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Alkylation and Acylation of the 1,2,3-Triazole Ring

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Trimethylsilylation of 1,2,3-triazole regioselectively proceeded to give 2-trimethylsilyl-2*H*-1,2,3-triazole, which was treated with primary alkyl halides in the presence of tetrabutylammonium fluoride to give 1-alkyl-1*H*-1,2,3-triazoles as a sole product. 1-Methyl-5-substituted 1*H*-1,2,3-triazoles were prepared by alkylation of 5-lithio-1-methyl-1*H*-1,2,3-triazole, and 1-methyl-4-substituted 1*H*-1,2,3-triazoles were obtained by alkylation of 4-lithio-1-methyl-5-phenylthio-1*H*-1,2,3-triazole followed by reductive desulfurization.

Key words 1,2,3-triazole; lithiation; 2-trimethylsilyl-1,2,3-triazole; alkylation; acylation

The 1,2,4- and 1,2,3-triazole rings are of interest to medicinal chemists as constituents of the side chains of synthetic β-lactam antibiotics.[1] Since basic azole compounds such as imidazole, triazole and pyrazole are now available commercially, generally applicable methods are needed for the preparation of their derivatives. The chemistry of 1*H*-1,2,4-triazole compounds has been well investigated,[2] but that of 1*H*-1,2,3- and 2*H*-1,2,3-triazole compounds is relatively unexplored. Existing methods for preparation of substituted 1,2,3-triazole compounds are mainly based on construction of the ring through addition–cyclization of alkyl azide with alkyne.[3] Regarding alkylation at the 1- and 2-positions of 1*H*-1,2,3-triazole (**1**),[4] both regioisomers of *N*-alkyl derivatives (**2**, **3**) were produced at the same time by methylation of **1** with methyl iodide or dimethyl sulfate in the presence of alkali. This simultaneous production of the regioisomers is a weak point of any synthetic method involving *N*-alkylation. We have investigated the preparation of substituted 1,2,3-triazoles starting from commercially available 1,2,3-triazole (**1**), and this paper deals with a generally applicable procedure for the regioselective introduction of carbogenic substituents into the 1-, 4- and/or 5-position(s) of the 1*H*-1,2,3-triazole ring.

In our experiments, reaction of 1,2,3-triazole (**1**) with phenethyl bromide in the presence of sodium hydride in *N*,*N*-dimethylformamide (DMF) gave 1-phenethyl-1*H*-1,2,3-triazole (**3a**; 30.4%) and 2-phenethyl-2*H*-1,2,3-triazole (**2a**; 23.5%). The structures of these products were easily distinguished on the basis of their ^{1}H-NMR spectra, in which the signals of 4- and 5-H in **2a** were observed at δ 7.59 ppm (s, 2H), while those in **3a** appeared separately at δ 7.62 (s, 1H) and 7.31 ppm (s, 1H).

In 1967, Birkofer and Wegner reported that the acylation of 1-methyl-2-trimethylsilyl-1,2,3-triazole regioselectively proceeded to give the corresponding 1-acyltriazole.[5a] The position of the introduced silyl group was estimated on the basis of the ^{1}H-NMR spectrum at −70 to 37 °C.[5b] We prepared *N*-trimethylsilyltriazole in 86.0% yield according to their method,[5a] and we also confirmed that the *N*-trimethylsilylation gave a single product, 2-trimethylsilyl-2*H*-1,2,3-triazole (**2c**), as judged from the ^{1}H-NMR spectrum (270 MHz) at 20 °C, in which a singlet signal (2H) assigned to the C-4 and C-5 protons appeared at δ 7.73 ppm. The exclusive formation of **2c** is presumably attributable to the relatively hard-base character of the N-2 atom compared with N-1 and N-3 due to its central position in the three serial nitrogens (=CH-N^3=N^2–N^{1}H– ⇔ –CH=N^3–N^{2}H–N^1=).

The reaction conditions were examined in order to improve the yield of the alkylated product, and the results are summarized in Table 1. As shown in Table 1,

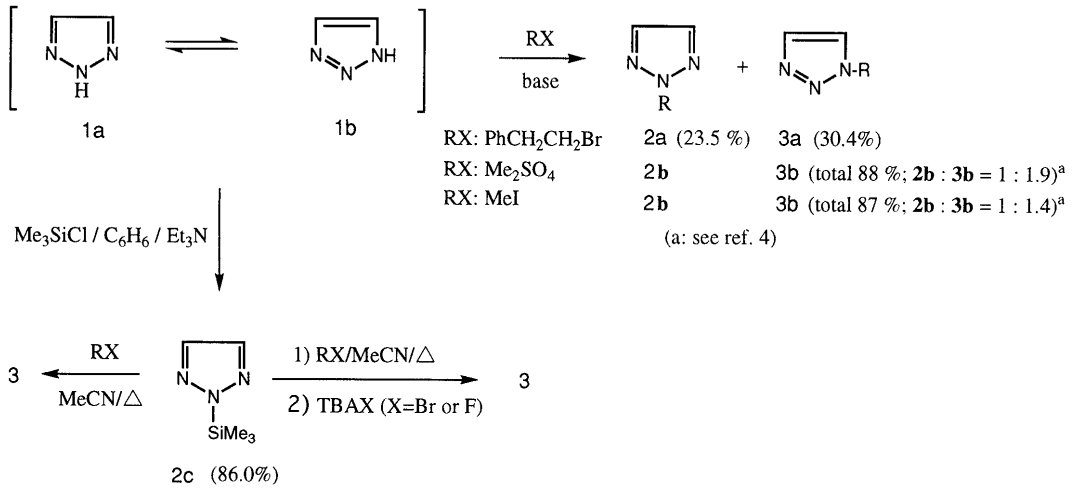

Chart 1

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Table 1. Alkylation of 2-Trimethylsilyl-2*H*-1,2,3-triazole (**2c**)

Entry	RX	Temp. (°C)	Time (h)	Solv.	Additive	Product (3)	Yield (%)[a]
1	$PhCH_2CH_2Br$	100	2	None	None	**3a**	3.6
2	$PhCH_2CH_2Br$	80	2	DMF	None	**3a**	59.4[b]
3	$PhCH_2CH_2Br$	80	2	MeCN	None	**3a**	56.1
4	MeI	80	2	MeCN	None	**3b**	27.0
5	MeI	50	2	MeCN	None	**3b**	5.4
6	MeI	r.t.	2	None	KOH/TBAB[c,d]	**3b**	24.2
7	MeI	80	2	MeCN	TBAF[d]	**3b**	50.0
8	EtI	80	2	MeCN	TBAF[d]	**3c**	62.0
9	$MeOCH_2Cl$	80	2	MeCN	TBAF[d]	**3d**	56.6
10	Me_2CHI	Refl.	12	MeCN	TBAF[d]	—	No reaction
11	c-$C_6H_{11}Cl$	Refl.	48	MeCN	TBAF[d]	—	No reaction
12	$PhCH_2Cl$	Refl.	12	MeCN	TBAF[d]	**3e**	37.2
13	$PhCOCH_2Br$	Refl.	12	MeCN	TBAF[d]	**3f**	22.8

a) Isolated yield. *b*) Regioisomer (**2a**) was also isolated (7.4%). *c*) TBAB (tetrabutylammonium bromide). *d*) About 10 mol% was added.

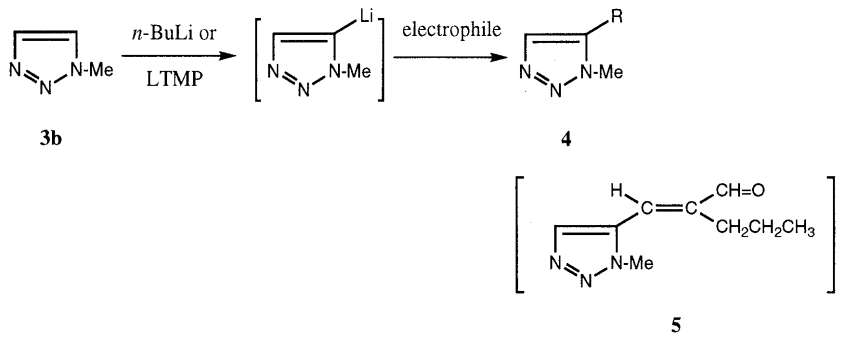

Chart 2

N-phenethyltriazole (**3a**) was obtained in 56.1% yield as a sole product (entry 3), but methylation of **2c** with methyl iodide resulted in a very low yield (27.0%) under the same conditions (entry 4). In entry 2, **3a** was obtained in 59.4% yield, but thin-layer chromatography of the reaction mixture showed the presence of a small amount (7.4% yield) of the regioisomer **2a**. The yield of **3b** was increased to 50% by addition of a catalytic amount of tetrabutylammonium fluoride (TBAF) to the reaction mixture (entry 7). Under the same reaction conditions, primary alkyl halide afforded the corresponding 1-alkyltriazoles (entries 8, 9, 12, 13) in various yields, but alkylation with secondary alkyl halides did not proceed at all (entries 10, 11). At the initial stage of this reaction, alkyl halide might attack at the 1-position of **2c** to produce the intermediary 1-alkyl-2-trimethylsilyl-2*H*-1,2,3-triazolium salt in equilibrium, and the silyl group of the intermediate might be removed by attack with the naked fluoride and/or halide ion.

It has been reported that lithiation of 1-(2-trimethylsilylethoxy)methyl-1*H*-1,2,3-triazole[6] occurs at the 5-position, probably due to the presence of the trimethylsilylethoxy group as a directing group. We tried to perform lithiation of 1-methyl-1*H*-1,2,3-triazole (**3b**), which does not have a directing group. Thus, the triazole was treated with various lithiating agents followed by treatment with piperonal to give 1-methyl-5-(3,4-methylenedioxyphenyl)-hydroxymethyl-1*H*-1,2,3-triazole (**4a**) as a sole product in fair yields; the results are listed in Tables 2 and 3. Differences in the abilities of these lithiating agents to lithiate the C-5 position were small (entries 1—4), and the presence of tetramethylethylenediamine (TMEDA) did not improve the outcome (entry 5). Therefore, we selected *n*-BuLi or lithium 2,2,6,6-tetramethylpiperidide (LTMP) as the lithiating agent in a general procedure for the introduction of a substituent into the 5-position of **3b** (entries 6—14 in Table 2). Reactions with other electrophiles under the above-mentioned reaction conditions were also carried out to obtain the corresponding 5-substituted 1,2,3-triazoles in moderate yields (Table 3).

In entry 4 of Table 3, the 5-deuterated triazole (**4m**) was obtained in 83.0% chemical yield and 95.3% deuteration yields. It was reported that the ^{1}H-NMR signals due to C4- and C5-H of **3b** appeared at δ 7.66 and 7.52 ppm, respectively,[7] and the peak area of the latter signal markedly decreased in the ^{1}H-NMR spectrum of **4m**, whereas that of the former did not change. These data support the conclusion that the lithiation and the introduction of these new substituents occurred at the 5-position of the triazole ring. In entry 11 of Table 2, the desired 5-formyltriazole was not obtained, but a crystalline alkenyltriazole (**5**) was formed in 33.2% yield. The stereochemistry of the double bond in **5** was determined to be *E*-form on the basis of the ^{1}H-NMR spectrum, in which a nuclear Overhauser effect (NOE; 17.0%) was observed between the formyl proton and the olefinic proton on the side-chain. The abnormal product **5** might be generated by an aldol condensation of the produced intermediate 5-triazolecarboxaldehyde with pentanal, produced by the reaction of *n*-BuLi with DMF.

Next, we examined the introduction of alkyl and acyl groups into the 4-position of the 1-methyltriazole ring.

Table 2. Alkylation and Acylation of 1-Methyl-1*H*-1,2,3-triazole (**3b**) at the 5-Position[a]

Entry	Lithiating agent	Electrophile	R	4	Isolated yield (%)
1	*n*-BuLi	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**4a**	50.7
2[b]	*tert*-BuLi	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**4a**	57.4
3	LDA	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**4a**	62.4
4	LTMP	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**4a**	63.9
5	LTMP[c]	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**4a**	63.4
6	*n*-BuLi	C_6H_5CHO	$C_6H_5CH(OH)$–	**4b**	61.0
7	*n*-BuLi	4-ClC_6H_4CHO	4-$ClC_6H_4CH(OH)$–	**4c**	62.0
8	*n*-BuLi	$C_6H_5CONMe_2$	C_6H_5CO–	**4d**	62.4
9	*n*-BuLi	4-$ClC_6H_5CONMe_2$	4-ClC_6H_4CO–	**4e**	67.0
10	LTMP	MeCON(Me)OMe	MeCO–	**4f**	77.5
11	*n*-BuLi	Me_2NCHO	—[d]	(**5**)[d]	(33.2)[d]
12	*n*-BuLi	MeI	Me–	**4g**	56.2
13	*n*-BuLi	EtI	Et–	**4h**	54.2
14	*n*-BuLi	$C_6H_5COCH_2Br$	$C_6H_5COCH_2$–	**4i**	66.2

a) Reaction was carried out at −40 °C—r.t., unless otherwise noted. *b*) at −78 °C—r.t. *c*) In the presence of TMEDA; 1 eq. *d*) The compound **5** was obtained instead of the corresponding **4**.

Table 3. Introduction of Substituents at the 5-Position of 1-Methyl-1*H*-1,2,3-triazole (**3b**)[a]

Entry	Electrophile	R	4	Isolated yield (%)
1	$(C_6H_5S–)_2$	C_6H_5S–	**4j**	78.0
2	*tert*-$BuSi(Me)_2Cl$	*tert*-$BuSi(Me)_2$–	**4k**	83.6
3	Br_2	Br–	**4l**	46.1
4	D_2O	D–	**4m**	83.0[b]

a) The reaction was carried out at −40 °C to room temperature, and *n*-BuLi was used as a lithiating agent. *b*) Deuterium was incorporated in 95.3% yield (calcd on the basis of ^{1}H-NMR).

5-(*tert*-Butyldimethylsilyl)-1-methyl-1*H*-1,2,3-triazole (**4k**) and 1-methyl-5-phenylthio-1*H*-1,2,3-triazole (**4j**) were selected as the starting materials because these compounds have an easily removable protecting group at the 5-position. The former was lithiated with LTMP followed by treatment with *N*,*N*-dimethylbenzamide to give, unexpectedly, the 1-phenacyltriazole (**7**) in 71.8% yield.[8] The structure of **7** was determined on the basis of the ^{1}H-NMR spectrum, which showed signals of 4-H and $>NCH_2$- at 7.96 (s, 1H), and 4.52 (s, 2H) ppm, respectively. In this case, lithiation at C4 may be difficult because of the steric hindrance of the *tert*-butyldimethylsilyl group at C-5, while the lithiated intermediate (**6**) might be stabilized by chelation involving the nitrogen atom of the 2-position.

On the other hand, lithiation of 1-methyl-5-phenylthiotriazole (**4j**) with LTMP at the 4-position proceeded successfully, and after quenching with aldehydes and carboxylic amides the corresponding 1-methyl-4-(1-hydroxyalkyl)triazole (**9a**, **9b**) and 1-methyl-4-acyltriazoles (**9c**, **9d**), respectively, were obtained in good yields (Table 4).

The 4-substituted 5-phenylthiotriazoles (**9a—d**) were treated with an excess of Raney Ni catalyst in refluxing ethanol or with nickel boride (Ni_2B)[9] in a mixture of methanol–tetrahydrofuran (THF) at 0 °C to give the corresponding desulfurization products (**10a—d**) in various yields (Table 5).

The ^{13}C-NMR, ^{1}H-NMR, ultraviolet (UV) and infrared (IR) spectral data of the 4- and 5-acetyl-1-methyl-1*H*-1,2,3-triazoles (**10d**, **4f**) are listed in Table 6. The ^{13}C-NMR spectra may be useful for the structural determination of new derivatives, but other spectral data did not show marked variations.

In conclusion, we have developed a generally applicable new synthetic route for the preparation of 1-monosubstituted, 1,5-disubstituted and 1,4-disubstituted 1*H*-1,2,3-triazoles (**3**, **4**, **10**).

Experimental

IR spectra were taken with a Shimadzu IR-435 spectrophotometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL EX-270 spectrometer (270 MHz for ^{1}H; 67.8 MHz for ^{13}C), and the chemical shifts are expressed in δ (ppm) values with tetramethylsilane as an internal standard. In the assignments of ^{1}H-NMR spectra, Tr indicates a 1,2,3-triazole ring. High recolution (HR-MS) were obtained on a JEOL JMS-SX 102A QQ spectrometer. A Kugelrohr apparatus was used for vacuum distillation of oily crude products. Silica gel 60 (Merck Art. 7734) and Silica gel 60 PF_{254} (Nacalai Tesque, Inc.) were used for column chromatography and preparative TLC (PTLC), respectively.

1-Phenethyl-1*H*-1,2,3-triazole (3a) and 2-Phenethyl-2*H*-1,2,3-triazole (2a) NaH (95%; 86.4 mg, 3.6 mmol) and β-phenethyl bromide (0.41 ml, 3.0 mmol) were added to a solution of 1,2,3-triazole (0.174 ml, 3.0 mmol) in DMF (3 ml) under an N_2 atmosphere, and the mixture was heated at 80 °C for 8 h. It was allowed to cool, then water (5 ml) was added and the product was extracted with AcOEt (5 ml × 3). The organic layer was dried over anhydrous $MgSO_4$ and evaporated under reduced pressure to give an oily residue, which was purified by column chromatography (solvent: AcOEt/hexane = 1/1).

2a: Yield, 122.3 mg (23.5%). Colorless oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.59 (s, 2H, Tr-H), 7.30—7.11 (m, 5H, Ph-H), 4.68 (t, 2H, $TrCH_2$-, J = 7.6 Hz), 3.27 (t, 2H, $PhCH_2$-, J = 7.6 Hz).

3a: Yield, 158.7 mg (30.4%). Colorless oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.62 (s, 1H, Tr-H), 7.31 (s, 1H, Tr-H), 7.33—7.03 (m, 5H, Ph-H), 4.63 (t, 2H, $TrCH_2$-, J = 7.1 Hz), 3.22 (t, 2H, $PhCH_2$-, J = 7.1 Hz).

2-Trimethylsilyl-2*H*-1,2,3-triazole (2c)[5] Chlorotrimethylsilane (10.7 ml, 84 mmol) was added to a solution of 1,2,3-triazole (4.7 ml, 80 mmol) and triethylamine (12.1 ml, 87 mmol) in benzene (80 ml) under an N_2 atmosphere with ice-cooling, and the mixture was stirred for 30 min and then refluxed at 80 °C for 2 h. After filtration, the filtrate was evaporated to afford a residue, which was distilled under atmospheric pressure. Yield, 9.72 g (86.0%). Colorless oil. bp 148 °C [lit. 147—148 °C].[5] ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.73 (s, 2H, Ar-H), 0.51 (s, 9H, $-CH_3$).

General Procedure for the Synthesis of 1-Alkyl-1*H*-1,2,3-triazoles (3); Synthesis of 1-Methyl-1*H*-1,2,3-triazole (3b) as an Example A mixture of 2-trimethylsilyl-2*H*-1,2,3-triazole (141 mg, 1.0 mmol), acetonitrile (1.0 ml), iodomethane (0.069 ml, 1.1 mmol) and TBAF (about 0.1 mmol)

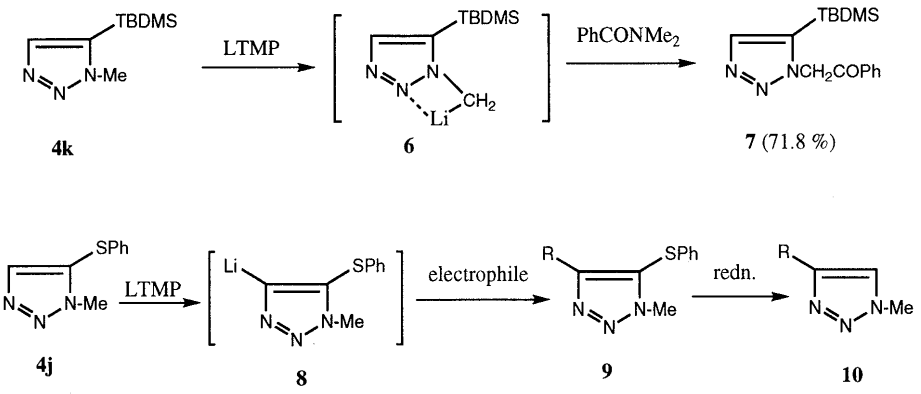

Chart 3

Table 4. C-4 Substitution of 1-Methyl-5-phenylthio-1*H*-1,2,3-triazole (**4j**)

Entry	Electrophile	R	Product	Isolated yield (%)
1	C_6H_5CHO	$C_6H_5CH(OH)$–	**9a**	85.6
2	Piperonal	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**9b**	71.0
3	$C_6H_5CONMe_2$	C_6H_5CO–	**9c**	73.0
4	MeCON(Me)OMe	MeCO–	**9d**	81.9

Table 5. Desulfurization of 4-Substituted 1-Methyl-5-phenylthio-1*H*-1,2,3-triazole (**9**)

Entry	Substrate	Method[a]	R	Product	Yield (%)
1	**9a**	A	$C_6H_5CH(OH)$–	**10a**	46.6
2	**9b**	A	3,4-$(OCH_2O)C_6H_3CH(OH)$–	**10b**	54.2
3	**9c**	B	C_6H_5CO–	**10c**	72.8
4	**9d**	B	MeCO–	**10d**	86.2

a) Method A (Ni_2B in MeOH/THF/0 °C/20 min). Method B (Raney Ni/EtOH/reflux).

Table 6. Spectral Data for 4- and 5-Acetyl-1-methyl-1*H*-1,2,3-triazole, and 1-Methyl-1*H*-1,2,3-triazole

Compd.	IR $\nu_{c=0}$ cm^{-1} (in $CHCl_3$)	^{1}H-NMR δ ppm[a]		^{13}C-NMR δ ppm[a]		UV λ_{max} nm (ε) (in EtOH)
		C4-H	C5-H	C-4	C-5	
3b	—	7.70[b]	7.55[b]	133.5	124.2	—[c]
4f	1688	8.16	—	138.1	133.8	232.0 (9120)
10d	1684	—	8.06	148.3	126.2	237.5 (8318)

a) Measured in $CDCl_3$. *b*) Ref. 7. *c*) Not measured.

was refluxed under an N_2 atmosphere for 2 h. Then 10% HCl (5 ml) was added to the mixture, the whole was washed with ether (3 ml × 2), and the aqueous layer was basified by addition of powdered $NaHCO_3$. The basified aqueous layer was extracted with AcOEt (3 ml × 3), and the organic layer was dried over anhydrous $MgSO_4$. Evaporation of AcOEt under reduced pressure gave an oily residue, which was distilled under vacuum. Yield, 41.5 mg (50.0%). Pale yellow oil. bp 83.3 °C (3 mmHg). ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.70 (s, 1H, Tr-H), 7.55 (s, 1H, Tr-H), 4.13 (s, 3H, $-CH_3$). ^{13}C-NMR spectrum ($CDCl_3$) δ: 133.5, 124.2, 36.1.

1-Ethyl-1*H*-1,2,3-triazole (**3c**)[10]: Yield, 60.2 mg (62.0%). Pale yellow oil. bp 97.1 °C (3 mmHg). ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.73 (s, 1H, Tr-H), 7.58 (s, 1H, Tr-H), 4.46 (q, 2H, $-CH_2$-, J=7.3 Hz), 1.58 (t, 3H, $-CH_3$, J=7.3 Hz).

1-Methoxymethyl-1*H*-1,2,3-triazole (**3d**): Yield, 64.0 mg (56.6%). Pale yellow oil. bp 109.6 °C (3 mmHg). ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.78 (s, 1H, Tr-H), 7.75 (s, 1H, Tr-H), 5.68 (s, 2H, Tr-CH_2-), 3.36 (s, 3H, $-OCH_3$). HR-MS (*m/z*): Calcd for $C_4H_7N_3O$, 113.0590. Found, 113.0572 (M^+).

1-Benzyl-1*H*-1,2,3-triazole (**3e**): Reaction time was 12 h. Yield, 59.1 mg (37.2%). Colorless oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.72 (s, 1H, Tr-H), 7.48 (s, 1H, Tr-H), 7.37—7.26 (m, 5H, Ph-H), 5.57 (s, 2H, $-CH_2$). HR-MS (*m/z*): Calcd for $C_9H_9N_3$, 159.0800. Found, 159.0772 (M^+).

1-Phenacyl-1*H*-1,2,3-triazole (**3f**): Reaction time was 12 h. Yield, 42.6 mg (22.8%). Colorless oil. IR ($CHCl_3$): 1703 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.00 (d, 2H, Ph-H, J=7.6 Hz), 7.80 (s, 1H, Tr-H), 7.75 (s, 1H, Tr-H), 7.68 (t, 1H, Ph-H, J=7.6 Hz), 7.54 (t, 2H, Ph-H, J=7.3 Hz), 5.90 (s, 2H, Tr-CH_2–CO–). HR-MS (*m/z*): Calcd for $C_{10}H_9N_3O$, 187.0750. Found, 187.0760 (M^+).

1-Methyl-5-[1-hydroxy-1-(3,4-methylenedioxyphenyl)methyl]-1*H*-1,2,3-triazole (4a) by Use of LTMP as a Lithiating Agent A 1.6 M solution of *n*-BuLi in hexane (0.75 ml, 1.2 mmol) was added dropwise at −40 °C under an N_2 atmosphere to a solution of 2,2,6,6-tetramethylpiperidine (0.20 ml, 1.2 mmol) in dry THF (4 ml), and the mixture was stirred for 15 min. A solution of 1-methyl-1*H*-1,2,3-triazole (83 mg, 1.0 mmol) in dry THF (1 ml) was added at −40 °C, followed by stirring for 1 h, and then piperonal (180 mg, 1.2 mmol) was added. Stirring was continued for 2 h at room temperature, water (5 ml) was added to the reaction mixture, and THF was removed by evaporation under reduced pressure. The aqueous residue was extracted with AcOEt (5 ml × 2) followed by drying of the organic phase over anhydrous $MgSO_4$. Evaporation of the solvent gave a solid residue, which was purified by column chromatography (solvent: AcOEt/hexane = 1/1), and the crystalline product was recrystallized from AcOEt–hexane. Yield, 148.9 mg (63.9%). Colorless prisms. mp 124.6—125.0 °C. IR ($CHCl_3$): 3154 (–OH) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.34 (s, 1H, Tr-H), 6.84 (s, 1H, Ph-H), 6.80 (d, 2H, Ph-H, J=1.0 Hz), 5.99 (s, 2H, O–CH_2–O), 5.86 (d, 1H, >C<u>H</u>–OH, J=4.3 Hz), 3.93 (s, 3H, $-CH_3$), 3.77 (d, 1H, >CH–O<u>H</u>, J=4.3 Hz). ^{13}C-NMR spectrum ($CDCl_3$) δ: 148.2, 147.9, 139.0, 133.6, 133.0, 120.1, 108.4, 107.0, 101.4, 67.0, 35.5. *Anal.* Calcd for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.78; H, 4.72; N, 18.33.

General Procedure for the Synthesis of 1-Methyl-5-substituted 1*H*-1,2,3-triazoles (4); Synthesis of 1-Methyl-5-(1-hydroxy-1-phenylmethyl)-1*H*-1,2,3-triazole (4b) as an Example A 1.6 M solution of *n*-BuLi in hexane (0.75 ml, 1.2 mmol) was added dropwise at −40 °C under an N_2 atmosphere to a solution of **3b** (83 mg, 1.0 mmol) in dry THF (5 ml), and the mixture was stirred for 2 h. Then, benzaldehyde (0.11 ml, 1.2 mmol) was added at −40 °C, and the whole was stirred overnight at room temperature. Water (5 ml) was added, and THF was evaporated under reduced pressure. The aqueous residue was extracted with AcOEt (5 ml × 2), and the organic layer was dried over $MgSO_4$. Evaporation of the solvent gave a solid residue, which was purified by column chromatography (solvent: AcOEt/hexane = 1/1). The crystalline product was recrystallized from AcOEt–hexane. Yield, 115.3 mg (61.0%). Colorless prisms. mp 133.3—134.0 °C. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.02 (s, 1H, Tr-H), 7.90 (d, 2H, Ph-H, J=6.9 Hz), 7.69 (t, Ph-H, 1H, J=7.6 Hz), 7.55 (t, 2H, Ph-H, J=7.9 Hz), 7.37 (d, 1H, >C<u>H</u>–OH, J=4.3 Hz), 4.70 (s, 1H, >CH–O<u>H</u>), 4.39 (s, 3H, $-CH_3$). *Anal.* Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.40; H, 5.82; N, 19.85.

1-Methyl-5-[1-hydroxy-1-(4-chlorophenyl)methyl]-1*H*-1,2,3-triazole

(**4c**): Purified by column chromatography (solvent: AcOEt/hexane = 1/2), followed by recrystallization from AcOEt. Yield, 138.6 mg (62.0%). Colorless needles. mp 142.0—142.5 °C. IR ($CHCl_3$): 3204 (–OH) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.38 (d, 2H, Ph-H, J = 8.6 Hz), 7.30 (d, 2H, Ph-H, J = 8.6 Hz), 7.29 (s, 1H, Tr-H), 5.96 (d, 1H, >C<u>H</u>–OH, J = 4.6 Hz), 3.94 (s, 3H, –CH_3), 3.71 (br, 1H, >CH–O<u>H</u>). *Anal.* Calcd for $C_{10}H_{10}ClN_3O$: C, 53.70; H, 4.51; N, 18.79. Found : C, 53.93; H, 4.50; N, 18.99.

5-Benzoyl-1-methyl-1*H*-1,2,3-triazole (**4d**): Purified by column chromatography (solvent: AcOEt/hexane = 1/4), followed by recrystallization from AcOEt–hexane. Yield, 116.7 mg (62.4%). Colorless needles. mp 188.7—190.0 °C. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.03 (s, 1H, Tr-H), 7.91 (d, 2H, Ph-H, J = 7.3 Hz), 7.70 (t, 1H, Ph-H, J = 7.3 Hz), 7.56 (t, 3H, Ph-H, J = 7.3 Hz), 4.40 (s, 3H, –CH_3). ^{13}C-NMR spectrum ($CDCl_3$) δ: 183.8, 138.4, 136.8, 133.5, 132.9, 128.9, 128.5, 37.4. *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.50; H, 4.87; N, 22.10.

5-(4-Chlorobenzoyl)-1-methyl-1*H*-1,2,3-triazole (**4e**): Purified by column chromatography (solvent: AcOEt/hexane = 1/4), followed by recrystallization from AcOEt. Yield, 148.4 mg (67.0%). Colorless needles. mp 130.7—131.0 °C. IR ($CHCl_3$): 1655 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.01 (s, 1H, Tr-H), 7.86 (d, 2H, Ph-H, J = 8.6 Hz), 7.53 (d, 2H, Ph-H, J = 8.6 Hz), 4.38 (s, 3H, –CH_3). *Anal.* Calcd for $C_{10}H_8ClN_3O$: C, 54.19; H, 3.64; N, 18.96. Found: C, 54.04; H, 3.61; N, 18.54.

5-Acetyl-1-methyl-1*H*-1,2,3-triazole (**4f**): Purified by column chromatography (solvent: AcOEt/hexane = 1/1), followed by recrystallization from AcOEt. Yield, 96.9 mg (77.5%). Colorless plates. mp 61.2—62.2 °C. IR ($CHCl_3$): 1688 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.16 (s, 1H, Tr-H), 4.31 (s, 3H, N–CH_3), 2.59 (s, 3H, –CH_3). ^{13}C-NMR spectrum ($CDCl_3$) δ: 187.5, 138.1, 133.8, 37.9, 28.6. *Anal.* Calcd for $C_5H_7N_3O$: C, 47.99; H, 5.64; N, 33.58. Found: C, 48.26; H, 5.72; N, 33.25.

(*E*)-5-(2-Formyl-1-pentenyl)-1-methyl-1*H*-1,2,3-triazole (**5**): Purified by column chromatography (solvent: AcOEt/hexane = 1/2), followed by recrystallization from AcOEt. Yield, 59.5 mg (33.2%). Colorless plates. mp 69.0—70.0 °C. IR ($CHCl_3$): 2706 (–CHO), 1683 (>C=O), 1633 (>C=C<) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 9.62 (s, 1H, –CHO), 7.95 (s, 1H, Tr-H), 7.08 (s, 1H, >CH=C<), 4.19 (s, 3H, >N–CH_3), 2.50 (t, 2H, –CH_2–, J = 7.9 Hz), 1.50 (sex, 2H, –CH_2–, J = 7.4 Hz), 1.01 (t, 3H, –CH_3, J = 7.4 Hz). ^{13}C-NMR spectrum ($CDCl_3$) δ: 193.2, 145.4, 134.4, 131.8, 129.3, 35.0, 27.2, 20.7, 14.1. *Anal.* Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.05; H, 7.15; N, 23.07.

1,5-Dimethyl-1*H*-1,2,3-triazole (**4g**): Purified by column chromatography (solvent: AcOEt). Yield, 54.5 mg (56.2%). Pale yellow oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.44 (s, 1H, Tr-H), 3.96 (s, 3H, >N–CH_3), 2.31 (s, 3H, –CH_3). HR-MS (*m/z*): Calcd for $C_4H_7N_3$, 97.0640. Found, 97.0658 (M^+).

5-Ethyl-1-methyl-1*H*-1,2,3-triazole (**4h**): Purified by column chromatography (solvent: AcOEt). Yield, 60.2 mg (54.2%). Pale yellow oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.46 (s, 1H, Tr-H), 3.96 (s, 3H, >N–CH_3), 2.66 (q, 2H, –CH_2–, J = 7.6 Hz), 1.31 (t, 3H, –CH_3, J = 7.6 Hz). HR-MS (*m/z*): Calcd for $C_5H_9N_3$, 111.0796. Found, 111.0838 (M^+).

1-Methyl-5-phenacyl-1*H*-1,2,3-triazole (**4i**): Purified by column chromatography (solvent: AcOEt/hexane = 1/2). Yield, 133.2 mg (66.2%). Pale yellow oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.76 (s, 1H, Tr-H), 7.38—7.35 (m, 3H, Ph-H), 7.20—7.16 (m, 2H, Ph-H), 3.86 (s, 3H, >N–CH_3), 3.47 (d, 1H, Tr-CHCO, J = 5.6 Hz), 3.18 (d, 1H, TrCHCO, J = 5.6 Hz). HR-MS (*m/z*): Calcd for $C_{11}H_{11}N_3O$, 201.0900. Found, 201.0906 (M^+).

1-Methyl-5-phenylthio-1*H*-1,2,3-triazole (**4j**): Purified by column chromatography (solvent: AcOEt/hexane = 1/1). Yield, 149.0 mg (78.0%). Pale yellow oil. ^{1}H-NMR spectrum ($CDCl_3$): 7.86 (s, 1H, Tr-H), 7.30—7.11 (m, 5H, Ph-H), 3.97 (s, 3H, >N–CH_3). ^{13}C-NMR spectrum ($CDCl_3$) δ: 139.7, 132.9, 129.6, 128.2, 127.7, 127.4, 34.8. HR-MS (*m/z*): Calcd for $C_9H_9N_3S$, 191.0534. Found, 191.0500 (M^+).

5-*tert*-Butyldimethylsilyl-1-methyl-1*H*-1,2,3-triazole (**4k**): Purified by column chromatography (solvent: AcOEt/hexane = 1/3) followed by vacuum distillation. Yield, 164.7 mg (83.6%). Pale yellow oil. bp 188.0 °C (3 mmHg). ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.69 (s, 1H, Tr-H), 4.14 (s, 3H, >N–CH_3), 0.93 (s, 9H, C–CH_3 × 3), 0.37 (s, 6H, Si-CH_3 × 2). HR-MS (*m/z*): Calcd for $C_9H_{19}N_3Si$, 197.1348. Found, 197.1320 (M^+).

5-Bromo-1-methyl-1*H*-1,2,3-triazole (**4l**): Purified by column chromatography (solvent: AcOEt). Yield, 74.7 mg (46.1%). Pale yellow plates of low melting point. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.66 (s, 1H, Tr-H), 4.06 (s, 3H, N–CH_3). ^{13}C-NMR spectrum ($CDCl_3$) δ: 134.3, 110.8, 35.1.

General Procedure for the Synthesis of 1-Methyl-4-substituted-5-phenylthio-1*H*-1,2,3-triazoles (9); Synthesis of 4-(1-Hydroxy-1-phenyl)-methyl-1-methyl-5-phenylthio-1*H*-1,2,3-triazole (9a) as an Example A THF solution of LTMP (1.2 mmol) was prepared as described above. A solution of the sulfide (**4j**; 191 mg, 1.0 mmol) in THF (1 ml) was added to the LTMP solution at −40 °C followed by stirring for 2 h, and then benzaldehyde (0.11 ml, 1.1 mmol) was added to the mixture. Stirring was continued at room temperature for 2 h, water (5 ml) was added, and THF was evaporated under reduced pressure. The aqueous residue was extracted with AcOEt (5 ml × 2) and the organic layer was dried over $MgSO_4$, followed by evaporation. The residue was purified by column chromatography (solvent: AcOEt/hexane = 1/3). Yield, 254.6 mg (85.6%). Colorless oil. IR ($CDCl_3$): 3550, 3350 (–OH) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.45—6.87 (m, 10H, Ph-H), 6.02 (s, 1H, >C<u>H</u>–OH), 3.91 (s, 3H, >N–CH_3), 3.44 (br s, 1H, >CH-O<u>H</u>). HR-MS (*m/z*): Calcd for $C_{16}H_{15}N_3OS$, 297.0953. Found, 297.0936 (M^+).

4-[1-Hydroxy-1-(3,4-methylenedioxyphenyl)methyl]-1-methyl-5-phenylthio-1*H*-1,2,3-triazole (**9b**): Purified by column chromatography (solvent: AcOEt/hexane = 1/2). Yield, 242.3 mg (71.0%). Pale yellow oil. IR ($CHCl_3$): 3373 (–OH) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.22—7.19 (m, 3H, Ph-H), 6.95—6.84 (m, 4H, Ph-H), 6.67 (d, 1H, Ph-H, J = 7.9 Hz), 5.92 (s, 1H, >C<u>H</u>–OH), 5.89 (s, 2H, O–CH_2–O), 3.93 (s, 3H, –CH_3), 1.50—1.70 (br, 1H, –OH). ^{13}C-NMR spectrum ($CDCl_3$) δ: 153.7, 147.7, 147.2, 135.8, 132.7, 129.5, 127.5, 127.1, 120.2, 108.0, 107.3, 101.0, 68.9, 35.1. HR-MS (*m/z*): Calcd for $C_{17}H_{15}N_3O_3S$, 341.0840. Found, 341.0818 (M^+).

4-Benzoyl-5-phenylthio-1-methyl-1*H*-1,2,3-triazole (**9c**): Purified by column chromatography (solvent: AcOEt). Yield, 215.6 mg (73.0%). Pale yellow oil. IR ($CDCl_3$): 1655 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.29 (d, 2H, Ph-H, J = 6.9 Hz), 7.62 (t, 1H, Ph-H, J = 7.3 Hz), 7.51 (t, 2H, Ph-H, J = 7.9 Hz), 7.29—7.27 (m, 5H, Ph-H), 3.95 (s, 3H, >N–CH_3). ^{13}C-NMR spectrum ($CDCl_3$) δ: 185.7, 136.7, 133.6, 133.3, 131.9, 130.7, 129.8, 129.7, 129.3, 128.3, 128.0, 35.6. HR-MS (*m/z*): Calcd for $C_{16}H_{13}N_3OS$, 295.0780. Found, 295.0767 (M^+).

4-Acetyl-1-methyl-5-phenylthio-1*H*-1,2,3-triazole (**9d**): Purified by column chromatography (solvent: AcOEt/hexane = 1/2). Yield, 190.8 mg (81.9%). Colorless oil. IR ($CHCl_3$): 1685 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.28—7.21 (m, 5H, Ph-H), 3.92 (s, 3H, >N–CH_3), 2.72 (s, 3H, –CH_3). HR-MS (*m/z*): Calcd for $C_{11}H_{11}N_3OS$, 233.0620. Found, 233.0662 (M^+).

5-*tert*-Butyldimethylsilyl-1-Phenacyl-1*H*-1,2,3-triazole (7) Prepared in the same manner as **9a**. Yield, 216.1 mg (71.8%). Pale yellow oil. IR ($CHCl_3$): 1703 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.96 (s, 1H, Tr-H), 7.88 (d, 2H, Ph-H, J = 6.9 Hz), 7.67 (t, 1H, Ph-H, J = 7.4 Hz), 7.54 (t, 2H, Ph-H, J = 7.9 Hz), 4.52 (s, 2H, –CH_2CO), 0.97 (s, 9H, C–CH_3 × 3), 0.02 (s, 6H, Si-CH_3 × 2). ^{13}C-NMR spectrum ($CDCl_3$) δ: 184.6, 138.8, 137.6, 133.7, 132.9, 129.2, 128.8, 39.1, 26.3, 16.6, −6.6. EI-MS (relative intensity): 286 (30), 246 (45), 245 (95), 244 (42), 216 (51), 115 (45), 105 (39), 86 (68), 77 (63), 73 (100). The peak of M^+ was too small to allow HR-MS measurement.

4-(1-Hydroxy-1-phenyl)methyl-1-methyl-1*H*-1,2,3-triazole (10a) Nickel(II) chloride hexahydrate (1070 mg, 4.5 mmol) and sodium borohydride (513 mg, 13.5 mmol) were added under an N_2 atmosphere at 0 °C to a solution of 4-(1-hydroxy-1-phenylmethyl)-1-methyl-5-phenylthio-1*H*-1,2,3-triazole (200 mg, 0.67 mmol) in MeOH/THF (3/1; 20 ml), and the mixture was stirred for 20 min. The whole was filtered through Celite and the filtrate was evaporated under reduced pressure to give an oily residue, which was purified by PTLC (solvent: AcOEt/hexane = 1/3). Yield, 59.0 mg (46.6%). Colorless oil. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.48—7.31 (m, 5H, Ph-H), 7.23 (s, 1H, Tr-H), 6.04 (d, 1H, >C<u>H</u>–OH, J = 2.4 Hz), 4.04 (s, 3H, >N–CH_3), 3.01 (br, 1H, >CH–O<u>H</u>). HR-MS (*m/z*): Calcd for $C_{10}H_{11}N_3O$, 189.0902. Found, 189.0897 (M^+).

4-[1-Hydroxy-1-(3,4-methylenedioxyphenyl)methyl]-1-methyl-1*H*-1,2,3-triazole (**10b**): This compound was prepared similarly to **10a**. Yield, 84.6 mg (54.2%). Colorless oil. IR ($CHCl_3$): 3350 (OH) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 7.27 (s, 1H, Tr-H), 6.92 (s, 1H, Ph-H), 6.91 (d, 1H, Ph-H, J = 7.9 Hz), 6.78 (d, 1H, Ph-H, J = 8.2 Hz), 5.94 (s, 2H, O–CH_2–O), 5.91 (s, 1H, >C<u>H</u>–OH), 4.04 (s, 3H, N–CH_3), 3.41 (br, 1H, >CH–O<u>H</u>). HR-MS (*m/z*): Calcd for $C_{11}H_{11}N_3O_3$, 233.0800. Found, 233.0843 (M^+).

4-Benzoyl-1-methyl-1*H*-1,2,3-triazole (10c) A mixture of 4-benzoyl-

1-methyl-5-phenylthio-1*H*-1,2,3-triazole (148 mg, 0.5 mmol), dry ethanol (5 ml) and Raney Ni (W4; wet catalyst about 1 g) was refluxed for 2 h under an N_2 atmosphere. After filtration of the reaction mixture, the solvent was evaporated under reduced pressure, and the residue was purified by PTLC (solvent: AcOEt/hexane = 1/1) followed by recrystallization from AcOEt–hexane. Yield, 68.1 mg (72.8%). Colorless needles. mp 106.7—107.3 °C. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.42 (d, 2H, Ph-H, J = 7.3 Hz), 8.25 (s, 1H, Tr-H), 7.62 (t, 1H, Ph-H, J = 7.3 Hz), 7.52 (t, 2H, Ph-H, J = 7.6 Hz), 4.20 (s, 3H, $-CH_3$). ^{13}C-NMR spectrum ($CDCl_3$) δ: 185.6, 148.2, 136.5, 133.3, 130.5, 129.2, 128.4, 36.9. *Anal.* Calcd for $C_{10}H_9N_3O$: C, 64.16; H, 4.85; N, 22.45. Found: C, 64.53; H, 5.13; N, 22.50.

4-Acetyl-1-methyl-1*H*-1,2,3-triazole (**10d**): This compound was prepared in the same manner as **10c** except for the reaction time (6 h), and purified by PTLC (solvent: AcOEt/hexane = 1/2) and recrystallization (solvent: AcOEt). Yield, 53.9 mg (86.2%). Colorless needles. mp 61.2—62.2 °C. IR ($CHCl_3$): 1684 (C=O) cm^{-1}. ^{1}H-NMR spectrum ($CDCl_3$) δ: 8.06 (s, 1H, Tr-H), 4.17 (s, 3H, $>N-CH_3$), 2.69 (s, 3H, $-CH_3$). ^{13}C-NMR spectrum ($CDCl_3$) δ: 192.8, 148.3, 126.2, 36.9, 27.1. HR-MS (*m/z*): Calcd for $C_5H_7N_3O$, 125.0589. Found, 125.0615 (M^+).

References and Notes

1) *a*) Bennett I. S., Brooks G., Broom N. J. P., Calvert S. H., Coleman K., Francois I., *J. Antibiotics*, **44**, 969—978 (1991); *b*) Im C., Maiti S. N., Micetich R. G., Daneshtalab M., Atchison K., Phillips O. A., Kunugita C., *ibid.*, **47**, 1030—1040 (1994).
2) Ohta S., Kawasaki I., Fukuno A., Yamashita M., Tada T., Kawabata T., *Chem. Pharm. Bull.*, **41**, 1226—1231 (1993); Ohta S., Maruyama A., Kawasaki I., Hatakeyama S., Ichikawa M., Guro T., *Heterocycles*, **31**, 2029—2036 (1990) and references cited therein.
3) Moulin F., *Helv. Chim. Acta*, **35**, 167—180 (1952); other method, Pedersen C., *Acta Chem. Scand.*, **13**, 888—892 (1959).
4) *a*) Begtrup M., Larsen P., *Acta. Chem. Scand.*, **44**, 1050—1057 (1990); *b*) Gold H., *Justus Liebigs Ann. Chem.*, **688**, 205—216 (1965).
5) *a*) Birkofer L., Wegner P., *Chem. Ber.*, **100**, 3485—3494 (1967); *b*) The instrument used was probably a 60 MHz machine in the 1960's; they observed a singlet signal of 2H assigned to C4-H and C5-H at −70—37 °C.
6) Holzer W., Ruso K., *J. Heterocycl. Chem.*, **29**, 1203—1207 (1992).
7) C4-H (7.66 ppm); C5-H (7.52 ppm); Holzer W., *Tetrahedron*, **47**, 9783—9792 (1991).
8) *a*) Katritzky A. R., Murugan R., Luce H., Zerner M., Ford G. P., *J. Chem. Soc., Perkin Trans. 2*, **1987**, 1695—1700; *b*) Alcamí M., Mó O., Yáñez M., Anvia F., Taft R. W., *J. Phys. Chem.*, **94**, 4796—4804 (1990).
9) Back T. G., Baron D. L., Yang K., *J. Org. Chem.*, **58**, 2407—2413 (1993).
10) Vereshchagin L. I., Maksikova A. V., Tikhonova L. G., Buzilova S. R., Sakovich G. V., *Khim. Geterotsikl. Soedin.*, **1981**, 688—693.