Turk J Chem
26 (2002) , 801 – 806.

Synthesis and Characterization of Some 3-alkyl-4-amino-5-cyanomethyl-4H-1,2,4-triazoles

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Received 25.01.2002

The preparation and characterization of some 3-alkyl-4-amino-5-cyanomethyl-4H-1,2,4-triazoles with active methylene groups are described and their structural properties using NMR and IR spectra and elemental analyses are given.

Key Words: 1,2,4-triazole, cyanoacet hydrazide, acylhydrazine, cyclization

Introduction

Over the last few decades, there has been considerable interest in the synthesis and characterization of derivatives of 1,2,4-triazoles because of the biological and pharmaceutical properties of this heterocycle[1−5]. In general, three methods have been developed for the formation of 4-amino-3,5-dialkyl-4H-1,2,4-triazoles. These methods involve either the reactions of carboxylic acids and their functional derivatives with hydrazine hydrate at a high temperature, or the treatment of diacylhydrazines with hydrazine[6,7] or, at high yields, the condensation of nitriles with hydrazine in the reaction mixtures containing sulfur or sulfur-containing compounds[8−13].

These three approaches have been used to synthesize symmetrical substituted 4-amino-3,5-dialkyl-4H-1,2,4-triazoles, but unsymmetrically substituted derivatives are considerably more difficult to obtain[9]. Recently, a general route for the synthesis of unsymmetrically substituted compounds was achieved[14] by treating *tert*-butoxycarbonylhydrazone esters **1** with some acylhydrazines such as acetic-, nicotinic-, isonicotinic-, and malonic acid hydrazides to yield the corresponding 3,5-dialkyl-4-*tert*-butoxycarbonylamino-4H-1,2,4-triazoles[14]. The precursor compounds, ester *tert*-butoxycarbonyl hydrazones **1**, for triazole formation have recently been synthesized by the reactions of alkylimidate hydrochlorides **2** with *tert*-butyl carbazate[15]. The reactions of compound **1** leading to the formation of 4,5-dihydro-1H-1,2,4-triazol-5-ones with ammonia, primary amines and hydrazine have been studied[15]. 3,5-dialkyl-4H-1,2,4-triazole derivatives have also been obtained by the treatment of various ester ethoxycarbonylhydrazones with some acylhydrazides and a general method has been developed[16].

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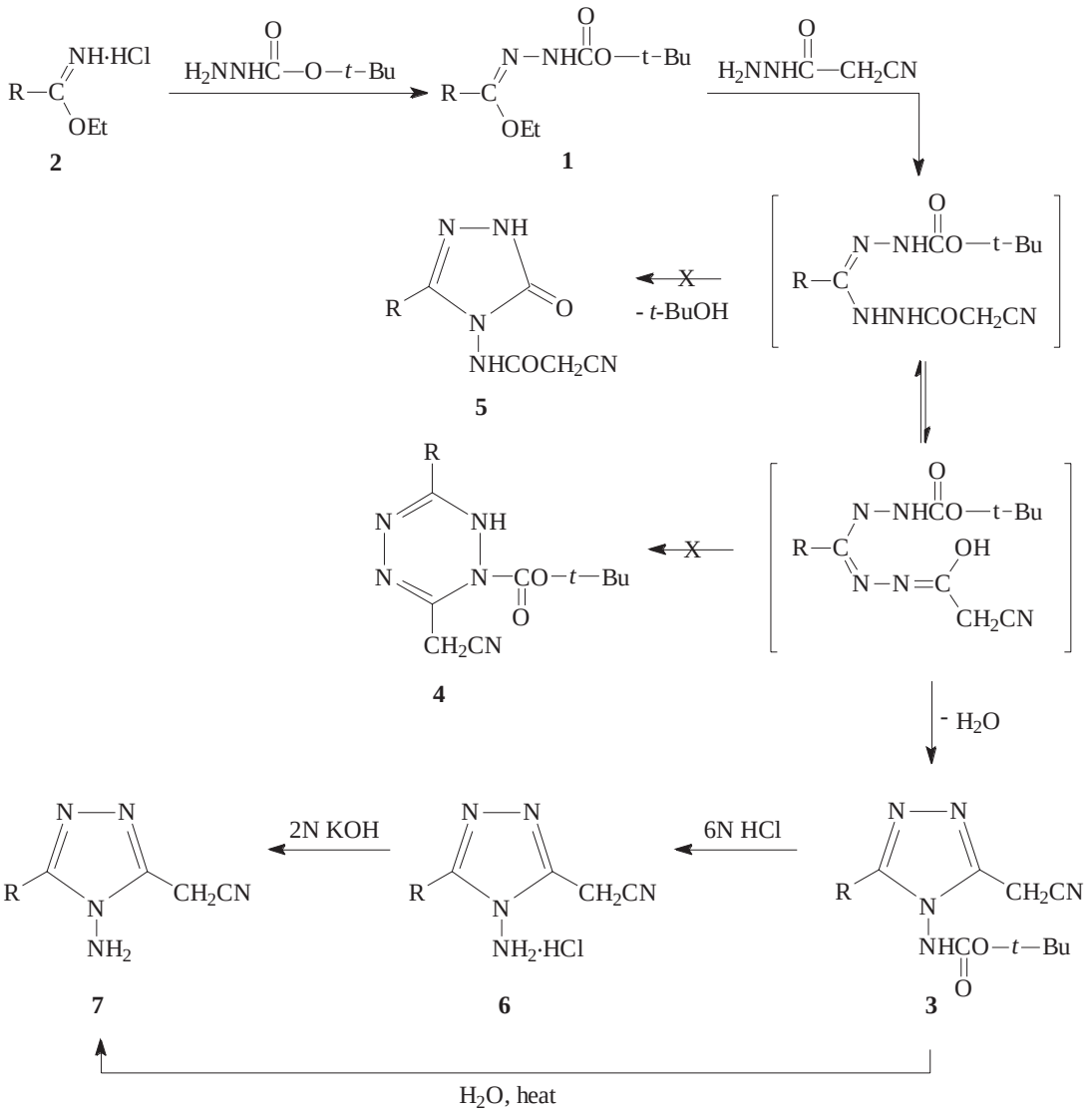
In addition, 3-alkyl-5-cyanomethyl-4H-1,2,4-triazole derivatives have been obtained by treating alkylimidate hydrochlorides and ester ethoxycarbonyl hydrazones with cyanoacetic acid hydrazide[17]. It was reported that *tert*-butyl carbazates can be hydrolyzed in acidic solutions to give hydrazinium salts[14,18,19]. Indeed, some 3,5-dialkyl-4-*tert*-butoxycarbonylamino-4H-1,2,4-triazole derivatives have also been hydrolyzed to their corresponding salts by treatment with 6N hydrochloric acid[14]. These hydrochlorides could be converted to 3,5-dialkyl-4-amino-4H-1,2,4-triazoles by using equivalent amounts of ethoxide anion/ethanol[14].

Results and Discussion

In the present study, compound **1** was treated with cyanoacetic acid hydrazide to obtain the corresponding 3-alkyl-4-*tert*-butoxycarbonylamino-5-cyanomethyl-4H-1,2,4-triazoles **3** as outlined in the reaction course shown in Scheme 1. As a result of instability at elevated reaction temperatures and conversion to 1,2,4-



Scheme

triazoles above 100°C[14], 1,2-dihydro-1,2,4,5-tetrazines **4** were not isolated as evidenced by ^{1}H-NMR spectral analyses. It is known that the nitrogen protons of dihydrotetrazines appear at δ 8.7-9.1 [9,10]. Nevertheless, the nitrogen protons of the isolated compounds appeared at a lower field (10.2-12.5 ppm) as expected from the structures.

Although compounds type **3** or **5** were expected to be formed, the spectroscopic data indicated that only compounds type **3** were obtained. Compounds **3a** and **3d** were converted to the corresponding 3-alkyl-4-amino-5-cyanomethyl-4H-1,2,4-triazole hydrochlorides (**6a**, **6d**) in good yields by treatment with 6N HCl. Formation of 3-alkyl-4-amino-5-cyanomethyl-4H-1,2,4-triazoles (**7a**, **7d**) was achieved when compounds **6a** and **6d** were treated with an equivalent amount of 2N KOH.

In conclusion, a group of triazole derivatives incorporating active methylene groups were synthesized and characterized. These compounds seem to have potential as precursors for the synthesis of triazole structures with diverse biological or pharmacological properties.

Experimental

Melting points were determined by a Gallenkamp melting point apparatus and the uncorrected experimental data of compounds **3**, **6** and **7** are given in Table 1. ^{1}H-NMR and ^{13}C-NMR spectra (δ, ppm) were recorded on a Mercury-VX Varian Model 200 mHz-NMR spectrometer using TMS as internal reference (Tables 2 and 3). IR spectra (ν, cm^{-1}) were run as potassium bromide pellets on a Perkin Elmer 1600 Series FTIR spectrophotometer (Table 4). Microanalyses were performed on a Carlo Erba 1106 elemental analyzer. Starting compound **1** was synthesized by previously reported routes[15]. The necessary chemicals were obtained from Fluka AG (Switzerland).

Table 1. Physical data of the compounds **3a**, **3b**, **3c**, **3d**, **6a**, **6d**, **7a** and **7d**

Compound	Yield (%) (%)	Molecular m.p. (°C) Solvent	formula M.w.	Analysis (%) calcd. (found) C	H	N
3a	37	73 – 75	$C_{10}H_{15}N_5O_2$	50.60	6.35	29.50
		isobut.acetate-pet.ether	273.20	(50.56)	(6.48)	(29.77)
3b	40	101	$C_{11}H_{12}N_5O_2$	50.60	6.10	27.85
		isobut.acetate-pet.ether	251.29	(50.76)	(6.15)	(27.98)
3c	81	96	$C_{16}H_{19}N_5O_2$	61.30	6.10	22.35
		benzene-pet.ether	313.36	(61.24)	(6.23)	(22.46)
3d	68	130-133	$C_{16}H_{18}ClN_5O_2$	55.25	5.20	20.25
		benzene-pet.ether	347.81	(55.25)	(5.18)	(20.43)
6a	60	165-167	$C_5H_8ClN_5$	34.60	4.65	40.35
		ethanol-diethylether	173.61	(34.72)	(4.58)	(40.52)
6d	83	164	$C_{11}H_{11}Cl_2N_5$	46.50	3.90	24.65
		ethanol-diethylether	284.15	(46.55)	4.14)	(24.59)
7a	48	130-131	$C_5H_7N_5$	43.80	5.15	51.07
		ethyl acetate-pet.ether	137.15	(43.69)	(5.09)	(50.87)
	44 M1					
7d[*]	64 M2	127-130	$C_{11}H_{10}ClN_5$	53.35	4.06	28.30
	79 M3	ethyl acetate-pet.ether	247.69	(53.35)	(4.10)	(28.45)

[*]M1, M2 and M3 represent the method employed.

General Method for the Synthesis of 3-Alkyl(alkylaryl)-4-tert-butoxycarbonylamino-5-cyanomethyl-4H-1,2,4-triazoles (3a, 3b, 3c, 3d)

The corresponding ethyl carboxylate tert-butoxycarbonylhydrazone **1** (0.01 mol) was heated in an oil bath with cyanoacetic acid hydrazide (0.01 mol) at 110-115°C for 1 h. After cooling to room temperature 3-4 mL of a (1:2) mixture of ethyl acetate-petroleum ether was added to the viscous reaction mixture. On cooling the mixture in a deep freeze, a white solid appeared. This crude product was recrystallized from an appropriate solvent to afford the desired compound. Compounds **3a** and **3b** were recrystallized from isobutylacetate-petroleum ether (1:2), and compounds **3c** and **3d** were from ethylacetate-petroleum ether (1:2).

General Method for the Synthesis of 3-Alkyl(alkylaryl)-4-amino-5-cyanomethyl-4H-1,2,4-triazole hydrochlorides (6a, 6d)

Hydrochloric acid was added dropwise to a solution of corresponding compound **3** (0.01 mol) in a minimum quantity of tetrahydrofuran. After heating on a steam bath for 15 min, the resulting solution was evaporated at 30-35 ° C under reduced pressure and dried in vacuo. The solid residue was recrystallized from an appropriate solvent to give the desired compound. Compounds **6a** and **6d** were recrystallized from ethanol-diethylether (1:2).

Synthesis of 3-Alkyl(alkylaryl)-4-amino-5-cyanomethyl-4H-1,2,4-triazoles (7a, 7d)

The corresponding compound, **6** (0.01 mol), was treated with an equivalent amount of 2N KOH in ethanol and the mixture was refluxed for 5 h. After evaporation at 35-40°C under reduced pressure a white solid was formed. This solid compound was recrystallized from an appropriate solvent to afford compound **7**. Compounds **7a** and **7d** were recrystallized from ethylacetate-petroleum ether (1:2).

Method 2: 3-p-chlorobenzyl-4-amino-5-cyanomethyl-4H-1,2,4-triazole (7d;$C_{11}H_{10}ClN_5$)

An equivalent amount of K_2CO_3 (3% in water) was added dropwise to a solution of compound **6d** (0.01 mol) in the minimum quantity of water and a white solid was filtered and recrystallized from an appropriate solvent to afford compound **7d**.

Method 3: 3-p-chlorobenzyl-4-amino-5-cyanomethyl-4H-1,2,4-triazole (7d;$C_{11}H_{10}ClN_5$)

Compound **3d** was refluxed for 5 h in the mixture of ethanol-water (1:6). After evaporation at 50-55°C under reduced pressure the crude product was obtained. This compound was recrystallized from an appropriate solvent to afford compound **7d**.

Table 2. ^{1}H-NMR Data of Compounds **3a**, **3b**, **3c**, **3d**, **6a, 6d**, **7a** and **7d** (δ, ppm, in DMSO-d_6^a)

Comp.	$(CH_3)_3$	CH_3	CH_2	CH_2	Ar-H	NH	Other Groups
3a	1.33(s,9H)	2.38(s,3H)	-	3.95(s,2H)	-	10.22 (s,1H)	-
3b[b]	1.42(s,9H)	1.20(t,3H)	-	4.15(s,2H)	-	-	-
3c	1.40(s,9H)	-	2.05(s,2H)	4.05(s,2H)	7.15-7.35 (m,5H)	-	-
3d	1.42(s,9H)	-	-	4.05(s,2H)	7.20 (AA'BB',4H)	10.55 (s,1H)	-
6a	-	2.70(s,3H)	-	4.65(s,2H)	-	-	7.10 (s,3H) ($^{+}NH_3$)
6d	-	-	4.39(s,2H)	4.55(s,2H)	7.38-7.48 (AA'BB',4H)	-	7.20 (s,3H) ($^{+}NH_3$)
7a	-	2.32(s,3H)	-	4.15(s,2H)	-	-	5.92(s,2H) (NH_2)
7d	-	-	4.09(s,2H)	4.18(s,2H)	7.35 (AA'BB',4H)	-	5.92(s,2H) (NH_2)

[a] $CDCl_3$ for compounds **3a**, **3c**, **3d** and **6a**

[b] 2.52 (q, 2H, CH_2)

Table 3. ^{13}C-NMR Data of Compounds **3a**, **3b, 3c**, **3d**, **6a**, **6d**, **7a**, **7d** (δ, ppm in DMSO-d_6^a)

	Compound No							
	3a	**3b**	**3c**	**3d**	**6a**	**6d**	**7a**	**7d**
$(CH_3)_3$	28.0	28.0	27.5	27.8	-	-	-	-
CH_3	9.5	11.0	-	-	9.0	-	9.5	-
CH_2(-R)	-	17.0	-	-	-	-	-	-
CH_2(-Ar)	-	-	30.5	28.8	-	28.0	-	28.2
CH_2(-CN)	15.1	14.1	15.0	15.1	14.3	15.1	14.1	14.5
C(-CH_3)$_3$)	83.5	82.0	83.5	83.8	-	-	-	-
C=O	154.1	156.0	155.0	155.1	-	-	-	-
C≡N	113.5	115.5	113.5	113.5	114.2	114.8	115.5	114.8
C-3(triazole)	153.1	153.5	153.2	153.1	153.5	154.5	152.5	154.8
C-5(triazole)	146.0	146.1	147.0	147.1	148.2	148.5	146.0	148.5
C_1 (ar.)	-	-	134.0	134.1	-	132.2	-	132.0
C_2, C_6 (ar.)	-	-	129.1	129.1	-	128.5	-	128.5
C_4 (ar.)	-	-	127.1	136.0	-	132.5	-	133.1
C_3,C_5 (ar.)	-	-	128.5	131.0	-	131.0	-	131.1

[a] $CDCl_3$ for compounds **3a, 3c**, **3d** and **6a**

Table 4. IR Data of Compounds **3a**, **3b**, **3c**, **3d**, **6a**, **6d**, **7a** and **7d** (ν cm^{-1})

Comp.	ν_{NH}	ν_{NH2}	ν^{+}_{NH3}	$\nu_{C\equiv N}$	$\nu_{C=O}$	$\nu_{C=N}$	aromatic ring
3a	3145	-	-	2263	1735	1684, 1560	-
3b	3130	-	-	2262	1728	1560, 1490	-
3c	3146	-	-	2262	1720	1537, 1490	735, 695
3d	3140	-	-	2262	1719	1537, 1490	798
6a	-	-	3118	2280	-	1634, 1572	-
6d	-	-	3268	2259	-	1633, 1492	786
7a	-	3264, 3160	-	2267	-	1535, 1655	-
7d	-	3328, 3203	-	2260	-	1526, 1490	797

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