Asian Journal of Chemistry; Vol. 24, No. 6 (2012), 2422-2424

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in

Synthesis, Structure and Alkylation of 4-(4-Fluoro phenyl)-5-(isomeric pyridyl)-1,2,4-triazole-3-thiole†

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(*Received*: 30 March 2011; *Accepted*: 6 January 2012) AJC-10917

New 3,5-disubstituted-1,2,4-triazole and their derivatives **3(a-c)** were synthesized in excellent yield by the intra molecular cyclization of 1,4- disubstituted thiosemicarbazides **2(a-c)** with sodium hydroxide. Their further alkylation with methyl iodide in OH- medium led to the formation of biologically active **4(a-c)**. These new compounds have been characterized by MS, ^{1}H NMR and IR spectroscopy. In addition, the yield and reaction time of **4(a-c)** have been compared with gently reflux and ultrasonic bath ways.

Key Words: Hetrocycle, Thiosemicarbazide, 1,2,4-Triazole, Methylation.

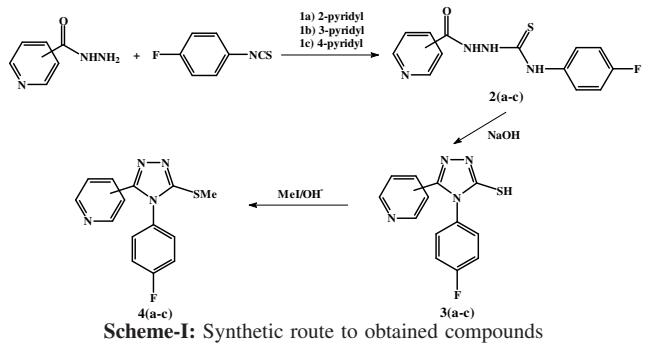
INTRODUCTION

The name triazole was first given to the carbon-nitrogen ring system $C_2N_3H_3$ by Bladin[1,2]. Publications devoted to the chemistry of triazoles in recent decade refer to the synthesis of 1,2,4-triazoles derivatives. 1,2,4-Triazole containing molecules have increasing interest as anticancer[3,4], fungicidal and antimicrobial[5-7], antitubercular[8,9] or antiinflammatory[10-13] agents. Further, they are significant in agrochemical industry as plant protecting materials[14,15], pharmacological activities such as anticonvulsing[16,17] and as well as photosensitive materials, industrial and biological activities, bactericides, pesticides and fungicides[18-22]. All triazoles are of synthetic origin and there is no report in nature[23].

The 3,5-disubstituted 1,2,4-triazole comprises a large number of the disubstituted triazole. Different approaches have been reported for the preparation of 3,5-disubstituted- 1,2,4-triazole system. 5-Amino-3-nitro-1,2,4-triazole (ANTA) have been synthesized by Kofman[24], Bayer *et al.*[25] reported the 3-aminio-5-methyl-l,2,4-triazole, direct synthesis of a variety of 3,5-disubstituted 1,2,4-triazoles from nitriles and hydrazides in the presence of catalytic amount of K_2CO_3 in *n*- BuOH[26], 3-dimethylamino-5-phenyl-1,2,4-triazole[27], 3(5)-dimethylamino-1,2,4-triazole was prepared from dimethylcyanamide and formyl hydrazine at 140 ºC[28], conjugated triazole moieties (*e.g.*, 3-(4-biphenylyl)-4-phenyl-5-(4-tert-butylphenyl)-1,2,4-triazole (TAZ)[29,30] and 3,5-dichloro-4-(4-methoxyphenyl)-4H-1,2,4- triazole[31].

Since we did not come across any reference on the preparation of **3(a-c)** and **4(a-c)** compounds the applicability of this procedure was considered. These efforts brought some fruitful results.

Herein, we would like to report our finding about an efficient procedure for the synthesis of of new 3,5-disubstituted-1,2,4-triazole containing isomeric pyridyl and their derivatives *via* the intra molecular cyclization of 1,4-disubstituted thiosemicarbazides under alkaline conditions (**Scheme-I**).



Scheme-I: Synthetic route to obtained compounds

Chemistry: The synthetic path way for compounds, described was achieved by a sequence of reactions starting from the respective **2(a-c)** (**Scheme-I**).

In the first step, the chemicals that were purchased from Merck Chemical Company (Darmstadt, Germany) were converted into products.

†Dedicated to memorial of Dr. Khosrow Zamani.

4-(4-Fluoro phenyl)-1-(isomeric pyridol) thiosemicarbazides **2(a-c)** were used as the key intermediates for the synthesis of heterocyclic compounds. Various thiosemi-carbazides were synthesized by condensing 4-fluoro phenyl isothiocyanate with isomeric pyridine carboxylic acid hydrazides **1(a-c)**.

The base catalyzed intramolecular dehydrative cyclization of the thiosemicarbazides **2(a-c)** furnished the corresponding substituted 1,2,4-triazole **3(a-c)** respectively. Compounds **3(a-c)**, when treated with methyl iodide in the presence of potassium hydroxide, yielded methylthio derivatives of 1,2,4- triazole **4(a-c)**. Use of methyl iodide over dimethyl sulfate for S-methylation was experimentally found to be superior in terms of yield.

EXPERIMENTAL

Melting points were measured with an electrothermal digital melting point apparatus and are uncorrected. The IR spectra were recorded on a spectrum UNICAM GALAXY series FTIR 5000 as potassium bromide pellets. The ^{1}H NMR spectra (DMSO) were recorded on a Bruker AV 300 MHZ instrument. Mass spectra were recorded on an EX1100 (Shimadzu, Kyoto, Japan) Model GC MS-QP instrument. The course of reactions and purity of compounds was controlled by TLC on Merck 60 F254 silica gel-coated aluminum sheets and spots were detected by UV light (ethanol/*n*-hexane = 2/3). Chemicals were purchased from MERCK.

Synthesis of 4-(4-fluoro phenyl)-1-(isomeric pyridol)-thiosemicarbazides 2(a-c): Respective substituted pyridine carboxylic acid hydrazides **1(a-c)** (7.9 mmol) were dissolved in ethanol (96 %, 50-100 mL), depending upon the solubility of the compounds. The 4-fluoro phenyl isothiocyanate (7.9 mmol) was separately dissolved in ethanol (96 %, 10 mL) then the solution of the isothiocyanate was poured in to the solution of hydrazide with continuous stirring. The reaction mixture was then refluxed. Each reaction required different times determined by TLC. After the completion of the reaction, the mixture cooled to room temperature. As a result a white solid crystal appeared. The crude solid was then filtered off and recrystallized from appropriate solvent to yield the compounds.

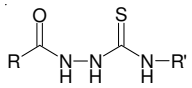
Synthesis of 4-(4-fluoro phenyl)-5-(isomeric pyridyl)-1,2,4-triazole-3-thiole 3(a-c): Solid thiosemicarbazides **2(a-c)** (2.1 mmol) were added portionwise to 20 mL of 2 N sodium hydroxide solution. The reaction mixture was refluxed and completion of the reaction checked by TLC. After the completion of the reaction, the mixture was allowed to cool and then it was acidified with 2 N hydrochloric acid to reach pH = 4. The crude products obtained upon cooling was filtered off and washed with water. In addition, to obtain purified compounds, the products were also dissolved in concentrated NaOH and then the HCl was added drop wise by this moment, the pH value attained 7.

Synthesis of 3-(methyl thio)-4-(4-fluoro phenyl)-5-(isomeric pyridyl)-1,2,4-tri azole 4(a-c): A mixture of suitable substitute-triazole-3-thiole (0.034 mmol), corresponding methyl iodide (0.034 mmol) in ethanolic alkali (0.019 g KOH in 20 mL aqueous EtOH); **Method A:** The reaction mixture was refluxed and completion of reaction checked by using TLC. The reaction conditions were established experimentally. On the cooling of the reaction mixture, the crude precipitate was collected, washed with ether and finally recrystallized; **Method B:** The reaction mixture was transferred to an isolated volumetric flask and then was placed in ultrasonic bath. The completion of reaction checked by using TLC. On the cooling of the reaction mixture, the solid compounds were washed with ether and then recrystallized.

RESULTS AND DISCUSSION

1,2,4-Triazoles play an important role due to their ubiquitous presence in many pharmaceutical agents and, more recently, in other functional materials with uses in engineering as corrosion inhibitors and in high-end technologies with conducting and optical properties. The more important uses are discussed such as here and may be regarded as falling into many classes: polymers, agricultural chemicals, pharmaceuticals, photographic chemicals, dyestuffs, *etc*.

In the present work 4-(4-fluoro phenyl)-1-(isomeric pyridol) thiosemicarbazides **2(a-c)** were used as the key intermediates for the synthesis of heterocyclic compounds. The majority of obtained compounds are new and spectral and elemental analyses have not been reported in the literature as yet. The structure of products **2(a-c)**, **3(a-c)** and **4(a-c)** was proved by the ^{1}H NMR spectra. These data suggest unsymmetrical structure of products, which means that the substitution occurred at the triazol ring. Chemical shift values were mentioned in δ ppm. The infrared spectra of compounds **2(a-c)** exhibited a characteristic strong absorption at 1230-1203 cm^{-1} attributable to the (C=S) of the thiourea residue. The carbonyl absorption in these compounds was observed at 1665-1651 cm^{-1}.



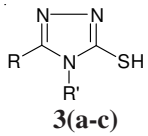
2(a-c)

2a: (R = 2-pyridoyl), (R' = fluoro phenyl); m.p. 191-192 ºC, yield 90 %; FT IR (KBr, ν_{max}, cm^{-1}) : 3261(NH), 3092 (Ar-H), 1657 (C=O), 1562-1427 (C=N, C=C), 1221 (C=S).

2b : (R = 3-pyridoyl), (R' = fluoro phenyl); m.p. 194-195 ºC, yield 82 %; FT IR (KBr, ν_{max}, cm^{-1}) : 3246 (NH), 3174 (Ar-H), 1651 (C=O), 1500 (C=N, C=C), 1203 (C=S). ^{1}H NMR δ(DMSO-d_6): 7.14-7.4 (4H, Ar-H), 7.53-9.1 (4H, Py-H), 9.84 (2H, s, CSNH), 10.77 (1H, s, CONH).

2c : (R = 4-pyridoyl), (R' = fluoro phenyl) ; m.p. 197-198 ºC, yield 97 %; FT IR (KBr, ν_{max}, cm^{-1}): 3209 (NH), 3100 (Ar-H), 1665 (C=O), 1532-1420 (C=N, C=C), 1230 (C=S). ^{1}H NMR δ (DMSO-d_6): 7.14-7.39 (4H, Ar-H), 7.83-8.78 (4H, Py-H), 9.86 (2H, s, CSNH), 10.87 (1H, s, CONH).

The dehydrative cyclization of **2(a-c)** in sodium hydroxide afforded corresponding substituted 1,2,4-triazole **3(a-c)** respectively. In the infrared spectra of compounds **3(a-c)** the absence of signals in the region 1665-1651 cm^{-1} established the lack of a (C=O) group. ^{1}H NMR and mass spectral data of the compounds supported this. In the ^{1}H NMR data of compounds **3(a-c)** a single peak in the region 14.26-14.37 ppm was observed due to (S-H) proton.



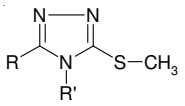
3(a-c)

3a: (R = 2-pyridyl), (R' = fluoro phenyl); m.p. 243-245 ºC, yield 93 %; FT IR (KBr, ν_{max}, cm^{-1}): 3109 (Ar-H), 2818 (SH), 1540-1514 (C=N, C=C). ^{1}H-NMR δ (DMSO-d_6): 7.26-7.4 (4H, Ar-H), 7.42-8.35 (4H, Py-H), 14.26(1H, s, SH).

3b: (R = 3-pyridyl), (R' = fluoro phenyl); m.p. 277-279 ºC, yield 90 %; FT IR (KBr, ν_{max}, cm^{-1}): 3068 (Ar-H), 2706 (SH), 1552-1450 (C=N, C=C). ^{1}H-NMR δ (DMSO-d_6): 7.32-7.5 (4H, Ar-H), 7.6-8.6 (4H, Py-H), 14.28 (1H, s, SH), MS (m/z): 272 (100 %), 271 (90 %), 239 (10 %), 213 (30 %).

3c: (R = 4-pyridyl), (R' = fluoro phenyl); m.p. 272-273 ºC, yield 97 %; FT IR (KBr, ν_{max}, cm^{-1}): 3057 (Ar-H), 2731 (SH), 1590-1552 (C=N, C=C). ^{1}H-NMR δ (DMSO-d_6): 7.23-7.41 (4H, Ar-H), 7.48-8.6 (4H, Py-H), 14.37 (1H, s, SH).

The refluxing of compounds **3(a-c)** with methyl iodide in alkaline ethanol yielded methylthio derivatives of 1,2,4-triazole and the absence of signals in the region 1203-1230 cm^{-1} and above 3200 cm^{-1} in IR spectral data established the absence of (C=S) and (NH) respectively. ^{1}H-NMR and mass spectral data of the compounds supported this. In the ^{1}H-NMR data of compounds **4(a-c)** the absence of signals in the region 14.26-14.37 ppm established the lack of a (S-H) proton.



4(a-c)

4a : (R = 2-pyridyl), (R' = fluoro phenyl); m.p. 152-154 ºC; FT IR (KBr, ν_{max}, cm^{-1}): 3078 (Ar-H), 2933 (R-H), 1553-1510 (C=N, C=C). ^{1}H-NMR δ (DMSO-d_6): 7.3-7.4(4H, Ar-H),7.47-8.31(4H,Py-H),2.63(3H,s,CH3). MS (m/z): 287 (100 %), 286 (90 %), 271 (20 %), 239 (17 %).

4b : (R = 3-pyridyl), (R' = fluoro phenyl); m.p. 144-145 ºC; FT IR (KBr, ν_{max}, cm^{-1}) : 3015 (Ar-H), 2928 (R-H), 1536 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.39-7.58 (4H, Ar-H), 7.58-8.59 (4H, Py-H), 2.63 (3H,s,CH3).

4c : (R = 4-pyridyl), (R' = fluoro phenyl); m.p. 189-190 ºC; FT IR (KBr, ν_{max}, cm^{-1}): 3053 (Ar-H), 2935 (R-H), 1506-1442 (C=N, C=C). ^{1}H NMR δ (DMSO-d_6): 7.3-7.47 (4H, Ar-H), 7.59-8.57 (4H, Py-H), 2.63 (3H, s, CH3).

As can be seen the results, the products **2(c), 3(c), 4(c)** by making use of R = 4-pyridyl have been shown the maximum yield (97 %). In addition, Table-1 compares the reaction time and yield of alkylation of **3(a-c)** to synthesize **4(a-c)** in two methods **A** (reflux) and **B** (ultrasonic bath). It is seen that the ultrasonic bath is quite satisfactory: lower reaction time along with the higher reaction yield.

TABLE-1
COMPARISON BETWEEN THE REACTION TIME (SEC.) AND YIELD EVALUATED BY REFLUX (A) AND ULTRASONIC BATH (B)

Method	Derivation	Reaction time (sec.)	Yield (%)
A	**4a**	8	78
	4b	10	75
	4c	7	80
B	**4a**	6	85
	4b	8	83
	4c	4	92

Conclusion

In this work, an easy and useful method to synthesize the new 3,5-disubstituted-1,2,4-triazole and biologically active **4(a-c)** has been presented. The 97 % maximum yield shown by R = 4- pyridyl and 92 % yield of alkylation of **3(a-c)** to synthesize **4(a-c)** obtained from ultrasonic bath.

The quantum chemical investigation of the presented compounds will be reported in the future publications. Overall, research in this area of heterocyclic chemistry has remained vibrant and will continue to be.

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