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STRUCTURAL NMR ANALYSIS OF TRIAZOLIC COMPOUNDS DERIVED FROM ISONICOTINIC ACID

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SUMMARY

The present article is aimed towards the structural NMR analysis of 4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole (**3**) and its product of alkylation (*via* sodium salt) with ethyl chloroacetate in absolute ethanol. 4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole and 4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-3-(4-pyridil)-1,2,4-triazole (**4**) were characterized by IR, ^{1}H-NMR, ^{13}C-NMR spectroscopy and structures were elucidated by 2D-^{1}H-^{13}C-HMBC spectroscopy.

Keywords: isonicotinic acid derivatives; S-alkylation; mercapto-1,2,4-triazole; NMR analysis; 2D-^{1}H-^{13}C-HMBC.

INTRODUCTION

Pyridinecarboxylic acids exist as three isomers with different position of carboxylic acid relative to nitrogen in pyridine. Isonicotinic acid (4-pyridinecarboxylic acid) is a heterocyclic acid used in manufacturing pharmaceuticals and agrochemicals. It is chiefly used in antituberculosis drugs, such as Isoniazid (isonicotinic acid hydrazide) - which is the most effective one, and Ethionamide (2-ethylthioisonicotinamide) [1], in

antidepressant and anxyolitic medication as Iproniazid (*N'*-isopropylisonicotinohydrazide) [2] or Nialamide (*N*-benzyl-3-(*N'*-(pyridine-4-carbonyl)hydrazino)propanamide).

A large number of 1,2,4-triazole-containing rings were incorporated into a wide variety of therapeutically drug candidates, including NSAIDs, CNS stimulants, antianxiety and antimicrobial agents and antimycotic "conazoles" [3]. 1,2,4-triazole groups are already used as pharmacophores in certain drugs like Triazolam, Alprazolam, Etizolam and Furacylin [3]. Sulfur-containing heterocycles such as mercapto- and/or thione-substituted 1,2,4-triazole ring systems (**1**) have been well studied and so far a variety of pharmacological activities were achieved[3].

The present article is aimed towards the structural NMR analysis of 4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole (**3**) and its product of alkylation (*via* sodium salt) with ethyl chloroacetate in absolute ethanol, namely 4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-3-(4-pyridil)-1,2,4-triazole (**4**). The synthesized compounds were characterized by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

MATERIALS AND METHODS

The reagents were commercial products (Merck, Fluka, Aldrich) and used without further purification. Melting points were determined on a Böetius PHMK (Veb Analytik Dresden) instrument, and thin-layer chromatography was carried out on silica gel-coated plates 60 F_{254} Merck using benzene:methanol 7:3, benzene:methanol 3:7 or benzene:ethyl acetate 1:1 (v/v) as eluants. IR spectra were recorded in KBr pellet on a Jasco FT/IR-410 spectrophotometer. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker Avance III 400 spectrometer in DMSO-d_6, using TMS as reference, chemical shifts being reported in ppm.

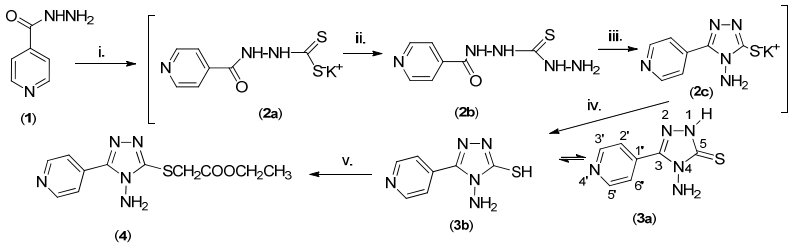
In our previous works [4], we established an efficient method for the synthesis of S-alkylated products, after studying different possible routes, such as:

A) suspending the triazolic compound in absolute ethanol, followed by the addition of ethyl chloroacetate (molar ratio 1:1), then heating the mixture under reflux for several hours, cooled at room temperature and filtered under vacuum;

B) suspending the triazolic compound in a $NaOH_{aq}$ solution in a 1:1 molar ratio under heating. The mixture is distilled to dryness at 40^{o}C under vacuum, the solid product is suspended in absolute ethanol, heated under reflux, then ethyl chloroacetate is added (molar ratio 1:1). After 15 to 30 minutes of reflux, the mixture is cooled at room temperature and distilled water is added, then the aqueous suspension is filtered under vacuum.

RESULTS

4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole was obtained accordingly to literature, by the reaction of hydrazide of isonicotinic acid with carbon disulfide in presence of ethanolic KOH [5]; the synthesis was performed without the isolation of the potassium N''acyl-dithiocarbazates intermediates (**2**), which treated with hydrazine hydrate at room temperature, then heating at reflux with an excess amount of hydrazine hydrate lead to 4*H*-4-amino-3-mercapto-5-(4-pyridyl)-1,2,4-triazole (**3**) *via* potassium salt (**2c**). The alkylation of 4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole (**3**) was achieved following the protocol previously described (route B) [6]



i=CS_2 / KOH / EtOH / r.t.; ii= a)$N_2H_4{\cdot}H_2O$ / r.t.; iii= $N_2H_4{\cdot}H_2O$ / Δ t; iv= HCl;
v= a) NaOH / H_2O / Δ t; b) $ClCH_2COOCH_2CH_3$ / EtOH / Δ t

Triazoles (**3**) and (**4**) were characterized by melting point, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole (**3**)

White powder (η=15%), **m.p**. 204-206°C;

IR (KBr, cm^{-1}): 3272m; 3162m; 1608i; 1318i; 944i; 826; 736;

^{1}H-RMN δ_H (DMSO-d_6, 400MHz): 14,18 (s, 1H, -NH); 8,77 (d, 2H, $J_{3'\text{-H, }5'\text{-H}}$ =5.6Hz, 3'H, 5'H); 8,04 (d, 2H, $J_{2'\text{-H, }6'\text{H}}$ =5,6Hz, 2'-H, 6'-H), 5,87 (s.l., 2H, $-NH_2$);

^{13}C-RMN δ_C (DMSO-d_6, 100MHz): 167,6 (3-C); 150,07 (3'-C, 5'-C); 147,28 (5-C); 132,8 (1'-C); 121,48 (2'-C, 6'-C).

4*H*-4-amino-5-ethoxycarbonyl-methylsulfanyl-3-(4-pyridil)-1,2,4-triazole (**4**)

White powder (η=38,6%); **m.p** 179-181°C; TLC one spot;

IR (cm^{-1})= 3262, 3143, 1731 (C=O), 1653, 1508, 1443, 1310, 1179, 1021, 823, 725, 419;

^{1}H-RMN δ_H (DMSO-d_6, 400MHz): 8.74-8.00 (2xd, 2x2H, 2'-H, 6'-H, 3'-H, 5'-

H); 6.34 (s, 2H, -N<u>H</u>$_2$); 4.17-4.12 (m, 4H, -O-C<u>H</u>$_2$-CH$_3$, -S-C<u>H</u>$_2$-); 1.21 (t, 3H, -O-CH$_2$-C<u>H</u>$_3$);

^{13}C-RMN δ_C (DMSO-d_6, 100MHz): 168.3 (-C=O); 154.3 (5-C); 152.0 (3-C); 150.0 (2'-C, 6'-C); 133.8 (4'-C); 121.2 (3'-C, 5'-C); 61.2 (-O-<u>C</u>H$_2$-CH$_3$); 33.0 (-S-<u>C</u>H$_2$-); 13.9 (-O-CH$_2$-<u>C</u>H$_3$).

DISCUSSION

The analysis of ^{13}C-NMR spectrum of compound (**3)** evidence only the presence of thione tautomeric form (C=S) through the signals with δ = 167.6 ppm, corresponding to exocyclic C=S bonds (Figure 1) and through the signal with δ = 14.18 ppm corresponding to 1-NH proton (Figure 2). The thionic tautomeric form is also confirmed by the long distance couplings $^3J_{3\text{-}C,1\text{-}NH}$ and $^3J_{5\text{-}C,1\text{-}NH}$ of 3-C and 5-C carbon atoms with the triazolic proton 1-NH (Figure 3). Analyzing 2D-^{1}H-^{13}C-HMBC spectrum, long distance coupling $^3J_{3\text{-}C,\text{-}NH2}$ and $^3J_{5\text{-}C,\text{-}NH2}$ of 3-C and 5-C carbon atoms with the protons of the -NH$_2$ group are observed, which confirms the presence of the amino group grafted on the triazolic ring (Figure 3).

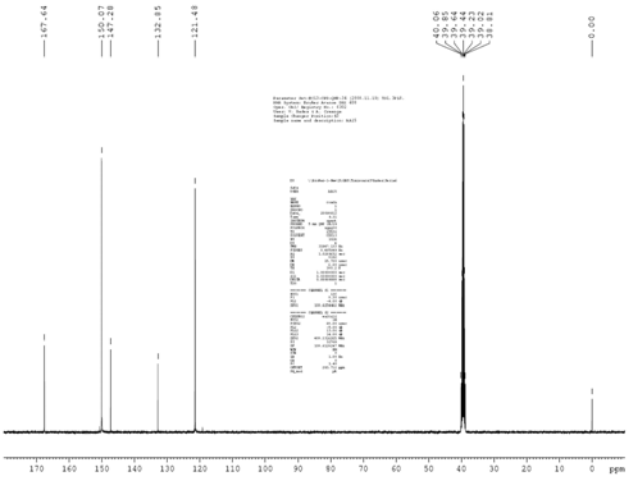


Figure 1. ^{13}C-NMR spectrum of (**3**), revealing tautomeric form (**3a**)

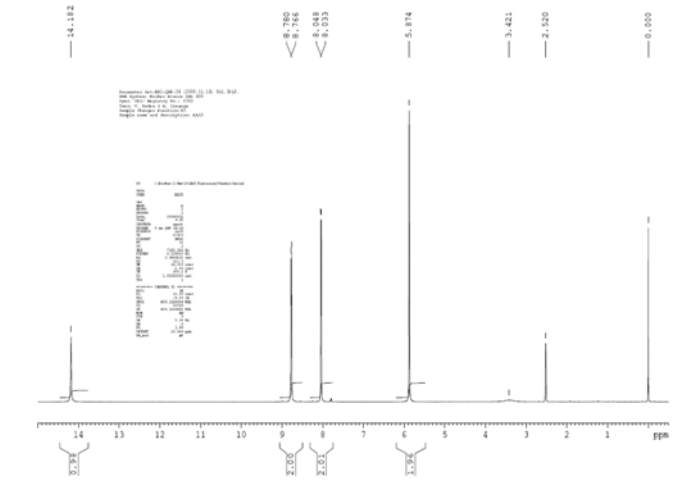


Figure 2. ^{1}H-NMR spectrum of (**3**), revealing tautomeric form (**3a**)

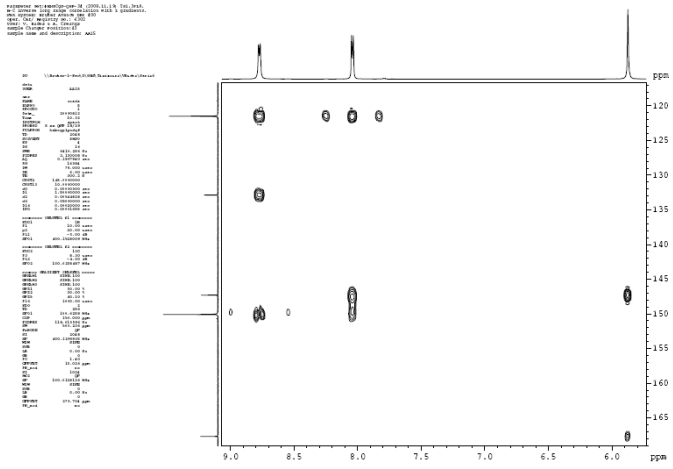


Figure 3. 2D HMBC ^{1}H-^{13}C spectrum of (**3**)

As for the alkylated triazole (**4**), S-alkylation and not N-alkylation was also confirmed by ^{13}C-NMR spectroscopy, where the chemical shift characteristic for C=S group (δ=180 ppm), possible only in N-alkylated compounds does not appear (Figure 4).

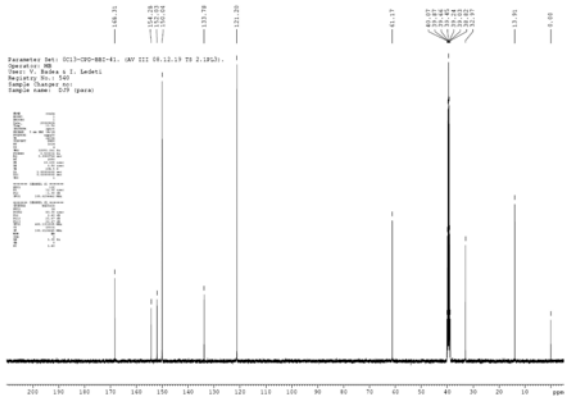


Figure 4. ^{13}C-NMR spectrum of (**4**)

CONCLUSION

The method in which potassium N''-acyldithiocarbazate **(2)**, obtained by treating hydrazide of isonicotinic acid (**1)** with carbon disulfide in ethanolic KOH, followed by the reaction with hydrazine hydrate, in two steps, at room temperature, then with an excess amount of hydrazine hydrate, at reflux, lead to pure 4*H*-4-amino-3-mercapto-5-(4-pyridyl)-1,2,4triazole(3), in modest yield.

The alkylation of sodium salt of 4*H*-4-amino-3-mercapto-5-(4-pyridil)-1,2,4-triazole (**3**), prepared *in situ*, with ethyl chloroacetate in absolute ethanol, is a convenient method for the synthesis of pure S-alkylated product.

The compounds were caracterised by IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy, and structures were elucidated by 2D-^{1}H-^{13}C-HMBC spectroscopy.

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