

Synthesis and Application of Triazole Derivatives. Synthesis of 3- and 5-Acyl-1,2,4-triazoles *via* Lithiation of 1-Alkyl-1*H*-1,2,4-triazoles

Shunsaku OHTA,^{*,a} Ikuo KAWASAKI,^a Akihisa FUKUNO,^a Masayuki YAMASHITA,^a Toshiji TADA,^b and Tetsuo KAWABATA^b

Kyoto Pharmaceutical University,^a Misasagi-Nakauchicho 5, Yamashinaku, Kyoto 607, Japan and Analytical Research Laboratories of Fujisawa Pharmaceutical Co., Ltd.,^b Kasima 2-1-6, Yodogawaku, Osaka 532, Japan.

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N-Unsubstituted 3-acyl-1*H*-1,2,4-triazoles (3), and 5-acyl-1-alkyl-1*H*-1,2,4-triazoles (4) were synthesized by acylation of 5-lithiotriazoles with amides. The 3-position of 1-methyl-5-phenylthio-1*H*-1,2,4-triazole (11) was lithiated by lithium 2,2,6,6-tetramethylpiperidide, and acylation of the produced carbanion with amides followed by desulfurization with Raney nickel give the 3-acyl derivatives (5). The structural isomers, 3-acyl-4-alkyl-4*H*-1,2,4-triazoles (6), were prepared by *N*-methylation of 3.

Keywords lithiation; 1*H*-1,2,4-triazole; 4*H*-1,2,4-triazole; acyl-1,2,4-triazole; nuclear Overhauser effect; X-ray crystallography

The 1,2,4-triazole ring is an important heterocyclic moiety of pharmacologically interesting drugs, such as the antifungal agent fluconazole.¹⁾ We previously reported a method for introduction of a 1,2,4-triazol-1-yl group into several drugs containing the carbamoyl (—NHCO—) function in order to investigate a new prodrug system.²⁾ Very little work has been reported on preparation of *C*-acyl derivatives of 1,2,4-triazole,³⁾ so we attempted to develop a convenient synthetic method for these compounds. This paper deals with synthesis of all types of *C*-acyl-1,2,4-triazoles and their structural elucidation.

Two regioisomers (1 and 2) are possible in *N*-substituted 1,2,4-triazole and three tautomers (3A, 3B, and 3C) of *N*-unsubstituted *C*-acyl 1,2,4-triazole exist in equilibrium, although the tautomeric isomers are, in general, treated as a single compound.⁴⁾ In *N*-substituted *C*-acyl-1,2,4-triazoles, three isomers (4, 5, and 6) are possible (Chart 1).

Lithiation of 1-alkyl-1*H*-1,2,4-triazole with *n*-butyllithium occurs exclusively at the 5-position to produce the 5-lithio derivative (7).^{3b,5)} In our experiments, however, lithiation of 1a (R=CH₃) with *n*-butyllithium at −50 °C or with lithium diisopropylamide (LDA) at 0 °C followed by acetylation with *N,N*-dimethylacetamide (DMA) resulted

in low yields of 4a (R=CH₃) (Table I). So we examined the lithiation conditions and found that almost complete proton abstraction at the 5-position of 1a occurred upon treatment with *n*-butyllithium at 0 °C for 15 min. The lithiation at the 5-position was confirmed by the formation of 5-deuterio-1-methyl-1*H*-1,2,4-triazole (1f), which was prepared by quenching of 7 with deuterium oxide. Namely, the proton nuclear magnetic resonance (¹H-NMR) spectrum of 1f shows the C³-H signal at 7.92 ppm (s, 1H), which is close to the reported value for the C³-H (7.93 ppm) rather than that for the C⁵-H (8.09 ppm) of 1a.⁶⁾ The lithiated compound 7 was treated with various tertiary amides to give the corresponding 5-acyl-1-alkyl-1*H*-1,2,4-triazoles (4) in 43.3—99.3% yields. Physical and spectral data for these 5-acyl-1-alkyl-1*H*-1,2,4-triazoles (4) are listed in Table II.

N-Unsubstituted 3- or 5-acyl-1*H*-1,2,4-triazoles (3A, 3B or 3C) were synthesized as follows. The 1-position of

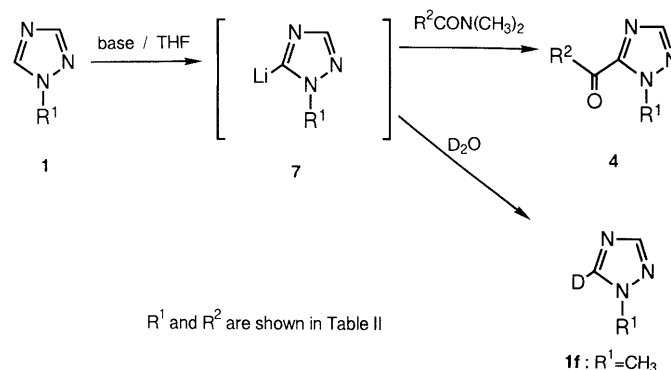


Chart 2

TABLE I. 5-Acetylation of 1a (R=CH₃) with DMA

Reaction temp. (°C)	Deprotonation time (min) (1a → 7a)	Base	Yield (%) ^a of 4a (R=CH ₃)
−50	15	<i>n</i> -BuLi	56.5
0	15	LDA	26.9
0	30	LDA	35.1
0	15	<i>n</i> -BuLi	98.0

^a) Determined by GLC with an internal standard.

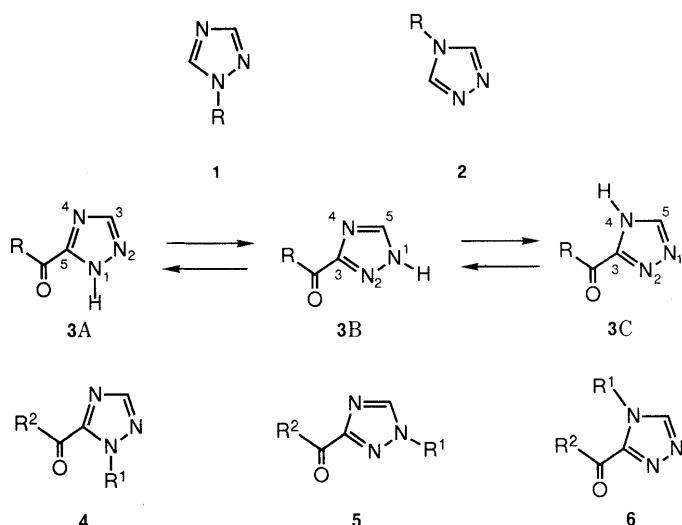
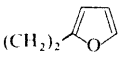
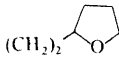


Chart 1

TABLE II. 5-Acyl-1-alkyl-1*H*-1,2,4-triazoles (**4**) Prepared

Compd.	R ¹	R ²	Isolated yield (%)	mp or bp _{mmHg} (°C)	Formula	Anal. (%) or HRMS (m/z, M ⁺)			IR (ν _{C=O}) cm ⁻¹ (in CHCl ₃)	¹ H-NMR (δ, ppm)
						Calcd (Found)	C	H	N	
4a ^{d,e}	CH ₃	CH ₃	82.1 ^a	bp _{0.3} 55–60	C ₅ H ₇ N ₃ O					
4b ^e	CH ₃	C ₆ H ₅	61.8	mp 64–65 ^f	C ₁₀ H ₉ N ₃ O		64.16 (64.16)	4.85 (4.85)	22.45 (22.39)	1700, 1720, 1655
4c	CH ₃	C ₂ H ₅	97.6	bp _{0.3} 70 mp 40 ^e	C ₆ H ₉ N ₃ O			139.0750 (139.0769)		1690
4d ^{d,e}	CH ₃	CH ₃ (CH ₂) ₅	91.3	bp ₁ 101	C ₁₀ H ₁₇ N ₃ O			195.1370 (195.1382)		1690
4e ^d	CH ₃	Cyclohexyl	77.5	bp ₁ 101	C ₁₀ H ₁₅ N ₃ O			193.1220 (193.1186)		1690
4f ^d	CH ₃	C(CH ₃) ₃	49.1	bp _{0.05} 62	C ₈ H ₁₃ N ₃ O			167.1060 (167.1044)		1675
4g	CH ₃	C ₆ H ₅ CH ₂	60.4	bp _{0.02} 97–102	C ₁₁ H ₁₁ N ₃ O			201.0900 (201.0878)		1690
4h	CH ₃	4-ClC ₆ H ₄ CH ₂	43.3	mp 93–95 ^f	C ₁₁ H ₁₀ ClN ₃ O		56.06 (56.26)	4.28 (4.27)	17.83 (17.96)	1695
4i	CH ₃		84.5	mp 46–48 ^f	C ₁₀ H ₁₁ N ₃ O ₂		58.53 (58.54)	5.40 (5.46)	20.48 (20.66)	1700
4j	CH ₃		70.3	bp _{0.03} 110	C ₁₀ H ₁₅ N ₃ O ₂			209.1170 (209.1181)		1690
4k	CH ₃	4-Cl-C ₆ H ₄	55.5	mp 103–104 ^f	C ₁₀ H ₈ ClN ₃ O		54.19 (54.34)	3.64 (3.58)	18.96 (19.19)	1660
4l	CH ₃	2,4-Cl ₂ C ₆ H ₃	77.6	mp 142–143 ^f	C ₁₀ H ₇ Cl ₂ N ₃ O		46.90 (47.08)	2.76 (2.73)	16.41 (16.59)	1697
4m	CH ₃	4-CH ₃ OC ₆ H ₄	83.4	mp 84–85 ^f	C ₁₁ H ₁₁ N ₃ O ₂		60.82 (61.07)	5.10 (5.10)	19.34 (19.56)	1654
4n ^d	C ₂ H ₅	CH ₃	81.3	bp _{0.3} 60	C ₆ H ₉ N ₃ O			139.0750 (139.0721)		1695
4o	iso-Pr	CH ₃	94.3	bp _{0.3} 60	C ₇ H ₁₁ N ₃ O			153.0900 (153.0927)		1695
4p ^d	<i>n</i> -Hexyl	CH ₃	98.0	bp _{0.03} 76–79	C ₁₀ H ₁₇ N ₃ O			195.1370 (195.1348)		1700
4q	CH ₂ C ₆ H ₅	CH ₃	99.3	bp _{0.03} 115	C ₁₁ H ₁₁ N ₃ O			201.0900 (201.0882)		1695

^a Yield: 98.0% (GLC analysis). ^b Known compound: see ref. 3a. ^c Solidified after distillation. ^d UV λ_{max} (EtOH) nm (ε): **4a** 244 (7630); **4c** 244 (8380); **4d** 244 (7130); **4e** 244 (6000); **4n** 244 (6000); **4p** 244 (6380). ^e ¹³C-NMR (CDCl₃): **4a** 27.9 (COCH₃), 38.6 (NCH₃), 148.8 (–N=C(CO)N–), 149.9 (–N=CHN–), 189.9 (CO); **4b** 38.8 (NCH₃), 128.5, 130.9, 134.1, 135.8, (C₆H₅), 149.2 (–N=C(CO)N–), 149.9 (–N=CHN–), 183.3 (CO); **4d** 14.0, 22.5, 23.6, 28.8, 31.5, 38.7, 40.3 ((CH₂)₄CH₃), 148.8 (–N=C(CO)N–), 150.0 (–N=CHN–), 192.8 (CO). ^f Recryst. solvent: **4b**, **4h** (DMF–H₂O); **4i**, **4k**, **4l**, **4m** (*n*-hexane).

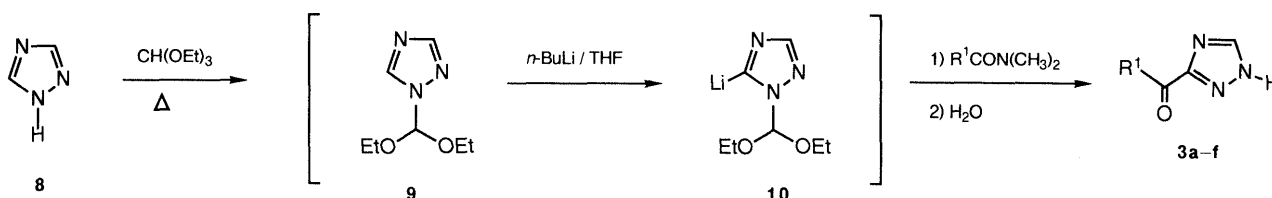


Chart 3

1*H*-1,2,4-triazole (**8**) was protected with a diethoxymethyl group by treatment with ethyl orthoformate at 100 °C according to the reported procedure, which was used in the protection of the 1-position of 1*H*-imidazole and benzimidazole.^{7,8} The 1-protected triazole (**9**) was lithiated

and then acylated by a similar procedure to that used for the conversion of **1a** to **4a** to give **3a–f** in moderate to good yields (Table III). The diethoxymethyl group was found to be useful as an easily introducible and removable protecting group of the 1-position of 1,2,4-triazole, whereas, several

TABLE III. 1-Unsubstituted 3-Acyl-1*H*-1,2,4-triazoles (**3**) Prepared

R ¹	Compd. ^{a)}	Isolated yield (%)	mp (°C)	Formula	Anal. (%)			IR cm ⁻¹ (KBr tab.)	¹ H-NMR (δ, ppm) (in <i>d</i> ₆ -DMSO)
					Calcd (Found)				
					C	H	N		
CH ₃	3a^{b)}	96.1	158—163	C ₄ H ₅ N ₃ O	43.24 (43.60)	4.54 (4.52)	37.82 (38.19)	3400 (NH) 1690 (C=O)	2.58 (s, 3H, COCH ₃), 8.30—8.91 (br, 1H, C ³ -H), 13.80—14.95 (br, 1H, NH)
C ₆ H ₅	3b	60.9	204—208 (dec.)	C ₉ H ₇ N ₃ O	62.42 (62.31)	4.07 (4.03)	24.67 (24.44)	3050 (NH) 1655 (C=O)	7.40—8.32 (m, 5H, Ph-H), 8.69 (s, 1H, C ³ -H), 13.80—15.25 (br, 1H, NH)
<i>n</i> -Hexyl	3c^{b)}	84.7	149—151	C ₉ H ₁₅ N ₃ O	59.64 (59.58)	8.34 (8.25)	23.19 (23.28)	3200 (NH) 1695 (C=O)	0.70—1.85 (m, 11H, (CH ₂) ₄ -CH ₃), 3.02 (t, 2H, CH ₂ CO, <i>J</i> = 7.0 Hz), 8.57 (s, 1H, C ³ -H), 13.50—15.45 (br, 1H, NH)
4-ClC ₆ H ₄	3d	58.4	217—221	C ₉ H ₆ ClN ₃ O	52.07 (52.05)	2.91 (2.83)	20.24 (20.33)	3000 (NH) 1659 (C=O)	7.45—8.45 (m, 4H, Ph-H), 8.74 (s, 1H, C ³ -H), 13.09—16.01 (br, 1H, NH)
2,4-Cl ₂ -C ₆ H ₃	3e	47.8	228—232	C ₉ H ₅ Cl ₂ N ₃ O	44.66 (44.57)	2.08 (2.08)	17.36 (17.34)	3000 (NH) 1675 (C=O)	7.60—7.79 (m, 3H, Ph-H), 8.77 (s, 1H, C ³ -H), 14.71—14.90 (br, 1H, NH)
4-CH ₃ OC ₆ H ₄	3f	53.2	179—181	C ₁₀ H ₉ N ₃ O ₂	59.11 (59.18)	4.46 (4.51)	20.68 (20.88)	3100 (NH) 1658 (C=O)	3.88 (s, 3H, OCH ₃), 7.06—8.45 (m, 4H, Ph-H), 8.63 (s, 1H, C ³ -H), 14.21—15.05 (br, 1H, NH)

a) All compounds were recrystallized from ethanol. b) Compd. [UV λ_{max} (EtOH) nm (ε)]: **3a**, [225 (6380)]; **3c**, [225 (5380)].

TABLE IV. Atomic Positional and Equivalent Isotropic Thermal Parameters with E.S.D. in Parentheses

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> _{eq} / <i>B</i> _{iso}
N1	0.6836 (3)	0.4491 (4)	0.2360 (6)	4.3
N2	0.7807 (3)	0.3526 (4)	0.2339 (5)	4.2
C3	0.7217 (4)	0.2202 (5)	0.2405 (6)	3.9
N4	0.5962 (3)	0.2274 (4)	0.2468 (6)	4.7
C5	0.5759 (5)	0.3728 (6)	0.2435 (8)	4.9
C6	0.7048 (6)	0.6127 (6)	0.231 (1)	5.8
C7	0.7948 (5)	0.0769 (5)	0.2427 (7)	5.0
O8	0.7399 (4)	−0.0417 (4)	0.2447 (6)	6.9
C9	0.9346 (6)	0.0896 (7)	0.242 (1)	6.5
H5	0.490 (5)	0.418 (5)	0.241 (7)	3.4
H6A	0.620 (5)	0.660 (6)	0.231 (8)	7.8
H6B	0.736 (5)	0.629 (6)	0.093 (8)	6.8
H6C	0.761 (5)	0.633 (6)	0.357 (8)	6.3
H9A	0.978 (5)	−0.021 (7)	0.242 (8)	7.1
H9B	0.978 (5)	0.135 (6)	0.358 (8)	5.5
H9C	0.960 (5)	0.129 (6)	0.115 (8)	5.9

TABLE V. Bond Lengths (Å) with E.S.D. in Parentheses

N1–N2	1.349 (5)	N1–C5	1.344 (7)	N1–C6	1.474 (9)
N2–C3	1.340 (6)	C3–N4	1.350 (6)	C3–C7	1.495 (7)
N4–C5	1.312 (7)	C7–O8	1.209 (7)	C7–C9	1.501 (10)
C5–H5	1.00 (5)	C6–H6A	1.00 (6)	C6–H6B	1.05 (6)
C6–H6C	0.99 (6)	C9–H9A	1.09 (6)	C9–H9B	0.95 (6)
C9–H9C	1.00 (6)				

other protecting groups (*e.g.*, benzyl,^{5d)} pyrrolidinomethyl^{5a)}) are not convenient. The ultraviolet (UV) spectrum of **3a** (R=CH₃) in ethanol is very similar to that of 1-methyl-3-acetyl-1*H*-1,2,4-triazole (**5a**: R¹=R²=CH₃), described below, so that **3a** seems to take the 3-acyl-1*H*-type structure (**3B**) in solution rather than the 5-acyl-1*H*-type (**3A**) or 3-acyl-4*H*-type (**3C**) structure.

Next, we planned to prepare 3-acyl-1-alkyl-1*H*-1,2,4-triazole (**5**) from **1**. Since lithiation at the 3-position of the triazole ring has not been reported,⁹⁾ introduction of an appropriate protecting group at the most reactive 5-position of **1** seems to be necessary. A phenylthio group was selected as the protecting group after several examinations.¹⁰⁾ The

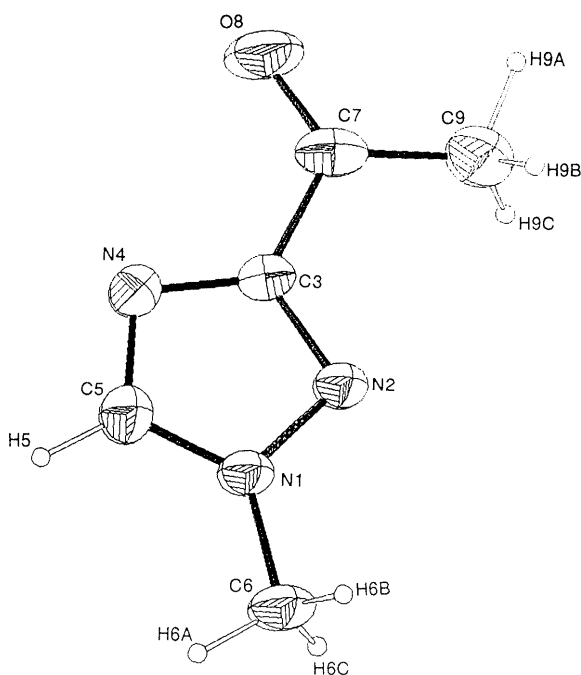
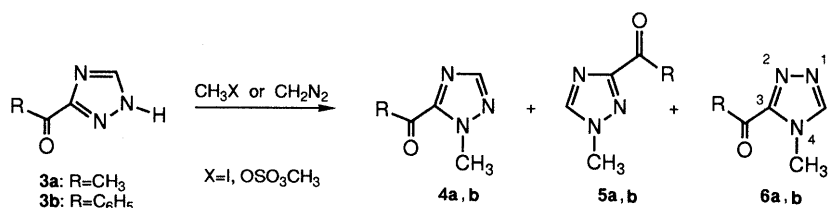
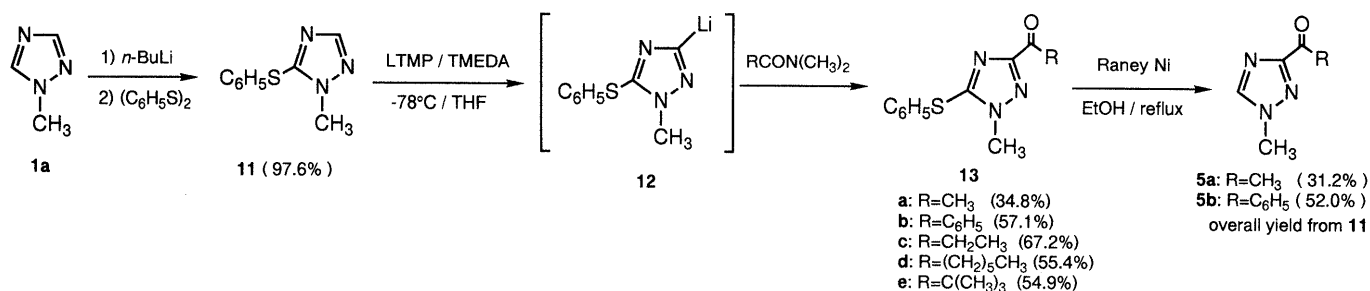
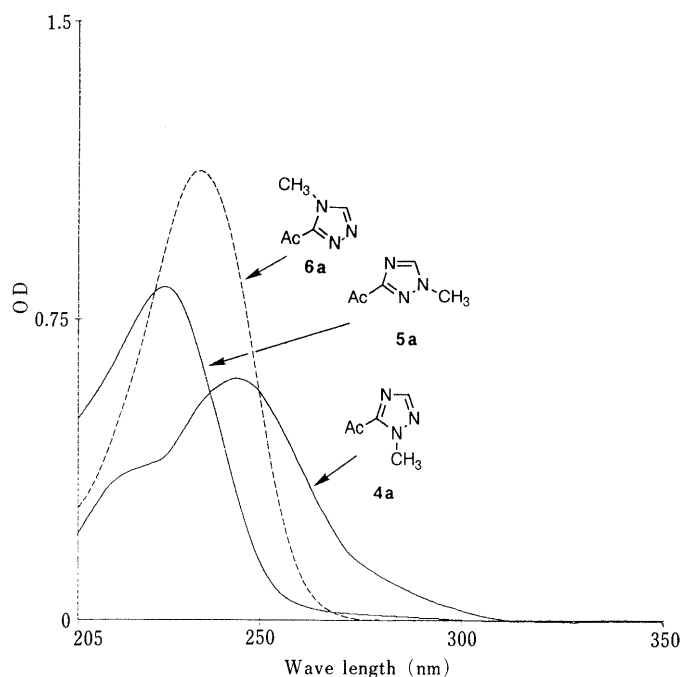
TABLE VI. Bond Angles (°) with E.S.D. in Parentheses

N2–N1–C5	110.1 (4)	N2–N1–C6	120.5 (5)
C5–N1–C6	129.4 (5)	N1–N2–C3	101.1 (3)
N2–C3–N4	115.7 (4)	N2–C3–C7	120.1 (4)
N4–C3–C7	124.2 (4)	C3–N4–C5	102.1 (4)
N1–C5–N4	111.0 (5)	C3–C7–O8	119.3 (5)
C3–C7–C9	117.2 (5)	O8–C7–C9	123.5 (6)
N1–C5–H5	126 (3)	N4–C5–H5	123 (3)
N1–C6–H6A	106 (3)	N1–C6–H6B	103 (3)
N1–C6–H6C	104 (3)	H6A–C6–H6B	110 (5)
H6A–C6–H6C	111 (5)	H6B–C6–H6C	121 (5)
C7–C9–H9A	111 (3)	C7–C9–H9B	114 (3)
C7–C9–H9C	115 (3)	H9A–C9–H9B	103 (5)
H9A–C9–H9C	99 (4)	H9B–C9–H9C	114 (5)

lithiotriazole (**7**) was treated with diphenyl disulfide to give the oily 5-phenylthiotriazole (**11**) in 97.6% yield. Lithiation at the 3-position of the sulfide (**11**) at −78 °C with *n*- or *sec*-butyllithium produced several by-products in considerable amounts together with recovery of **11**. The lithiation of **11** with LDA did not proceed satisfactorily; most of the starting material was recovered. The best result was obtained by treatment of **11** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) at −80—−100 °C. The resulting 3-lithiotriazole (**12**) was treated with tertiary amides to give the corresponding 3-acyl-5-phenylthiotriazole (**13**) in moderate yields (Chart 4).

The sulfides (**13**) were hydrogenated with a large excess of Raney nickel catalyst to afford 3-acyltriazoles (**5**) in moderate yields. The ¹H-NMR spectrum of **5a** shows the H-5 signal at 8.16 ppm, which agrees with the reported value (8.09 ppm) of 1-methyl-1*H*-1,2,4-triazole (**1a**).⁶⁾ An X-ray crystallographic analysis of **5a** confirmed that the acetyl group was introduced at the 3-position of the triazole ring (Fig. 1).

Finally, synthesis of 3-acyl-4-methyl-4*H*-1,2,4-triazoles¹¹⁾ (**6**: R¹=CH₃) was planned, and we examined *N*-methylation of the 3-acyl-1*H*-1,2,4-triazoles (**3**) under various reaction conditions. The results are summarized in Table VII. As shown in Table VII, reaction of **3a** with methyl iodide or dimethyl sulfate gave a mixture of **4a**, **5a**, and **6a**, but in both cases the ratio of **6a** was very low. These com-

Fig. 1. ORTEP Drawing for **5a**Fig. 2. UV Spectra of **4a**, **5a** and **6a** in EtOH (8.0×10^{-5} M)TABLE VII. Methylation of **3**

Methylation reagent	Reaction medium	R = CH ₃		R = C ₆ H ₅	
		Total yield (%) ^{a)}	Ratio of 4a : 5a : 6a (%) ^{a)}	Total yield (%) ^{a)}	Ratio of 4b : 5b : 6b (%) ^{a)}
NaH/(CH ₃) ₂ SO ₄	DMF	75	32:41:2	44	19:24:1
NaOH/CH ₃ I	MeOH/H ₂ O	80	26:48:6	74	22:45:7
KOH/CH ₃ I	MeOH/H ₂ O	91	29:53:9	85	26:50:9
LiOH/CH ₃ I	MeOH/H ₂ O	85	6:65:14	64	5:50:9
CH ₂ N ₂	MeOH/Et ₂ O	51	18:6:27	76	24:30:22
(CH ₃) ₃ SiCHN ₂	MeOH/benzene	63	25:14:24	85	37:27:21

a) Determined by GLC with an internal standard.

pounds could be separated by silica gel chromatography. The produced **4a** and **5a** were easily identified by comparing their spectral and physical data with those of the

corresponding above-mentioned synthetic samples. The structure of **6a** was determined based on the analytical and spectral data. For example, the ¹H-NMR spectrum of **6a** showed the 5-H signal at 8.21 ppm (s, 1H). In nuclear Overhauser effect (NOE) experiments, relatively large NOE enhancements (2.7% and 2.8%, respectively) between *N*-CH₃ protons and the C-3 or C-5 proton of **5a** and **6a** were observed, but relatively small NOE enhancement (1.8%) was obtained for **4a**. These data support the structures shown in Chart 5. On the other hand, reaction of **3a** with diazomethane gave **6a** as a major product.

The UV spectra of **4a**, **5a**, and **6a** are shown in Fig. 2; since each spectrum is characteristic, they may be useful for the structural identification of *C*-acyl triazoles.

In conclusion, we have prepared *N*-unsubstituted *C*-acyl-1,2,4-triazole and three types of *N*-substituted *C*-acyl-1,2,4-

triazoles, and confirmed their structures.

Experimental

Melting points were measured with a Yanaco MP micro-melting point apparatus, without correction. Infrared (IR) spectra were taken with a Shimadzu IR-410 spectrometer. ^1H -NMR and ^{13}C -NMR spectra were obtained on Varian CFT-20 (80 MHz for ^1H) and XL-300 (300 MHz for ^1H and 75.4 MHz for ^{13}C) spectrometers and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. Abbreviations of ^1H -NMR signal patterns are as follows: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). NOE experiments were performed with the XL-300 spectrometer. UV spectra were obtained on a Shimadzu UV-200S spectrometer. High-resolution mass spectra (HRMS) were obtained on a Hitachi M-80 spectrometer. All solvents were removed under reduced pressure in the usual work-up procedure. Unless otherwise stated, anhydrous sodium sulfate was used as a drying agent. A Kugel-Rohr apparatus was used for vacuum distillation of oily crude products. Silica gel (Merck Art. 7734) was used in column chromatography.

General Procedure for Synthesis of 5-Acyl-1-alkyl-1H-1,2,4-triazoles (4); Synthesis of 5-Acetyl-1-methyl-1H-1,2,4-triazole (4a) as an Example A solution of 1.6 M *n*-butyllithium in hexane (3.75 ml, 6.0 mmol) was added under an N_2 atmosphere at 0°C to a solution of 1-methyl-1H-1,2,4-triazole (**1a**; 415 mg, 5.0 mmol) in tetrahydrofuran (THF; 20 ml). The mixture was stirred for 15 min, then DMA (523 mg, 6.0 mmol) was added and the whole was stirred for 30 min. The product was extracted by addition of water (10 ml) and CH_2Cl_2 (20 ml $\times$ 2) to the reaction mixture, and the organic layer was dried. Evaporation of the solvent gave an oily residue, which was purified by distillation *in vacuo*. Oil, bp $55\text{--}60^\circ\text{C}$ (0.3 mmHg) [lit. bp $58\text{--}62^\circ\text{C}$ (0.08 mmHg)].^{3a)} Yield, 513 mg (82.1%). The analogs (**4b**–**4q**) were similarly prepared, and data for these products are listed in Table II.

General Procedure for Synthesis of 3-Acyl-1H-1,2,4-triazole (3); Synthesis of 3-Acetyl-1H-1,2,4-triazole (3a) as an Example A suspension of 1H-1,2,4-triazole (**8**; 207 mg, 3.0 mmol) in ethyl orthoformate (4.45 g, 30 mmol) was stirred for 1 h under an N_2 atmosphere at 100°C , and then the reaction mixture was concentrated to give an oily residue. A solution of 1.6 M *n*-butyllithium in hexane (2.25 ml, 3.6 mmol) was added dropwise to a solution of the residue in THF (12 ml) at 0°C with stirring under an N_2 atmosphere, and then the mixture was stirred for 15 min. DMA (314 mg, 3.6 mmol) was added to the mixture. After stirring for 30 min at 0°C , the resulting solution was neutralized with 1 N HCl (3.6 ml) and extracted with CH_2Cl_2 (150 ml). The extracts were dried and evaporated to give a solid residue, which was recrystallized from EtOH to give **3a** as a white powder. mp $158\text{--}163^\circ\text{C}$ (dec.). Yield, 320 mg (96.1%). The analogs (**3b**–**3f**) were similarly synthesized, and data for these products are listed in Table III.

5-Phenylthio-1-methyl-1H-1,2,4-triazole (11) A solution of 1.6 M *n*-butyllithium in hexane (22.5 ml, 36 mmol) was added under an N_2 atmosphere at 0°C to a solution of **1a** (2.49 g, 30 mmol) in THF (120 ml). The mixture was stirred for 15 min, then diphenyl disulfide (7.86 g, 36 mmol) was added at 0°C , and the whole was stirred for 30 min at 0°C . Water (30 ml) was added after removal of the solvent and the mixture was extracted with ethyl acetate (200 ml). The extract was washed with water and brine, dried and evaporated to give an oily residue, which was purified by distillation *in vacuo*. Oil, bp $155\text{--}159^\circ\text{C}$ (0.2 mmHg). Yield, 5.59 g (97.6%). IR (CHCl₃): 1480 cm^{-1} .¹²⁾ ^1H -NMR (CDCl₃, 80 MHz): 3.88 (s, 3H, NCH₃), 7.30–7.52 (m, 5H, C₆H₅), 7.93 (s, 1H, C³-H). HRMS *m/z*: Calcd for C₉H₉N₃S, 191.0520. Found, 191.0528 (M^+).

General Procedure for Synthesis of 3-Acyl-1-methyl-5-phenylthio-1H-1,2,4-triazole (13); Synthesis of 1-Methyl-5-phenylthio-3-propanoyl-1H-1,2,4-triazole (13c) as an Example A THF solution (4 ml) of 2,2,6,6-tetramethylpiperidine (TMP, 170 mg, 1.2 mmol) and *N,N,N',N'*-tetramethylethylenediamine (TMEDA; 151 mg, 1.3 mmol) was cooled to -78°C , and a solution of 1.6 M *n*-butyllithium in hexane (0.69 ml, 1.1 mmol) was added under an N_2 atmosphere. The mixture was stirred for 10 min at -78°C , then a solution of the sulfide (**11**, 191 mg, 1.0 mmol) in THF (1 ml) was added dropwise, and the whole was stirred for 1 h at the same temperature. *N,N*-Dimethylpropanamide (121 mg, 1.2 mmol) was added to the mixture and stirring was continued overnight at room temperature. Water (3 ml) and ethyl acetate (10 ml $\times$ 2) were added to the reaction mixture and the whole was shaken. The organic layer was washed with water and brine, dried and evaporated to give an oily residue, which was purified by preparative thin-layer chromatography (PTLC; ethyl acetate–*n*-hexane, 1:1). Oil. Yield, 166 mg (67.2%). IR (CHCl₃): 1695 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 1.21 (t, 3H, CH₂CH₃, $J=7.3\text{ Hz}$), 3.07 (q, 2H, CH₂CH₃, $J=7.3\text{ Hz}$), 3.89 (s, 3H, NCH₃), 7.20–7.38 (m, 5H, C₆H₅).

HRMS *m/z*: Calcd for C₁₂H₁₃N₃OS, 247.0780. Found, 247.0764 (M^+).

3-Acetyl-1-methyl-5-phenylthio-1H-1,2,4-triazole (13a): Oil. Compound **13a** was purified by PTLC (CH₂Cl₂/MeOH, 100:3). Yield, 81 mg (34.8%). IR (CHCl₃): 1700 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 2.63 (s, 3H, COCH₃), 3.90 (s, 3H, NCH₃), 7.26–7.55 (m, 5H, C₆H₅). HRMS *m/z*: Calcd for C₁₁H₁₁N₃OS, 233.0620. Found, 233.0606 (M^+).

3-Benzoyl-1-methyl-5-phenylthio-1H-1,2,4-triazole (13b): Oil. Compound **13b** was purified by PTLC (ethyl acetate–*n*-hexane, 1:1). Yield, 169 mg (57.1%). IR (CHCl₃): 1660 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 3.94 (s, 3H, NCH₃), 7.26–7.62 (m, 8H, Ar-H), 8.20–8.39 (m, 2H, Ar-H). HRMS *m/z*: Calcd for C₁₆H₁₃N₃OS, 295.0780. Found, 295.0770 (M^+).

3-Heptanoyl-1-methyl-5-phenylthio-1H-1,2,4-triazole (13d): Oil. Compound **13d** was purified by PTLC (ethyl acetate–*n*-hexane, 1:1). Yield, 168 mg (55.4%). IR (CHCl₃): 1695 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 0.76–1.95 (m, 11H, (CH₂)₄CH₃), 3.04 (t, 3H, CH₂CO, $J=7.3\text{ Hz}$), 3.89 (s, 3H, NCH₃), 7.25–7.55 (m, 5H, C₆H₅). HRMS *m/z*: Calcd for C₁₆H₂₁N₃OS, 303.1410. Found, 303.1403 (M^+).

3-(2,2-Dimethylpropanoyl)-1-methyl-5-phenylthio-1H-1,2,4-triazole (13e): Oil. Compound **13e** was purified by PTLC (ethyl acetate–*n*-hexane, 1:1). Yield, 151 mg (54.9%). IR (CHCl₃): 1683 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 1.39 (s, 9H, C(CH₃)₃), 3.88 (s, 3H, NCH₃), 7.26–7.53 (m, 5H, C₆H₅). HRMS *m/z*: Calcd for C₁₄H₁₇N₃OS, 275.1090. Found, 275.1110 (M^+).

General Procedure for Synthesis of 3-Acyl-1-methyl-1H-1,2,4-triazole (5); Synthesis of 3-Benzoyl-1-methyl-1H-1,2,4-triazole (5b) as an Example Raney nickel catalyst (W2-type; about 3.0 g) was added to a solution of crude **13b** (prepared from 3 mmol of **11**) in ethanol (20 ml), and the reaction mixture was refluxed for 3 h. The mixture was filtered and evaporated to give a crystalline residue, which was recrystallized from isopropyl ether. White needles, mp $86\text{--}88^\circ\text{C}$. Yield, 292 mg (52.0% from **11**). IR (CHCl₃): 1660 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 4.06 (s, 3H, NCH₃), 7.40–7.75 (m, 3H, Ar-H), 8.20 (s, 1H, C⁵-H), 8.27–8.42 (m, 2H, Ar-H). ^{13}C -NMR (CDCl₃, 75.4 MHz): 36.86 (NCH₃), 128.32, 130.69, 133.39, 136.29 (C₆H₅), 144.67 (N=CHN), 160.49 (N=C(CO)N), 184.92 (CO). Anal. Calcd for C₁₀H₉N₃O: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.21; H, 4.86; N, 22.79.

3-Acetyl-1-methyl-1H-1,2,4-triazole (5a): Compound **5a** was recrystallized from ethyl acetate. White needles, mp $113\text{--}114^\circ\text{C}$. Yield, 117 mg (31.2% from **11**). IR (CHCl₃): 1700 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 2.68 (s, 3H, COCH₃), 4.03 (s, 3H, NCH₃), 8.16 (s, 1H, C⁵-H). ^{13}C -NMR (CDCl₃, 75.4 MHz): 26.88 (COCH₃), 36.57 (NCH₃), 145.01 (N=CHN), 160.27 (N=C(CO)N), 191.10 (CO). UV λ_{max} (EtOH) nm (ϵ): 227 (10500). Anal. Calcd for C₅H₇N₃O: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.00; H, 5.79; N, 33.84.

General Procedure for the Synthesis of 3-Acyl-4-methyl-4H-1,2,4-triazole (6); Synthesis of 3-Acetyl-4-methyl-4H-1,2,4-triazole (6a) as an Example A solution of diazomethane (about 20 mmol) in ether (50 ml) was added to a stirred solution of **3a** (666 mg, 6 mmol) in methanol at 0°C , then the mixture was stirred overnight at room temperature. After evaporation of the solvents, the residue was purified by column chromatography (CHCl₃/acetone, 1:1). Recrystallization of the solid residue of the main fraction from ether gave pure **6a**. White needles, mp $65\text{--}69^\circ\text{C}$. Yield, 158 mg (21.1%). IR (CHCl₃): 1690 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 2.78 (s, 3H, COCH₃), 3.98 (s, 1H, NCH₃), 8.21 (s, 1H, C⁵-H). UV λ_{max} (EtOH) nm (ϵ): 235 (14100). Anal. Calcd for C₅H₇N₃O: C, 47.99; H, 5.64; N, 33.58. Found: C, 47.99; H, 5.67; N, 33.51. Compounds **4a** and **5a** were not isolated in this experiment.

3-Benzoyl-4-methyl-4H-1,2,4-triazole (6b): Compound **6b** was purified by column chromatography (CHCl₃–acetone, 5:1) and recrystallization from ethyl acetate–*n*-hexane. White needles, mp $112\text{--}113^\circ\text{C}$. Yield, 207 mg (18.4%). IR (CHCl₃): 1650 cm^{-1} (C=O). ^1H -NMR (CDCl₃, 80 MHz): 4.03 (s, 1H, NCH₃), 7.50–7.65 (m, 3H, Ar-H), 8.31 (s, 1H, C⁵-H), 8.41–8.44 (m, 2H, Ar-H). ^{13}C -NMR (CDCl₃, 75.4 MHz): 33.9 (NCH₃), 128.5, 131.1, 134.1, 135.8 (C₆H₅), 146.9 (N=CHN), 150.3 (N=C(CO)N), 183.2 (CO). Anal. Calcd for C₁₀H₉N₃O: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.48; H, 4.95; N, 22.59.

5-Deuterio-1-methyl-1H-1,2,4-triazole (1f) A solution of 1.6 M *n*-butyllithium in hexane (0.75 ml, 1.2 mmol) was added under an N_2 atmosphere at 0°C to a solution of **1a** (83 mg, 1 mmol) in THF (4 ml). The mixture was stirred for 15 min, then deuterium oxide (203 mg, 10 mmol) was added and the whole was stirred for 1 h. Water (5 ml) and CH_2Cl_2 (10 ml $\times$ 3) were added, and the organic layer was dried and evaporated to give an oily residue. The crude oily product was purified by column chromatography (CHCl₃–CH₃OH, 10:1). Oil. Yield, 82 mg (97.9%).

¹H-NMR (CDCl₃, 80 MHz); 3.94 (s, 3H, NCH₃), 7.92 (s, 1H, C³-H), 8.04 (s, 0.2H, C⁵-H).

X-Ray Crystallography of 5a The crystal data for **5a** were collected on a Rigaku Denki AFC-5R diffractometer using CuK_α radiation ($\lambda = 1.54178 \text{ \AA}$) at room temperature. The intensities of all the reflections with 2θ values from 5° to 130° were measured by the ω - 2θ scanning technique at $4^\circ/\text{min}$ (in ω). In total, 2879 independent reflections were obtained.

Crystal Data for **5a**: C₅H₇N₃O. $M_r = 125.13$. Monoclinic (obtained by recrystallization from ethyl acetate). Lattice parameters: $a = 10.699$ (2), $b = 8.896$ (1), $c = 6.792$ (1) $\text{\AA}$; $\beta = 98.02$ (3) $^\circ$, $V = 640.1$ (2) $\text{\AA}^3$. $D_{\text{calc}} = 1.298 \text{ g cm}^{-3}$. Space group, $P2_1/c$, $Z = 4$. Crystal dimensions, $0.20 \times 0.20 \times 0.15 \text{ mm}^3$.

Structure Analysis and Refinement for **5a**: The structure was solved by the direct method using the RANTAN program, and refined by the full-matrix least-squares method. The final $R\{\sum(|F_o| - |F_c|)/\sum|F_o|\}$ value was 0.071. An ORTEP drawing of the molecule, the atomic parameters, bond lengths and bond angles are given in Fig. 1, Tables IV, V and VI, respectively.

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