4] triazole-1-sulfonyl)-phenyl]-acetamide (3): Place 3-Amino-1,2,4-triazole (0.01 mol, 0.84 g), hydrochloric acid (1ml) and water (4ml) in a round bottom flask and stirred it for ten minutes on a magnetic stirrer at 0-5^{o}C and add saturated $NaNO_2$ solution in small lots in excess with continuous stirring. Temperature of the reaction mixture was maintained between 0-5^{o}C. Thus diazonium salt so formed is used directly for further reaction. (C.f. Scheme-II)

General procedure for synthesis of novel 1,3-Diketones (5a-e): The diazonium salt of compound 2 and 3 were condensed with (0.01 mol) β-diketones (viz: Acetylacetone, Dibenzoylmethane, Benzoylacetone) in presence of sodium methoxide, reaction proceeds with continuous stirring for 4-6 hours at room temperature. The progress of reaction was monitored through TLC. After completion of the reaction, reaction mixture was concentrated under reduced pressure and reaction mass was extracted with acetone and distilled to yield solid product. The crude product was purified through column chromatography over silica gel using chloroform: acetone (50:50) as eluent. It was purified by recrystallization from ethanol to obtain pure β-diketone derivatives. Purity of compounds was checked by TLC using 9:1 ($CHCl_3$: Methanol) upper layer as mobile phase.

Spectral Data

3-(1H-[1,2,4]Triazol-3-ylazo)-pentane-2,4-dione(5a)

Yield: 58%, m.p. 114-116^{0}C; Anal.Cald.for $C_7H_9N_5O_2$: C, 43.08; H, 4.65; N, 35.88; O, 16.39. Found: C, 43.06; H, 4.63; N, 35.87; O, 16.37; IR ν_{max} (KBr, cm^{-1}): 3343(N-H), 3100(enolic O-H), 3040(Ar-H), 2930(C-H),1716(C=O),1585(>C=N); ^{1}HNMR (300.13 MHz, $CDCl_3$, δ/ppm): 14.31 (s,1H,enolic-OH), 11.95(bs,1H,N-H), 8.53-8.46 (d,1H,=C-H-triazole), 7.08 (s,1H,-**CH**-CO),2.34(s, 6H, **-CH$_3$-**CO); ^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 21.4(-**CH$_3$**-CO), 148(,-**CH**-CO) 164.6,168.20(C=N-triazole),193.7(**C**=O); LCMS(m/z): 196 [M+H$^+$]

1,3-Diphenyl-2-(1H-[1,2,4]triazol-3-ylazo)-propane-1,3-dione(5b)

Yield: 62%, m.p. 98-99^{0}C; Anal.Cald.for $C_{17}H_{13}N_5O_2$: C, 63.94; H, 4.10; N, 21.93; O, 10.02. Found: C, 63.92; H, 4.09; N, 21.91; O, 10.01.; IR ν_{max} (KBr, cm^{-1}): 3343(N-H), 3100(enolic O-H), 3050(Ar-H), 2915(C-H),1725(C=O),1620(>C=N); ^{1}HNMR (300.13 MHz, $CDCl_3$, δ/ppm): 15.76 (s,1H,enolic-OH),11.95 (bs,1H,N-H), 8.48-8.50 (d,1H,=C-H-triazole), 6.38 (s,1H,-**CH**-CO),7.73-7.87(m,10H,Ar-H); ^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 122-128(Ar-C), 157(,-**CH**-CO) 164.6,168.20(C=N-triazole),197.6(**C**=O); LCMS(m/z): 320 [M+H$^+$]

1-Phenyl-2-(1H-[1,2,4]triazol-3-ylazo)-butane-1,3-dione(5c)

Yield: 56%, m.p. 107-108^{0}C; Anal.Cald.for $C_{12}H_{11}N_5O_2$: C, 56.03; H, 4.31; N, 27.22; O, 12.44. Found: C, 56.02; H, 4.30; N, 27.21; O, 12.42.; IR ν_{max} (KBr, cm^{-1}): 3343(N-H), 3100(enolic O-H), 3030(Ar-H), 2920(C-H),1719(C=O),1590(>C=N); ^{1}HNMR (300.13 MHz, $CDCl_3$, δ/ppm): 14.87 (s,1H,enolic-OH), 11.95 (bs,1H,N-H), 8.48-8.50 (d,=C-H,1H), 5.77 (s,1H,-**CH**-CO), 2.22-2.26(s, 3H, **-CH$_3$-**CO), 7.72-7.84(m,5H,Ar-H);^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 20.3(-**CH$_3$**-CO), 151(,-**CH**-CO) 124-129(Ar-C), 164.6,168.20(C=N-triazole),193.7, 197.6(**C**=O); LCMS(m/z): 258 [M+H$^+$]

N-{4-[3-(1-Acetyl-2-oxo-propylazo)-[1,2,4]triazole-1-sulfonyl]-phenyl}-acetamide(5d)

Yield: 46%, m.p. 157-158^{0}C; Anal.Cald.for $C_{15}H_{16}N_6O_5S$: C, 45.91; H, 4.11; N, 21.42; O, 20.39; S, 8.17.Found: C, 45.90; H, 4.09; N, 21.41; O, 20.37; S, 8.15; IR ν_{max} (KBr, cm^{-1}): 3345(N-H), 3100 (enolic-OH), 3040(Ar-H), 2930(C-H), 1716(C=O), 1680 (CONH-amide-I-band), 1535(N-H-amide-II-band), 1585(>C=N), 1370&1155 (S=O), 835 (p-subs.benzene); ^{1}HNMR (300.13MHz, $CDCl_3$,δ/ppm): 14.31 (s,1H,enolic-OH), 10.38 (s,1H,**NH**$COCH_3$),8.48-8.50 (d,1H,=CH-triazole), 7.71 (d,2H,J=8.4Hz, Ar-H), 7.79 (d,2H,J=8.1Hz, Ar-H),7.08(s,1H,-**CH**-CO),2.34(s, 6H, **-CH$_3$-**CO), 2.15(s,1H,NHCO**CH$_3$**); ^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 17.4(NHCO**CH$_3$**), 21.4(-**CH$_3$**-CO), 126.4, 129.6, 134.9, 144.5(p-subs.benzene),148 (-**CH**-CO), 164.6, 168.20 (C=N-triazole),169.7 (**CO**-NH), 193.7(**C**=O); LCMS(m/z): 393 [M+H$^+$]

N-{4-[3-(1-Benzoyl-2-oxo-2-phenyl-ethylazo)-[1,2,4]triazole-1-sulfonyl]-phenyl}-acetamide(5e)

Yield: 47%, m.p. 176-178^{0}C; Anal.Cald.for $C_{25}H_{20}N_6O_5S$: C, 58.13; H, 3.90; N, 16.27; O, 15.49; S, 6.21.Found: C, 58.11; H, 3.89; N, 16.25; O, 15.47; S, 6.19; IR ν_{max} (KBr, cm^{-1}): 3345(N-H), 3100(enolic-OH), 3050(Ar-H), 2915(C-H), 1719(C=O), 1682 (CONH-amide-I-band), 1535(N-H-amide-II-band), 1590(>C=N), 1370&1155 (S=O), 822 (p-subs.benzene); ^{1}HNMR (300.13MHz, $CDCl_3$,δ/ppm): 15.76 (s,1H,enolic-OH), 10.38 (s,1H,**NH**$COCH_3$), 8.48-8.50 (d,1H,=CH-triazole), 7.71 (d,2H,J=8.4Hz, Ar-H), 7.79 (d,2H,J=8.1Hz, Ar-H), 6.38(s,1H,-**CH**-CO), 7.73-7.87(m,10H,Ar-H), 2.15(s,1H,NHCO**CH$_3$**); ^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 17.4(NHCO**CH$_3$**), 122-128(Ar-C), 126.4, 129.6, 134.9, 144.5(p-subs.benzene),157 (-**CH**-CO), 164.60, 168.20 (C=N-triazole),169.7 (**CO**-NH), 197.6(**C**=O); LCMS(m/z): 517 [M+H$^+$]

N-{4-[3-(1-Benzoyl-2-oxo-propylazo)-[1,2,4]triazole-1-sulfonyl]-phenyl}-acetamide(5f):

Yield: 43%, m.p. 167-168^{0}C; Anal.Cald.for $C_{20}H_{18}N_6O_5S$: C, 52.86; H, 3.99; N, 18.49; O, 17.60; S, 7.06.Found: C, 52.85; H, 3.97; N, 18.48; O, 17.58; S, 7.04. IR ν_{max} (KBr, cm^{-1}): 3350(N-H), 3100(enolic-OH),

3020(Ar-H), 2920(C-H), 1719(C=O), 1682 (CONH-amide-I-band), 1535(N-H-amide-II-band), 1590(>C=N), 1370&1155 (S=O), 822 (p-subs.benzene); ^{1}HNMR (300.13MHz, $CDCl_3$,δ/ppm): 14.87 (s,1H,enolic-OH), 10.38 (s,1H,**NH**$COCH_3$), 8.48-8.50 (d,1H,=CH-triazole), 7.71 (d,2H,J=8.4Hz, Ar-H), 7.79 (d,2H,J=8.1Hz, Ar-H), 5.77(s,1H,**-CH-**CO), 7.72-7.84(m,5H,Ar-H), 2.34(s, 3H, **-CH_3-**CO), 2.15(s,1H,NHCO**CH_3**); ^{13}CNMR (75.48 MHz, $CDCl_3$, δ/ppm): 17.5(NHCO**CH_3),** 20.3(-**CH_3**-CO), 124-128(Ar-C), 126.4, 129.6, 134.9, 144.5(p-subs.benzene), 151 (-**CH-**CO), 164.60, 168.20 (C=N-triazole), 169.5 (**CO**-NH), 193.7, 197.6(**C**=O); LCMS(m/z): 455[$M+H^+$]

DISCUSSION

The synthetic procedures adopted to obtain the target compounds are depicted. (C.f. Scheme I and scheme II) Acetanilide was sulfonated with chlorosulfonic acid, to obtain 4-Acetylamino-benzenesulfonyl chloride (1). Compound 1, on condensation with 3-Amino-1,2,4-triazole (2) in the presence of pyridine and acetic anhydride it formed (N-acetyl pyridinium)complex, an electrophilic complex which facilitate the condensation to give compound (3) N-[4-(3-Amino-[1, 2, 4] triazole-1-sulfonyl)-phenyl]-acetamide by removal of HCl. Then compound 2 and 3 were condensed with various β-diketones in the presence of sodium methoxide via diazotination yielded corresponding novel β-diketones(5a-f).

The structures suggested for all compounds (5a-f) are in good agreement with their analytical and spectroscopic data.

The IR spectrum of compound (5a-c) showed absorption band at 3345, 3100, 3040, 2930, 1716, 1585 cm^{-1} corresponding to N-H, enolic(O-H), Ar-H, C=O, C=N group respectively. Whereas compound (5d-f) showed no N-H absorption band at 3345 and showed other peaks at 1685, 1535, 1370 &1155, 835 corresponding to amide (I) band, N-H bending, SO_2 and p-substituted benzene ring respectively.

^{1}HNMR spectra of compounds (5a-f) showed a singlet in the region of δ 5.77 to 7.08 ppm assignable to methine proton of β-diketones attached with azo group and another singlet at δ 14.31 to 15.76 ppm corresponding to enolic proton of β-diketones. Compound 5a-c exhibited a broad singlet at δ 11.95 assignable to N-H proton in triazole ring. This peak was absent in compounds (5d-f). Compounds (5d-f) showed a singlet at δ 10.35 and 2.15ppm accounted for N-H and CH_3 protons of acetanilide. Two doublet at δ 7.71 (J=8.4Hz) and δ 7.79 (J=8.1Hz) each integrating for two protons corresponding to p-substituted benzene ring. ^{13}CNMR spectrum of 5a showed the signals at 21.4, 148, and 193.7 corresponding to methyl, methine and keto carbon of β-diketone. Compound 5d showed the signal at δ 17.5, 169.7 corresponding to methyl and keto carbon of acetanilide. Other peaks observed at δ 126.4, 129.6, 134.9, 144.5ppm which accounted for p-substituted benzene ring. Mass spectrum of compounds (5a-f) showed the signal of the molecular ion peak which is in agreement with molecular formula.

CONCLUSION

In conclusion, We have approached to an easy and convenient synthetic method for the preparation of six novel β-Diketone derivatives (5a-e) of 3-Amino-1,2,4-Triazole (2) and N-[4-(3-Amino-[1, 2, 4] triazole-1-sulfonyl)-phenyl]-acetamide (3) via diazotination with various β-diketones in good yield.

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