SYNTHESIS OF NEW 1,2,3-TRIAZOL-4-YL-6-SUBSTITUTED-S-TRIAZOLO[3,4-B]-1,3,4-THIADIAZOLE DERIVATIVES VIA DIAZONIUM SALTS.

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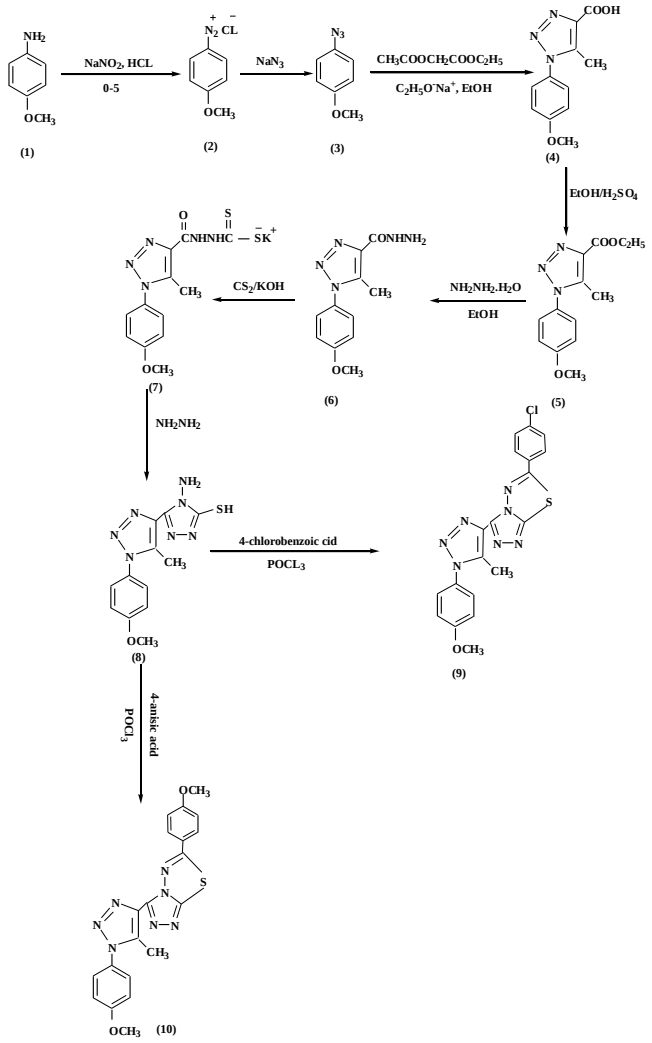
Abstract

Derivatives of 6-aryl-[5-methyl-1-(4-methoxy phenyl)-1,2,3-triazol-4-yl-s-triazolo[3,4-b]-1,3,4-Thiadiazoles (9) and (10) were synthesized by treating p-anisidine with sodium nitrite followed by the addition of sodium azide. Treating azide compound (3) with ethylacetoacetate yielded 1,2,3-triazolo-4-carboxylic acid (4), which was converted to ester (5) using absolute ethanol. Treating the ester with hydrazine hydrate afforded the acid hydrazide derivative (6), which was reacted with CS_2 and KOH to produce the salt potassium dithiocarbazate (7). Addition of hydrazine to the salt produced 1-amino-2-mercapto-5-[5-methyl-1-(4-methoxy phenyl) –1,2,3-triazol-4-yl]-1,3,4-triazole (8). Treating (8) with p-chlorobenzoic acid and anisic acid afforded the target compounds (9) and (10).

Introduction

Compounds having a 1,2,3-triazole nucleus have been reported as antibacterial, fungicidal, antiviral, anti-inflammatory and analgesic [(1,2)]. Some new 1,2,3-triazole derivatives have been synthesized to inhibit tumor proliferation, invasion, metastasis[(3)] and are anti HIV[(4,5)]. Likewise the 1,3,4-thiadiazole nucleus which incorporates an N-C-S linkage exhibit a large number of biological activities[(6)]. The fused 1,3,4-triazole[3,4-b]-1,3,4-thiadiazole derivatives show various biological effects, such as antifungal[(7)], antibacterial, hypotensive and CNS depressant activities[(8)]. For this reason, synthesis of the fused triazolo thiadiazole rings are interesting and useful.



Scheme (I) : The synthesis route of the title compounds.

Experimental

Melting point were determine on a Gallen Kamp melting point apparatus and are uncorrected. . The IR spectra were measured as potassium bromide pellets using a Shimadzu FTIR 8300 spectrophotometer. ^{1}H NMR spectra were recorded on a Brüker ACF 300 MHz with TMS as internal standard (δ in ppm) spectrometer; measurements were made at the chemistry department of Exeter University, England.

Preparation of compounds

1)5-methyl-1-(4-methoxyphenyl)-1,2,3-triazol-4-carboxylic acid (4)

The acid was prepared from ρ-anisidine via azide derivative according to literture[9] white solid, yield: 80%; mp.158˚-160˚C; IR(KBr) (ν, cm^{-1}), 3350(OH), 3033 (Ar-H), 2957 (Alip. H), 1678 (-C=O).

2)5-methyl-1-(4-methoxyphenyl)-1,2,3-triazol-4-ethyl acetate (5)

A mixture of the acid (4) (2.33 gm, 0.01 mole), absolute ethanol (10 mL), and concentrated sulfuric acid (0.6 mL), was refluxed for 10 hours, cooled to room temperature and the refrigerated for 5 hours. A pale solid was obtained and filtered; the solid was washed and recrystillized from absolute ethanol. Yield 74%; pale yellow crystal; mp. 122˚-124˚C; IR(KBr)(ν, cm^{-1}), 2974 and 2887 (Alip. H), 1742(C=O) of ester.

3)5-methyl-1-(4-methoxyphenyl)-1,2,3-triazol-4-carbonyl hydrazine (6)

A mixture of the ester (5) (2.61 gm, 0.01 mole), 10 mL ethanol and (6 mL) of hydrazine hydrate was refluxed for 4 hours on a water bath. Then the mixture was poured onto ice. A pale yellow precipitated was formed, which was filtered and dried. Yield 62%; mp. 192˚-194˚C; IR(KBr) (ν, cm^{-1}), 3460, 3262, 3165(NH-NH$_2$), 1690 (C=O) amide I, 1598(δ NH) amide II band.

4)1Amino-2-mercapto-5-[(5-methyl)-1-4-methoxyphenyl)-1,2,3-triazol-4-yl]-1,3,4 -triazole (8)

Compound (8) was synthesized via preparation of the salt potassium dithiocarbazate by dissolving compound (6) (3.6 gm, 0.01 mole) in 15 mL ethanol at 0˚C. Potassium hydroxide (0.56 gm, 0.01 mole) was added to the mixture and kept stirring for 15 mins., followed by the addition of CS_2 (0.375 mL) and refluxed for 7 hours. Excess CS_2 was evaporated under vacuum, then (10mL) hydrazine hydrate and (40mL) ethanol was added to the salt (7). The solution was refluxed for 4 hours, cooled and poured onto ice bath. A precipitate was formed which filtered and dried. Yield 60%, dark yellow precipitate; mp. 144˚-146˚C; IR(KBr) (ν, cm^{-1}), 3320 and 3210 (NH$_2$), 2548 (SH).

5)(4-chlorophenyl)-[5-methyl-1-(4-methoxy-phenyl)1,2,3-triazol-4-yl]-s-triazolo[3,4-b]-1,3,4-thiadiazole (9)

A mixture of compound (8) (3.0 gm, 0.01 mole), ρ-chlorobenzoic acid (1.56 gm, 0.01 mole) and (10 mL) $POCl_3$ was refluxed for 6 hours. The mixture was poured onto ice water and neutralized by the addition of potassium hydroxide. Pale yellow precipitate formed, which was recrystallized using ethanol. Yield 54%, pale yellow; mp. 230˚-233˚C; IR(KBr) (ν, cm^{-1}), 2466 and 2887 (al. H), 1635 (C=N), 680(C-Cl).^{1}H NMR (DMSO-d$_6$) δ 3(3H,CH$_3$), 3.8 (3H,OCH$_3$), 6.5-8.35 ppm (8H,OCH$_3$).

6)6-(4-methoxyphenyl)-[5-methyl-1-(4-methoxyphenyl),2,3-triazol-4-yl]-s-triazolo[3,4-b]-1,3,4-thiadiazole (10)

Compound (10) was prepared following the same method for the preparation of compound (9), using anisic acid (1.52 gm, 0.01) instead of ρ-chlorobenzoic. A pale green solid was obtained. Yield 58%; mp. 225˚-228˚C; IR(KBr)(ν, cm^{-1}), 2976 and 2877 (al. H), 1601 (C=N). ^{1}H NMR (acetone-d$_6$) δ 3.2 (3H, CH$_3$), 4 (6H, 2 OCH$_3$) and 7-8 (8H, arm.).

Results and Discussion

The synthesized compounds were characterized from their FTIR and the target compounds were confirmed using ^{1}H NMR.

The azide compound (3) was confirmed by the disappearance of NH$_2$ group of ρ-anisidine at 3320 and 3220 cm^{-1} and the appearance of the azide group at 2137 cm^{-1}. FTIR for the acid derivative (4), showed a wide band at 3350 for OH group, 3033 for C-H arm., 2957and 2920 for C-H ali., C=O appeared at 1678 cm^{-1}. The azide band at 2137 cm^{-1} disappeared. Formation of the ester (5) was confirmed by

disappearance of the OH band of the acid (4) at 3350 cm^{-1} and shifting the carbonyl group of the ester to 1742 cm^{-1}. FTIR of carbonyl hydrazine derivative (6) showed three bands at 3460, 3262 and 3165 cm^{-1} for NH-NH_2 group and shifting of the carbonyl group to 1690 cm^{-1},a band at 1643 for C=N and δ NH at 1598 cm^{-1}.

Compound 1-Amino-2-mercapto-5-[(5-methyl)-1-(4-methoxy phenyl)-1,2,3 triazol-4-yl]-1,3,4-triazole (8) was confirmed from the disappearance of the three bands of NH-NH_2 of compound (6) and appearance of two bands at 3320 and 3210 cm^{-1} for asymmetrical and symmetrical stretching of NH_2. Carbonyl band at 1690 cm^{-1} of compound (6) disappeared. A band at 2548 cm^{-1} is due to SH group, which indicated that the compound exists in its thiol form instead of thione form. The formation of the target compounds (9) and (10) were indicated from the disappearance of the two bands of NH_2 for compound (8) at 3320 and 3210 cm^{-1} in addition of the disappearance of the SH band at 2548 cm^{-1}. Compound (9) showed a strong band at 680 cm^{-1} which is attributed to C-Cl. ^{1}H NMR of compound (9) figure 1, solvent DMSO showed the following chemical shifts: a peak at δ2.5 and 3.5 ppm are due to DMSO, a singlet at δ3.8 ppm is due to 3H of OCH_3. Two doublet doublet peaks at the range δ6.5-8.35 ppm were attributed to the two ρ-substituted phenyl rings, the chemical shifts of the triazole methyl group show in the range of δ2.30-2.51 ppm .^{1}H NMR of compound (10) Fig.(2), solvent (acetone d_6) showed a singlet at δ3.2 ppm due to 3H of CH_3. Peak due to acetone appeared at δ3.8 ppm, while OCH_3 peak was at δ4 ppm integrated (6H). Aromatic rings were at δ7-8 ppm which appeared as two doublet doublet due to ρ-substitution.

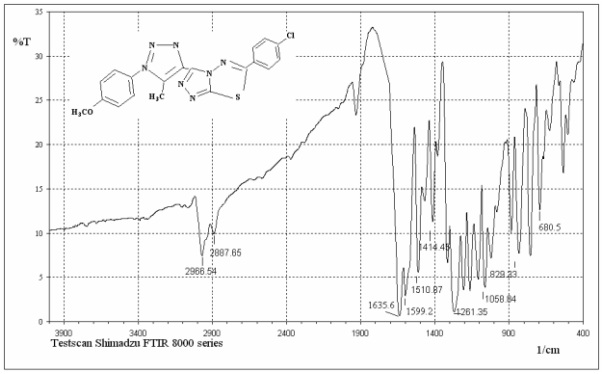


Fig. (1) : IR spectrum of compound (9).

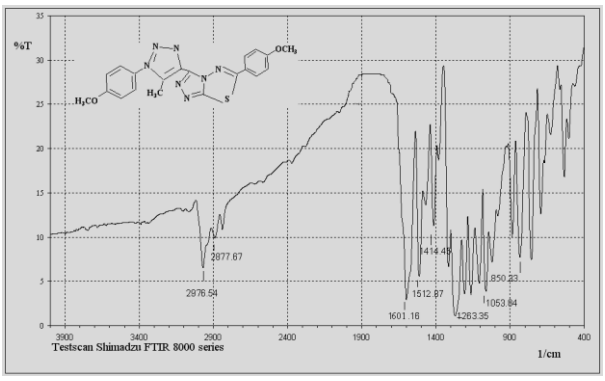


Fig. (2) : IR spectrum of compound (10).

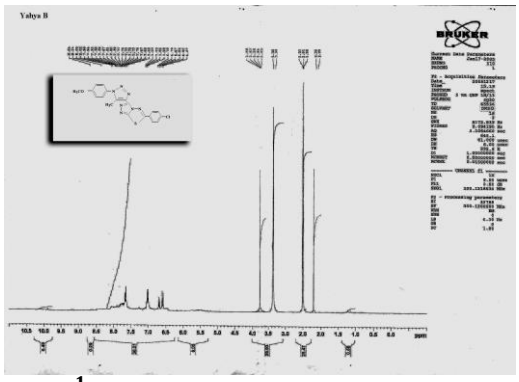


Fig.(3) : ^{1}HNMR spectrum of compound (9).

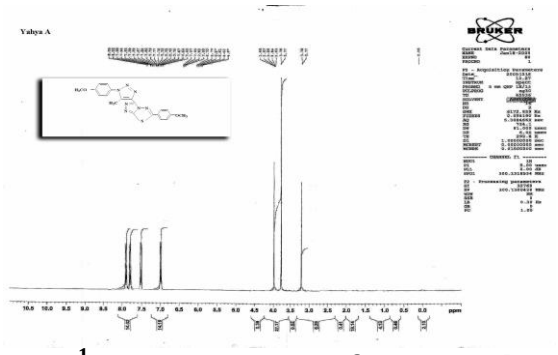


Fig.(4):^{1}HNMR spectrum of compound (10).

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