Synthesis of Triazole derivative: [4-(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol]

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Abstract

The basic nucleus 4-(amino)-5-phenyl-l-4H-1,2,4-triazole-3-thiol has been synthesized by cyclisation of potassium dithiocarbazinate with hydrazine hydrate using water as solvent under reflux condition for 3-4 h. The compound which has been synthesized successfully was subjected to condensation with benzaldehyde to synthesize 4-(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol (Schiff base). The compounds were confirmed by physical parameters (melting point), chromatographic methods (TLC) and spectroscopic methods (IR and NMR).

Keywords*: Triazole derivative, Schiff base, 4-(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol*

Introduction

Triazoles are heterocyclic organic compounds having a five-member ring molecular structure containing three nitrogen atoms. Triazoles are of two types: 1, 2, 4- triazole and 1, 2, 3-triazole. The chemistry of 1,2,3-triazoles and 1,2,4-triazoles were well documented[1-9]. The chemistry of triazole derivatives have been of interest due to its useful application in medicine[10], agriculture[11] and industry[12]. Further, some of these triazoles are known to be used as analytical reagents[13], dyes and photographic chemicals[14] and in the preparation of polymers[15].

The first 1, 2, 4-triazole derivative was synthesized by Bladin in 1885. Synthesis of various triazole derivatives have been reported[16-22]. Alkinson and Polya[23] synthesized 1,3-diphenyl 1,2,4,triazole. From diaroylhydrazines, Klingsberg[24]prepared triaryl-s-triazoles. Kurzer and Canelle[25] synthesized some 4-substitutetd 3-amino-5- mercapto-1,2,4-triazoles. Beresneva et al.[26] reported synthesis of 3-(1,2,4-trazole-4- yl)-5-amino 1,2,4-triazole. Preparation and characterization of four isomeric oxodihydro s-triazolo pyrimidines was studied by Reimlinger and Peiren[27]. Synthesis of various new triazoles have also been reported by several workers.[28-30] Preparation and reactivity of some mesoionic 1,2,4-triazolo-[4,3-b]-1,2,4-triazole derivatives have been documented by Molina et al[31]. Szilagyi et al[32] reported the preparation of new 1,5- diaryl-3-alkylthio-1H-1,2,4-triazoles and corresponding sulfoxides and sulfones. Reid and Heindal synthesized triazoles by the reaction of aryl acid hydrazide with CS_2/KOH and Hydrazine hydrate [33]. Yasin and co-workers synthesized new triazoles via conversion of 1-[á-aracyl-β-(2-thienyl)] acrocyl semicarbazides into 1, 2, 4-triazoles.[34] Kee-Jung Lee et al. prepared 1,2,4-triazoles from the elctrocyclic reaction of conjugated heterocumelenes.[35]

Various drugs have already been synthesized of the medicinal uses whichcontains the 1, 2, 4-triazole nucleus. Some of the drugs are: Fluconazole (antifungal), Rifavirin (antiviral, antiinfections), Diniconazole (agriculture- fungicide), Itraconazole (antifungal), Bitertanol (fungicide), Triazophose (pesticide), Letrozole (estrogen inhibitor- antineoplastic), Diclobutrazole (plant growth regulator) and Rilmazafone (sedative-hypnotic).

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Experimental

Scheme 1 shows the route of synthesis. Melting point points were determined in open glass capillaries on the Buchi oil-bath melting point apparatus and are uncorrected. Infrared absorption spectra were recorded on a FT-IR Shimadzu 8300 spectrophotometer, ^{1}HNMR spectra on a Hitachi R-600(60 MHz) NMR spectrophotometer using $CDCl_3$ as solvent with TMS as an internal standard.

Synthesis of methyl benzoate (Compound-1a)

Benzoic acid (0.01 mole) in 20 ml of anhydrous methanol and 0.5 ml of concentrated sulfuric acid was refluxed for 5 hours. The product was isolated and treated with sodium carbonate solution to give desired compound in 60% yield.

Synthesis of benzoic acid hydrazide (Compound-1b)

Methyl benzoate (1.36 ml, 0.01M) in 25ml of ethanol is taken in a round bottom flask. To that hydrazine hydrate (0.70 ml, 0.15M) is added and refluxed for 4 hours. The total volume of the solution is reduced to half and it is cooled in ice water. The solid is precipitated out and recrystallised with ethanol in 58% yield.

Synthesis of potassium dithiocarbazinate (Compound-1c)

To a solution of potassium hydroxide (8.5 g, 0.15M) in absolute ethanol (125ml), benzoic acid hydrazide (1.36 g, 0.1M) and carbon disulphide (14.5 ml, 0.15M were added and the mixture was stirred for 16 hrs. To the resulting solution anhydrous ether (250ml) was added and precipitated potassium dithiocarbazinate was collected by filtration, washed with diethyl ether and dried. The potassium salt obtained in quantitative yield was directly used without purification.
IR (KBr cm-1): 1662 (C=O str, amide), 3020 (Ar C-H str), 3300 (N-H str), 1487 (C-N str).

Synthesis of 4[amino]-5-phenyl-4H-1,2,4-triazole-3-thiol (Compound-1d)

A suspension of potassium salt dithiocarbazinate (4.44g, 0.02M), hydrazine hydrate (2ml, 0.04M) and water (80ml) was refluxed for 3 hrs. The color of the reaction mixture changed to green, hydrogen sulphide was evolved and a homogenous solution resulted. A white solid was precipitated by dilution with cold water (100ml) and acidification with concentrated hydrochloric acid. The
product was filtered, washed with cold water (2×30 ml) and recrystallised from ethanol in 42 % yield.
Melting point : 198 -200 ^oC.
IR (KBr cm-1): 943 (N-C-S str), 1278 (N-N-C str), 3365(N-H str), 696 (C-S str), 3082 (Ar CH str), 1446 (C-N str).
NMR (ppm): 7.7 (m, 5H, Ar-H), 7.9 (s, 2H, NH2), 14.6(s, 1H, S-H).

Synthesis of 4-(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol

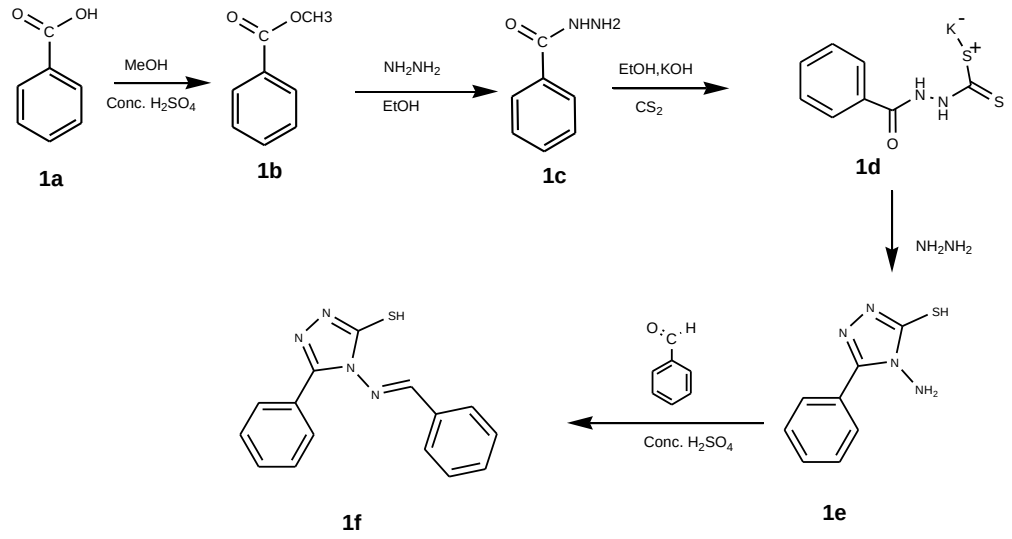
(Compound-1e)

A mixture of 4[amino]-5-phenyl-4H-1,2,4-triazole-3-thiol (1.98g, 0.001mol), Benzaldehyde (0.001mol) and 4-5 drops of concentrated sulphuric acid in ethanol medium was refluxed for 3 hrs. The resulting solution was cooled to room temperature and the precipitated solid was filtered under suction, washed with cold ethanol and recrystallised with hot ethanol in 39 % yield.

Melting point : 190-192 ^oC

IR (KBr cm-1): 943 (N-C-S str), 3144, 3099 (Ar-H str),698 (C-S str), 1305 (C-N str).
NMR (ppm): 7.5 (m, 5H, Ar-H), 7.85 (m, 5H, Ar-H),14.6 (s, 1H, SH), 8.7 (s, 1H, N=CH).

REACTION SCHEME 1



Result and discussion

All the synthesized final compounds were first purified by successive recrystallisation using appropriate solvents. The purity of the synthesized compounds were checked by performing thin layer chromatography and by determining melting points. Then the synthesized compounds were subjected to spectral analysis such as IR and NMR spectra to confirm the structures. All the spectras were consistent with the structures.

The synthesized benzoic acid hydrazide (compound 1c) from methyl benzoate and hydrazine hydrate using absolute alcohol. The peak at 3300 of N-H stretching peak and peak at 1662 of amide C=O in IR spectra confirm the formation of compound 1c. From the compound benzoic acid hydrazide, potassium dithiocarbazinate (compound- 1d) was synthesized. The compound-1d is confirmed by the presence of C=S stretching at 617 cm^{-1} in IR spectra. The potassium dithiocarbazinate was used to synthesize 4[amino]-5-phenyl-4H-1,2,4-triazole-3-thiol(1e) by cyclisation process. The presence of N-C-S stretching at 943 cm^{-1}, NN- C at *1278* cm^{-1}in IR spectra and the presence of SH and NH peak at 14.6 and 7.9 ppm in HNMR confirm the formation of the same. The nucleus 4-[amino]-5-phenyl- 1,2,4-triazole-3-thiol(1e) was used to synthesise 4-(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol [1f]. The compound *1e* is confirmed by the absence of NH peak in IR spectra and the presence of N=CH at 10.3 ppm at NMR spectra. The presence of -N-N-C- moiety along with mercapto group imparts activities. Also the aromatic/heterocyclic ring improves the Central nervous system penetration. The Schiff bases are important class of compounds due to their flexibility, structural similarities with natural biological substances and also due to their presence of imine (-N=CH-) .

Conclusion

The 4-[amino]-5-phenyl- 1,2,4-triazole-3-thiol and 4(benzylideneamino)-5-phenyl -4H-1,2,4 – triazole-3-thiol were prepared and have very use full application in medicine, agriculture and industry.

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