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A CONVENIENT METHOD FOR PREPARATION AND ISOLATION OF 4-n PROPYL-1,2,4-TRIAZOLINE-3,5-DIONE

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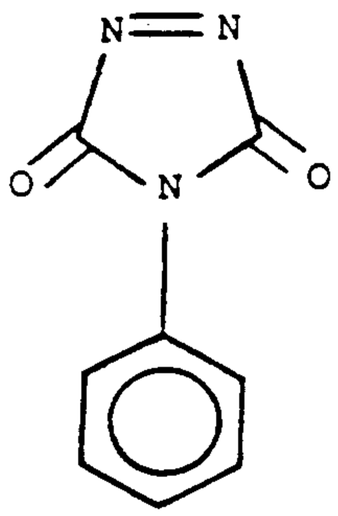
Abstract

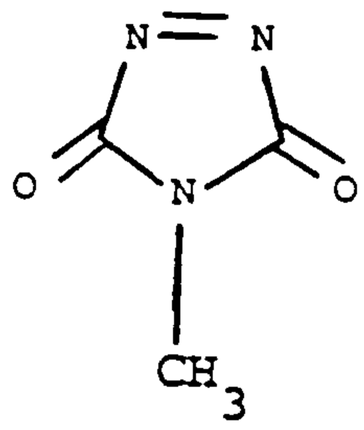
4-n- prophyl- 1,2,4- triazoline-3-5- dione was synthesized from n-propylisocyanate and ethylhydrazine carboxylate in several steps. The title compound was isolated as pink crystals in high yield and purity. This compound was fully characterized by IR and ^{1}H-NMR spectroscopy.

Introduction

4-substituted-1,2,4-triazoline-3,5-diones are among the most powerful dienophiles and enophiles known. 4-phenyl-1,2,4-triazoline-3,5-dione (1) is 1000 times more reactive in the Diels-Alder reaction with 2-chlorobutadiene than tetracyanoethylene (TCNE) [1] and 2000 times more reactive than maleic anhydride [2]. Also, 4-methyl-1,2,4-triazoline-3,5-dione (2) has been found to undergo the Diels-Alder reaction with cyclohexene at least 30000 times faster than ethylazodicarboxylate [3].



(1)

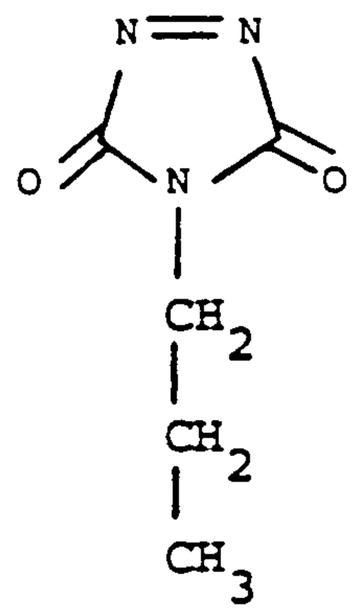


(2)

Keywords: Cyclization reaction; 4-n-propylurazole sodium salt; Oxidation; Dinitrogen tetroxide

Recently we reported the reaction of 4-substituted-1,2,4-triazoline-3,5-diones (1,2) with electron-rich aromatic small organic molecules as well as organic macromolecules [4-6]. These reactions are extremely fast and go through a series of spectacular color changes to yield small organic adducts as well as polymeric adducts by an electrophilic aromatic substitution mechanism.

The purpose of this investigation was to prepare 4-n-propyl-urazole from ethylcarbazate and then oxidize the urazole with gaseous dinitrogen tetroxide to yield 4-n-propyl-1,2,4-triazoline-3,5-dione (3). The latter compound is a very reactive dienophile, enophile and electrophile. Thus, its generation could be followed by Diels-Alder, ene, or electrophilic aromatic substitution reactions.

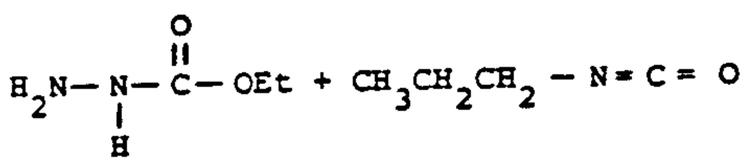


(3)

Results and Discussion

4-n-propyl-1,2,4-triazoline-3,5-dione (3) has not been reported as an isolated compound and no physical and spectroscopic data are available. Arya and Shenoy [7] have reported an *in situ* synthesis of this triazolinedione (3). They have prepared this compound by lead tetraacetate oxidation of 4-propylurazole (6), but they did not isolate it. Hall and Krishnan [8] reported the [2+2] cycloaddition reaction of compound (3) with diphenylketene, but, they did not give any experimental details about the synthesis of the compound (3).

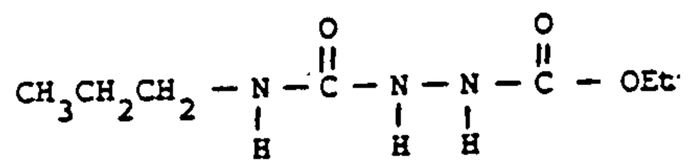
Our purpose in this study was to prepare 4-n-propyl-1,2,4-triazoline-3,5-dione (3) as an isolated, pure compound in a large quantity, which would allow us to follow Diels-Alder, ene or electrophilic aromatic substitution reactions with this compound.



(4)

1) below RT
2) RT

Toluene (eq. 1)

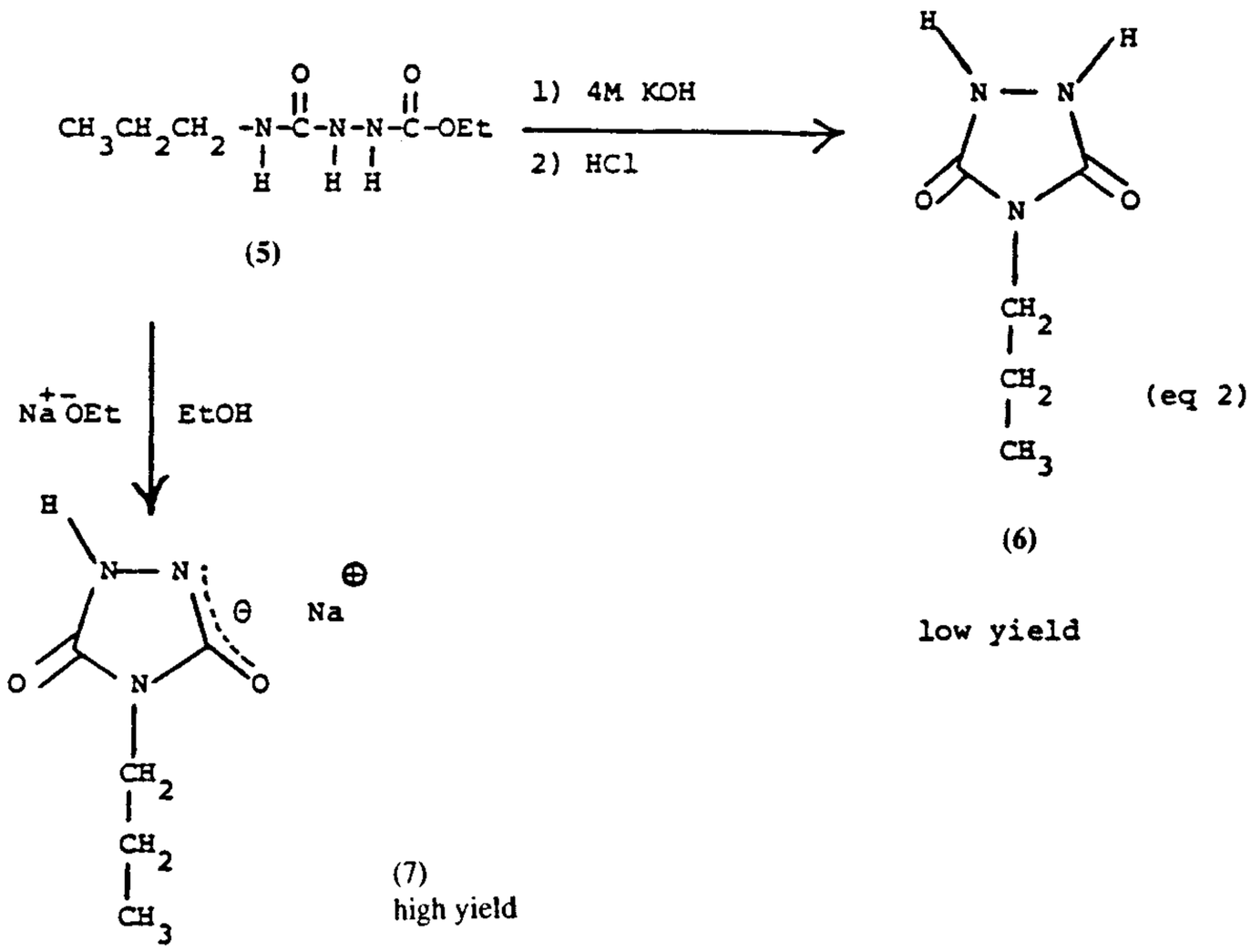


(5)

Ethyl carbazate (4) was prepared from the reaction of 1 mole of diethylcarbonate with 1 mole of hydrazine monohydrate at the refluxing temperature [9]. 1-ethoxycarbonyl-4-n-propylsemicarbazide (5) was synthesized from the reaction of ethylcarbazate (4) with n-propylisocyanate in toluene as a solvent instead of benzene [7]. The product was isolated as a white solid in a quantitative yield, in high purity (eq. 1).

The IR spectrum of compound (5) showed peaks at 3380 and 3200 cm^{-1} which were assigned to the two types of N-H stretchings. Peaks at 3000 and 2990cm^{-1} were assigned to the aliphatic C-H stretching. Peaks at 1720 and 1640 cm^{-1} were assigned to the two types of C=O stretchings.

4-n-propylurazole (6) was prepared from cyclization reaction of 1-ethoxycarbonyl-4-n-propylsemicarbazide (5) with 4M KOH followed by acidification with concentrated hydrochloric acid [7]. This procedure was repeated several times, but each time a low yield and purity of the compound (6) was obtained (eq. 2). Therefore, we developed a new procedure for the cyclization reaction of the compound (5). Thus, 1-ethoxycarbonyl-4-n-propylsemicarbazide (5) was reacted with sodium ethoxide in absolute ethanol at refluxing temperature (eq. 2).
The cyclization reaction product, 4-n-propylurazole sodium salt (7) was isolated as a white, pure solid in high yield.



(5)

1) 4M KOH
2) HCl

(6)

low yield

(eq 2)

Na⁺⁻OEt | EtOH

(7)
high yield

The IR spectrum of compound (7) showed two types of N-H stretching vibrations at 3400 and 3200 cm^{-1}. The first one is due to the free N-H stretching band, and the second one is due to hydrogen bonding. It also showed two types of C=O stretching vibrations at 1690 and 1590 cm^{-1}. Other bands are in agreement with the assigned structure (7) (Table I).

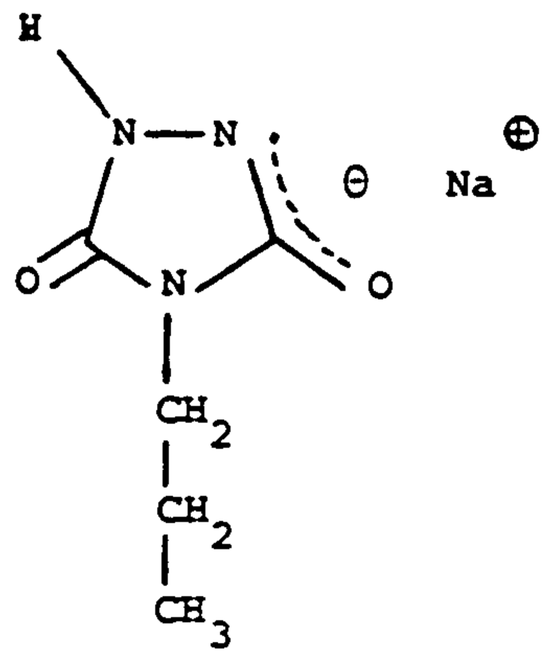
The ^{1}H-NMR spectrum of compound (7) (Fig. 1) in D_2O showed peaks at 0.85 ppm (triplat) which were assigned to the methyl protons. Peaks at 1.63 ppm (sextet) were assigned to the methylene protons attached to the methyl group. Peaks at 3.46 ppm (triplet) were assigned to the methylene protons attached to the nitrogen atom. N-H peak was exchanged with D_2O and peak of water covered between 4-5 ppm. A broad peak which was very weak also appeared around 8-9 ppm, which was assigned to the N-H proton. This could be due to the incomplete exchange of proton with deuterium.

The oxidation of 4-substituted-1,2,4-triazoline-3,5-diones can be accomplished with a wide variety of oxidizing reagents [9-17]. However, dinitrogen tetroxide gas is the most effective oxidizing agent which gives high yield and purity [18].

In this study, the oxidation was performed directly on 4-n-propylurazole sodium salt (7) instead of 4-n-propylurazole. A new method for the oxidation was used, which we had recently developed [19]. Thus dinitrogen tetroxide gas was generated and used immediately for the oxidation of 4-n-propylurazole sodium salt (7), equation 3, to give compound (3) as a pink crystalline solid in a high yield. This compound is very sensitive to acid, base, alcohol, light, heat, and moisture.

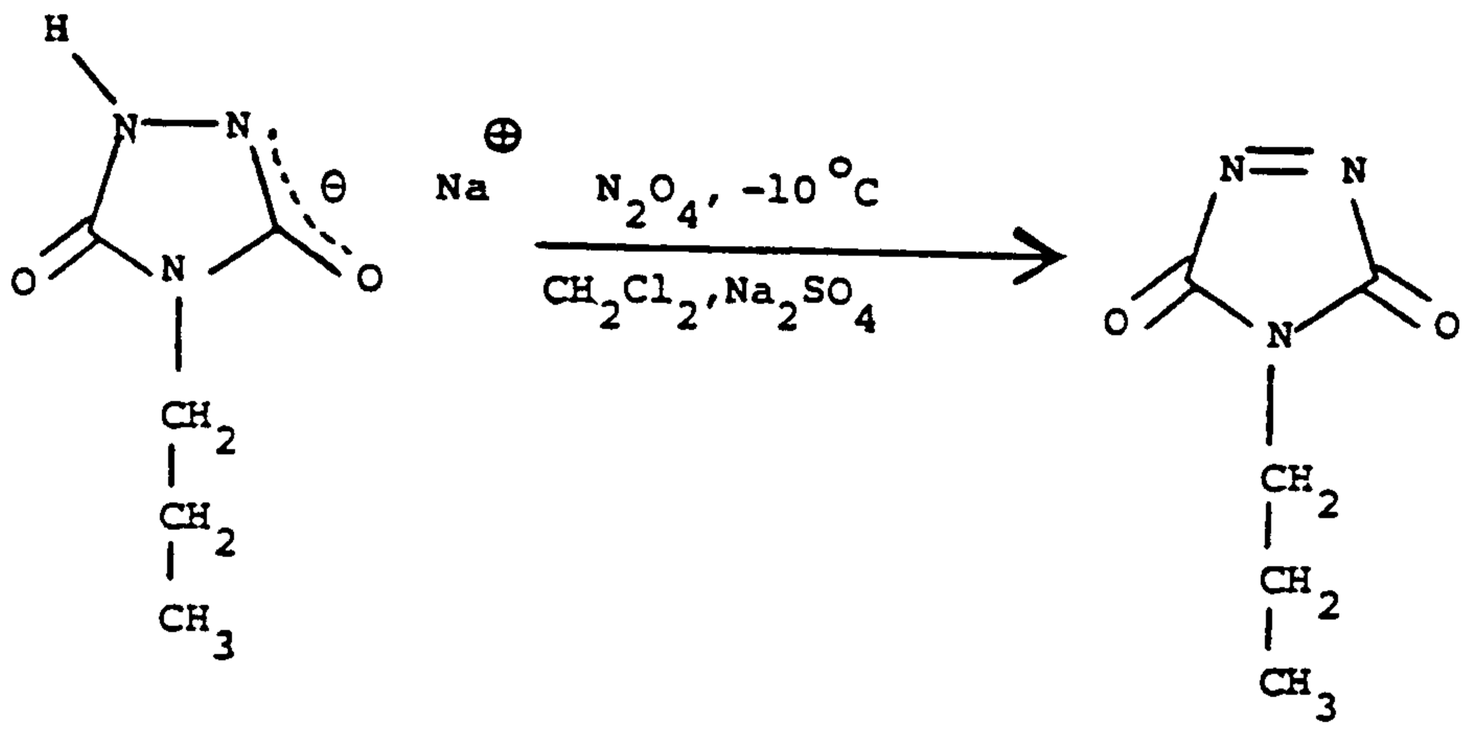
The IR spectrum of compound (3) showed peaks at 2995, 2950 and 2890 cm^{-1} which were assigned to C-H

Table I. IR data for 4-n-propylurazole sodium salt



(7)

Infrared Spectroscopy	KBr IR Band cm^{-1}	
	Frequency	Intensities
N-H Stretching (free)	3400	(s)
N-H Stretching (H-bonded)	3200	(s)
C-H Stretching	2990	(m)
	2920	(m)
	2880	(m)
C=0 Stretching	1690	(s)
C-------- 0 Stretching	1590	(s)
N-H Bending	1460	(s)



(7) (3) (eq.3)

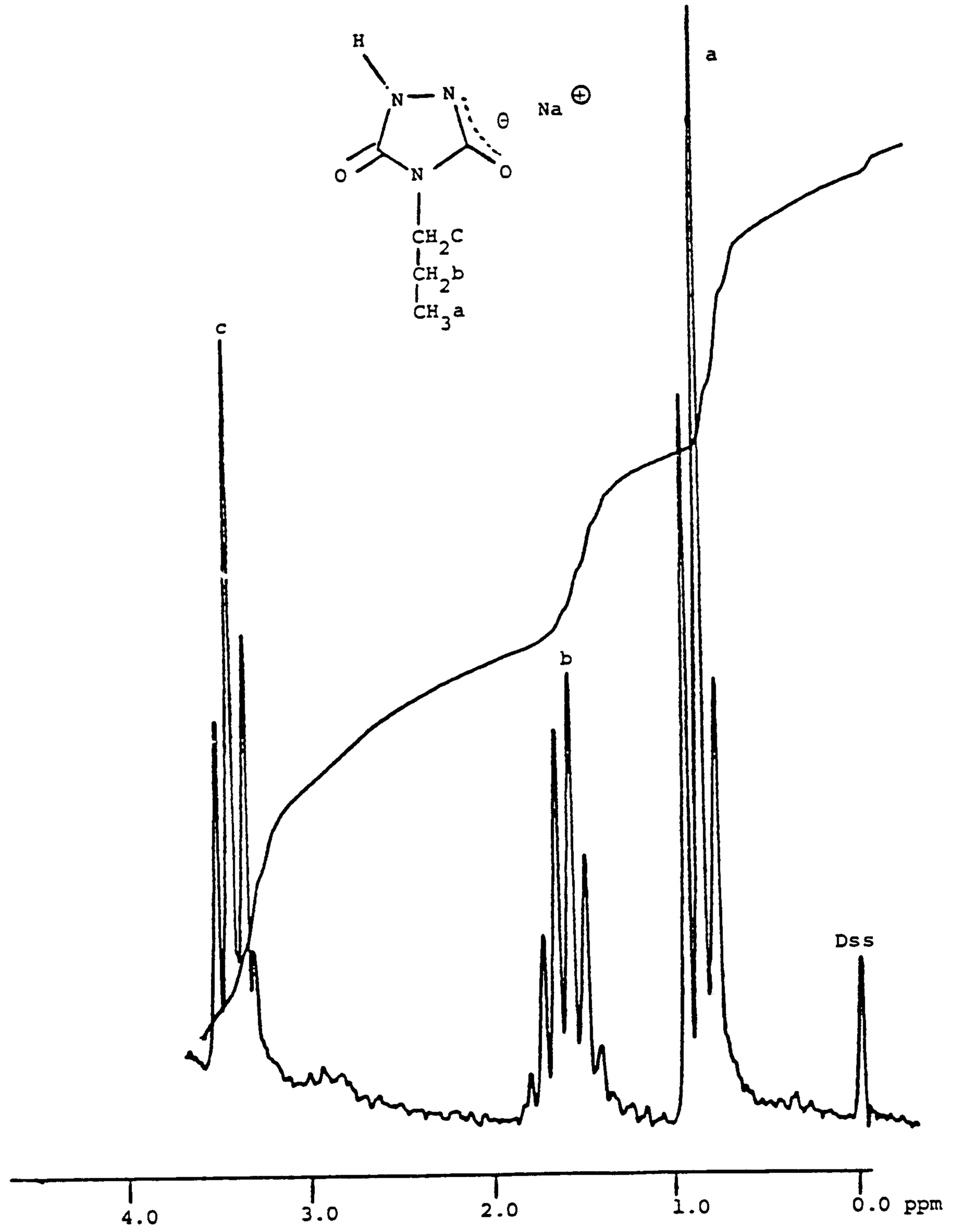


Fig.1. ^{1}H-NMR (90 MHz) spectrum of 4-n-propylurazole sodium salt (7) in D_2O at 25°C. N-H peak was exchanged with D_2O and peak of water covered between 4-5 ppm.

stretching. Peaks at 1760 and 1705 (sh) cm^{-1} were assigned to the C=O stretching. Other peaks are in agreement with the assigned structure (3).

The ^{1}H-NMR of compound (3) (Fig. 2) showed peaks at 0.90 ppm (triplet) which were assigned to the methyl protons. The peaks at 1.75 ppm (sextet) were assigned to the methylene protons attached to the methyl group. The peaks at 3.67 ppm (triplet) were assigned to the methylene protons attached to the nitrogen atom. The visible spectra of 4-n-propyl-1,2,4- triazoline-3,5- dione (3) were recorded in selected solvents (Table II).

Table II. Visible absorption of 4-n-propyl-1,2,4-triazoline 3,5-dione (3) in selected solvents at 25°C

	nm	
Solvent	2 λmax	ε
Methylene chloride	563.0,536.5, 520.0	131.0,162.7, 124.7
Toluene	567.0,540.0, 523.0	558,204,965
1,2-dichloroethane	563.0,536.5, 520.0	131.0,162.7, 124.7

Experimental Section

All chemicals were used as received; n-Propylisocyanate and diethylcarbonate were purchased from Fluka Chem. Co. All melting points were taken with a Gallenhamp melting point apparatus and are uncorrected. ^{1}H-NMR spectra (90 MHz) were recorded on a Varian EM-390 spectrometer. Infrared spectra were recorded on a Shimadzu 435 Infrared Spectrophotometer. Spectra of oils and liquids were obtained neat as a smear on sodium chloride or potassium chloride plates. Spectra of solids were carried out using KBr pellets. Vibrational transition frequencies are reported in wavenumber (cm^{-1}). Band intensities are assigned as weak (w), medium (m), shoulder (sh), strong (s), and broad (br).

Ethylhydrazine carboxylate was prepared from the reaction of hydrazine monohydrate (100%) with diethylcarbonate [4]. The product was a colorless liquid; b.p. 102-103°C at 18 mmHg.

Synthesis of 1-ethoxycarbonyl-4-n-propyl semicarbazide

In a 250 ml three-necked round-bottomed flask, which was equipped with a mechanical stirrer, a constant-pressure dropping funnel and a thermometer, a solution of 12.24 g (0.1176 mol) of ethyl hadrazine carboxylate (ethyl carbazate) and 120 ml of toluene was prepared and cooled in an ice-water bath to about 10°C. To the resulting solution, a solution of 10.00 g (0.1176 mol, 11.20 ml) of n-propylisocyanate in 60 ml toluene was added over a period of 30 mins. while being mechanically stirred. Upon addition of n-propylisocyanate solution, a white precipitate was formed. After the addition was completed, the reaction mixture was stirred at room temperature overnight.

The solid materials were isolated by filtration and dried at room temperature overnight.

m.p. 104°C; Lit [7], 110°C.

IR(KBr): 3380(s), 3200(s), 3000(s), 2990(s), 2890(m), 1720(s), 1700(s, sh), 1640 (s,br), 1550 (s,br), 1465(m), 1420(w), 1380(w), 1365(w), 1325(m), 1275(s), 1210(s), 1170(m), 1090(m), 1050(s), 700(m,br) cm^{-1}.

Synthesis of 4-n-propylurazole sodium salt

In a 1000-ml three-necked round-bottomed flask, which was equipped with a water-cooled condenser, a constant-pressure dropping funnel and a mechanical stirrer, sodium metal (3.88g, 0.1690 mol) was placed. To this metal, absolute ethanol (300 ml) was added dropwise over a period of 60 mins. while magnetically being stirred. At the end of the addition, a clear solution was obtained. 1-ethoxycarbonyl-4-n-propyl semicarbazide (32.00 g, 0.1690 mol) was added to the resulting clear solution under reflux conditions. Upon addition, an orange and then a red solution was obtained. After 2 hours, an orange slurry was formed which was refluxed for 54 hours. The hot reaction mixture was filtered and the desired solid compound was isolated as a white solid 17.82 g. Concentration of the filtrate to about 30 ml afforded more material 6.12g, yield; 23.94g, 85.5%, m.p. 230°C

IR(KBr): 3480 (m, sh), 3400 (s), 3200 (s), 2990(m), 2920(m), 2880(m), 1690(s), 1620(s, sh), 1590(s), 1460(s), 1420(m), 1370(m), 1260(m), 1050(m), 910(w), 807(s), 770(w), 720(w), 640(m, br)cm^{-1}.

^{1}H-NMR (D_2O, DSS): δ 0.85 (t, 3H, J= 9.0 Hz), 1.63 (sextet, 2H, J= 7.5 Hz), 3.46 (t, 2H, J=7.5 Hz).

Generation of No_2-N_2O_4 gas

Into a 250-ml one-necked round-bottomed flask was charged 60.00g of lead (II) nitrate (the lead (II) nitrate had been crushed to a fine powder with a mortar and pestle and then dried in an oven at 120°C for three days). The flask was equipped with a 35 cm column and was connected to a gas trap. Lead (II) nitrate was heated with a Bunsen burner. Brownish red No_2-N_2O_4 gas evolved and was used immediately in the following oxidation reaction.

Synthesis of 4-n-propyl-1,2,4-triazoline-3,5-dione

Into a 500 ml three-necked round-bottomed flask, which was equipped with a magnetic stirrer and a gas inlet tube, 8.00 g (0.0484 mol) of 4-n-propylurazole sodium salt, 350 ml methylene chloride, and 60.00 g of anhydrous sodium sulfate were added. The suspension was stirred by a magnetic stirrer and cooled to-10°C with an ice-salt bath. Generated No_2-N_2O_4 gas was bubbled through this solution for about 45 mins. After a few minutes, the solution

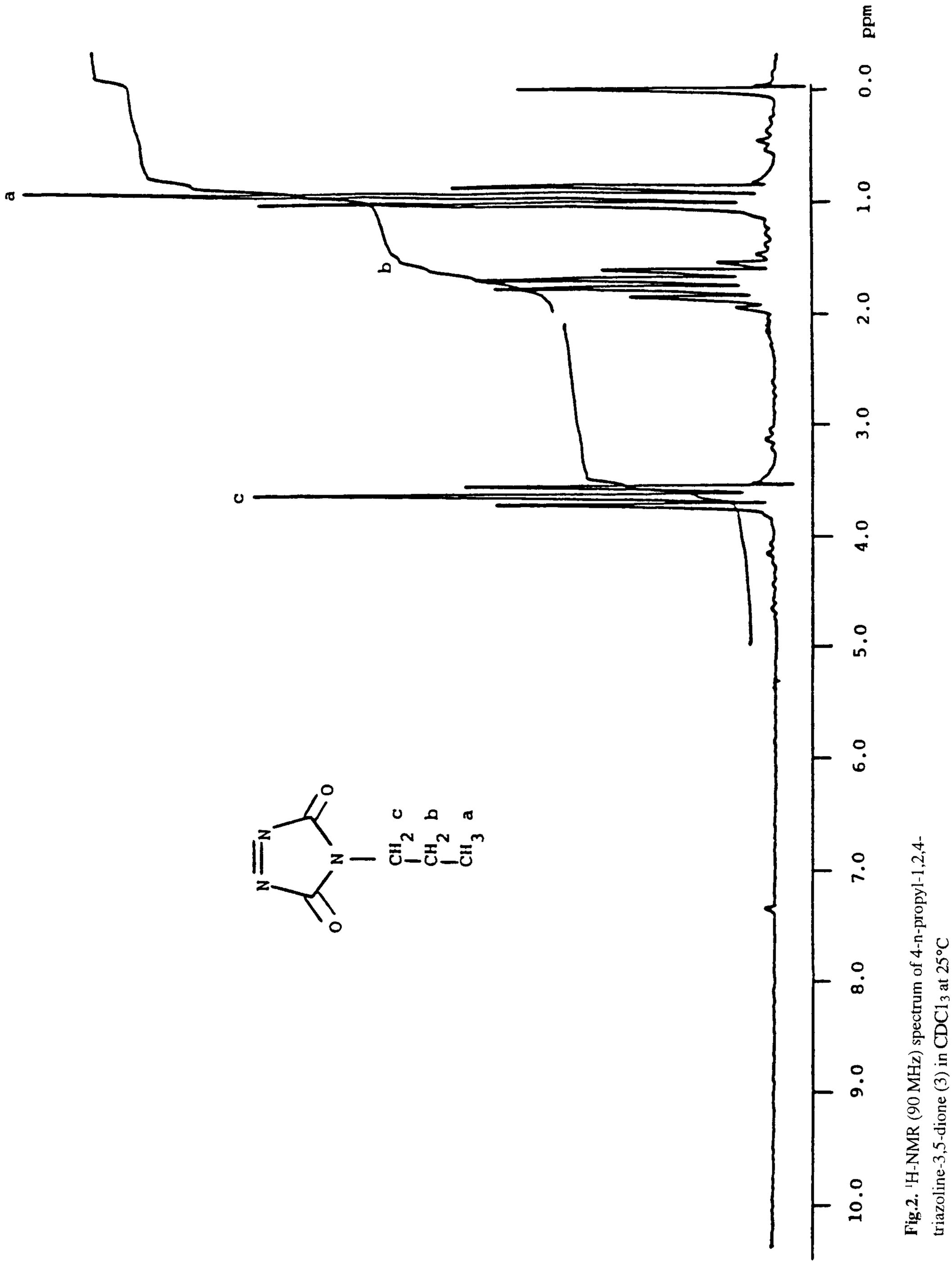


Fig.2. ^{1}H-NMR (90 MHz) spectrum of 4-n-propyl-1,2,4-triazoline-3,5-dione (3) in $CDCl_3$ at 25°C

turned light pink and then deep-pink. The temperature was kept below 0°C. The deep-pink colored solution was stirred for another 60 mins., it was then filtered using gravity filtration. The solvent was evaporated under vacuum to give a pink crystalline compound, yield; 6.00g, 87.6%, m.p. 44°C.

IR(KBr): 3560(w), 2995(m), 2950(m), 2890(w), 1760(s,br), 1705(s, sh), 1520(w), 1450(m), 1400(s), 1370(m), 1350(m), 1320(m), 1270(w), 1190(m), 1120(m), 980(m), 890(m), 860(m), 800(m), 740(s), 680(s), 618(w), 550(w) cm^{-1}.

^{1}H-NMR ($CDCL_3$, TMS): δ 0.90 (t, 3H, J=9.0 Hz), 1.75 (sexted, 2H, J= 7.5 Hz), 3.67 (t, 2H, J= 9.0 Hz).

Conclusion

1-ethoxy carbonyl-4-n-propyl semicarbazide can be readily prepared from the reaction of ethylcarbazide with n-propylisocyanate in a quantitative yield. Cyclization reaction of the semicarbazide with sodium ethoxide is very effective and gave 4-n-propylurazole sodium salt in high yield and purity. The oxidation of the urazole sodium salt with No_2-N_2O_4 gas yielded 4-n-propyl-1,2,4-triazoline-3,5-dione as a pink crystalline solid in high yield and purity.

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