Triazolopyridines 21.[1] The stereochemistry of 1-[1,2,3]triazolo [1,5-*a*] pyridin-7-yl-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienes and triazolo ring opening derivatives

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Dedicated to Professor Charles W. Rees on his 75th birthday
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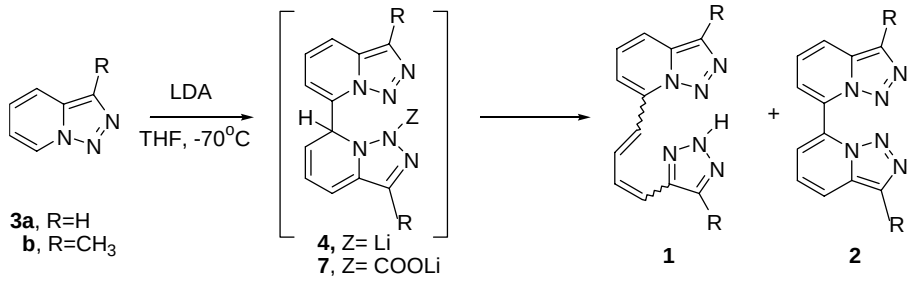
Abstract
The synthesis and NMR study of the geometry of 1-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienes **1a, 1b, 5** and of new 1-(6-substituted-2-pyridyl)-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienes **8-10** is reported. The stereochemistry of all butadienes studied is 1*E*, 3*E* except for compound **5** that is the 1*Z*, 3*Z* stereoisomer of **1a**.

Keywords: Triazolopyridines, alkenes, stereochemistry determination

Introduction

Previously, we have reported that 1-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienes **1** can be synthesized together with bitriazolopyridines **2** in the lithiation reaction of [1,2,3]triazolo[1,5-*a*]pyridines **3**, when reactions are carried out at –70 ºC in THF as solvent, and the mixture allowed to rise room temperature before hydrolysis,[2,3] (Scheme 1). We had nmr evidence that the intermediate **4** was formed, and this may undergo six-membered ring opening to give **1** or loss of hydride to give **2**. A similar intermediate has been reported in the reactions of ring opening of triazolopyridinium salts by nucleophiles.[4-6] In those cases azolyldiene derivatives with different geometry were found depending on nucleophile size and electronegativity. We now wish to report a study of the geometry of azolyldienes **1a,b** and of new 1-(6-substituted-2-pyridyl)-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienes **8-10**, obtained from compounds **1** and sulfuric acid, acetic acid, or selenium dioxide.



Scheme 1

Results and Discussion

When compound **1b** was described,[2] we assumed that the geometry of the butadiene was 1*E*, 3*Z*. It was known,[5] that similar azolyldiene derivatives were formed when [1,2,3]-triazolopyridinium salts reacted with nucleophiles. In all the reported cases the double bond of the diene attached to the triazole retained its original *cis* geometry. When we described compound **1a** we did not pay attention to its stereochemistry.[3] We realized later that coupling constant data do not fit for a *E, Z* configuration. A careful ^{1}H nmr study of compounds **1a**,**b** (Table 1) leads us now to propose the 1*E*, 3*E* configuration for both.

Table 1. ^{1}H NMR data of compounds **1a, 1b, 5, 6**: δ_H (ppm) and coupling constants J (Hz)

	H4	H5	H6	Hd	Hc	Hb	Ha	Other
1a	7.98	7.58-	7.45-	7.08 (d)	7.37 (dd)	8.07(dd)	7.45 (d)	8.37 (s,
DMSO	(dd)	7.50	7.35 (m)	$J_{d,c}$=15,60	$J_{c,d}$=15,60	$J_{b,a}$=15,60	$J_{a,b}$=15,60	1H3);
300MHz	$J_{4,5}$=8,28	(m)			$J_{c,b}$=10,90	$J_{b,c}$=10,90		8.22(s,
1b	7.56 (d)	7.23	7.09 (d)	6.88 (d)	7.24 (dd)	7.99 (dd)	7.28 (d)	2.65 (s,
$CDCl_3$	$J_{4,5}$=8,61	(dd)	$J_{6,5}$=6,90	$J_{d,c}$=15,70	$J_{c,d}$=15,70	$J_{b,a}$=15,58	$J_{a,b}$=15,58	3H);
500MHz		$J_{5,4}$=8,61			$J_{c,b}$=10,89	$J_{b,c}$=10.89		2.49 (s,
5	7.95 (d)	7.46	7.28 (d)	6.70 (d)	6.83 (dd)	7.76 (dd)	7.25 (d)	8.29 (s,
DMSO	$J_{4,5}$=8,50	(dd)	$J_{6,5}$=7,00	$J_{d,c}$=11,50	$J_{c,d}$=11,50	$J_{b,c}$=11,50	$J_{a,b}$=11,04	1H)
400MHz		$J_{5,4}$=8,50			$J_{c,b}$=11,50	$J_{b,a}$=11,04		8.15(s_a,
6	7.85 (d)	7.36	7.02 (d)	3.25	1,90-1,84	1.81-1.68	2.72	7.60 (s,
DMSO	$J_{4,5}$=8,80	(dd)	$J_{6,5}$=6,90	(t, 2H)	(m, 2H)	(m, 2H)	(t, 2H)	1H)
250MHz		$J_{5,4}$=8,80		J= 6,90			J= 6,90	

A 500 MHz ($CDCl_3$) spectrum of **1b** shows four different signals for the dienic protons at δ 6.88 (d, J=15.70 Hz), 7.24 (dd, J_1=15.70, J_2=10.89 Hz), 7.28 (d, J=15.58 Hz) and, 7.99 (dd, J_1=15.58, J_2=10.89 Hz) that indicate two *trans* coupling constants. Also in a 300 MHz (DMSO) spectrum of **1a** it is possible to distinguish the four dienic protons at δ 7.08 (J=15.6 Hz), 7.37 (J_1=15.6, J_2=10.9 Hz), 7.45 (d, J=15.6 Hz) and, 8.07 (dd, J_1=15.6, J_2=10.9 Hz), with two *trans*

coupling constants. To confirm the assignment of the double bond proton shifts, we did NOE-experiments.

Irradiation of the singlet due to the H3' in compound **1a** (δ 8.22) produced DIFNOE signals at δ 7.08 (Hd) and 7.37 (Hc); irradiation of the singlet at δ 8.37 (H3) did not produce appreciable DIFNOE signals.

Interestingly, we obtained compound **5**, the *Z, Z* isomer of compound **1a** (Figure 1), when we treated 7-lithiotriazolopyridine in ether with a large excess of solid CO_2. The coupling constants in this case J_1=11.5 and J_2=11.04 Hz fit perfectly for that configuration (see Table 1). Both compounds, **1a** and **5**, gave the same tetrahydro derivative **6** by hydrogenation.[1]

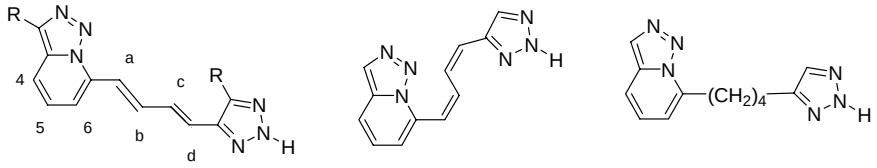
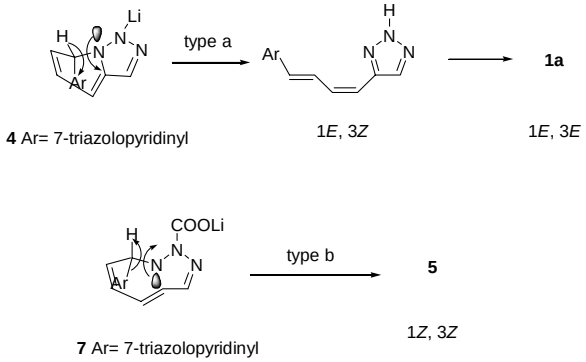


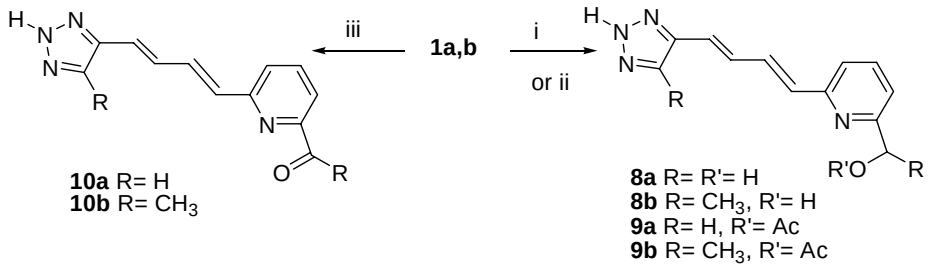
Figure 1

Experimental conditions used to obtain the two different isomers are very similar, with low temperatures, and similar reaction times (no differences in thermodynamic, or kinetic control). The change of solvent from THF to ether, known to coordinate differently with Li^+ ions, could be one reason for the observed outcome. Another possibility is shown in scheme 2. According to Messmer *et al.*[5,6] the proposed intermediate **4** must have the triazolopyridine group in an axial position and undergo ring opening by disrotation that should proceed in the sense portrayed in the scheme, since the lone pair of the bridge-head nitrogen can turn only inward with respect to the bond-breaking because it should get into the plane of the five membered ring. It implies that **4** can be opened only via route a leading to the 1*E*, 3*Z* compound, then a facile isomerization occurred to give 1*E*, 3*E* diene **1a**. The presence of CO_2 in the reaction medium may produce a lithium carbamate intermediate **7**. The stereoelectronic effect between the nitrogen lone pair and the carbamate ion produced nitrogen inversion and the triazolopyridine group in now in the pseudo ecuatorial position, ring opening of **7** may be only via the opposite sense of disrotation (route b) affording 1*Z*, 3*Z* diene **5**.



Scheme 2

The utility of azolylbutadienes in cycloaddition reactions[7-9] led us to look for new compounds of this type. We have synthesized compounds **8-10** using the known reaction of triazolopyridines with electrophiles that undergo triazole ring opening.[10] Thus, reaction of **1a,b** with sulfuric acid gave disubstituted pyridines **8a,b,** with acetic acid **9a,b** and with selenium dioxide **10b** (compound **10a** was not isolated) (Scheme 3), all of them with the *E, E* configuration (see Table 2).



i) H_2SO_4, H_2O, reflux, ii) AcOH, reflux, iii) SeO_2,dioxane/reflux

Scheme 3

Table 2. ^{1}H NMR data of compounds **8a,b, 9a,b, 10b**: δ_H (ppm) and coupling constants J (Hz)

	H	H	H	H	H	H	H	Other
			7.	o	o	o	o	8.03 (s, 1H)
8	7	7.	4	H	H	H	H	4.80 (s, 2H)
a	.	8	3	a	b	c	d	
C	4	3	(d					
			7.	o	o	o	o	4.86 (q,
8	7	7.	0	H	H	H	H	J=6,20, 1H)
b	.	5	3	a	b	c	d	2.36 (s, 3H)
Cl	1	8	(d					1.46 (d,
			7.	o	o	o	o	7.80 (s, 1H)
9	7	7.	2	H	H	H	H	5.25 (s, 2H)
a	.	7	1	a	b	c	d	2.18 (s, 3H)
	3	0	(d					
			7.	o	o	o	o	5.93 (q,
9	7	7.	1	H	H	H	H	J=6,60, 1H)
b	.	6	7	a	b	c	d	2.41 (s, 3H)
	2	2	(d					2.14 (s, 3H)
			7.		o	o		2.69 (s, 3H)
1	7	7.	3	6.	H	H	6.	2.37 (s, 3H)
0	.	6	2	7	b	c	7	
b	7	4	(d	0			0	

Experimental Section

General Procedures. Melting points were determined on a heated stage and are uncorrected. Nmr spectra were recorded on a Bruker AC250MHz, an Avance 300MHz Bruker DPX or an Avance 500MHz DRX instruments. DIFNOE experiments on an Unity 400MHz Varian. HRMS (EI) determinations were made using a VG Autospec Trio 1000 (Fisons).

(1*E*,3*E*)-1-[1,2,3]Triazolo[1,5-*a*]pyridin-7-yl-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadiene 1a and (1*E*,3*E*)-1-(3-Methyl-[1,2,3]triazolo[1,5-*a*]pyridin-7-yl)-4-(5-methyl-2*H*-[1,2,3]triazol-4-yl)-1,3-butadiene (1b).
Prepared as described.[3,2]

(1*Z*,3*Z*)-1-([1,2,3]Triazolo[1,5-*a*]pyridin-7-yl)-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadiene (5).
A solution of *n*-butyllithium in hexane (17mL, 1.6M) was added to diisopropylamine, freshly distilled from KOH (3.8 ml, 27.28 mmols), at -40ºC under argon. Equimolar amount of a solution of [1,2,3]triazolo[1,5-a]pyridine **1a** (3.25g, 27.28mmol) in anhydrous ether (130 mL) was added with stirring. A deep red colour developed. The mixture was kept at -40ºC (6h), and then a large excess of solid carbon dioxide was added (the temperature was reduced) and then left at room temperature overnight. The mixture was hydrolysed with a saturated solution of ammonium chloride. Extraction with dichloromethane gave, after drying and evaporation of the organic solvent, a residue which was purified by chromatography giving starting material **1a** (1,5g). The aqueous layer was acidified with HCl (10%), a precipitate was formed, filtered and purified by alumina chromatography. Elution with ethyl acetate/hexane (3:1) gave a yellow solid identified as **5** (0.71 g, 41%). mp 273-274ºC (methanol). Exact mass calcd. for ($C_{12}H_{10}N_6$): 238.0967; found 238.0969. MS (EI) m/z 238 (74); 210 (50); 209 (52); 181 (61); 154 (100); 140 (21); 127 (27); 115 (11); 77 (15). ^{13}C NMR δ (DMSO) 142.90 (C); 134.03 (C); 133.14 (C); 132.21 (CH); 126.40 (CH); 125.72 (2 CH); 125.02 (CH); 122.58 (CH); 121.07 (CH); 117.25 (CH); 116.83 (CH). Hydrogenation of compound **5** in ethanol with Pd/C catalyst gave the tetrahydro derivative **6**. mp 123-125ºC (methanol). Exact mass calcd. for ($C_{12}H_{14}N_6$): 242.1280; found 242.1281. MS (EI) m/z 242 (64); 214 (100); 185 (69); 172 (47); 157 (44); 144 (25); 107 (24); 105 (84); 78 (27). ^{13}C NMR δ (DMSO) 144.39 (C); 138.88 (C); 133.97 (CH); 129.37 (C); 126.01 (2 CH); 115.93 (CH); 113.72 (CH); 30.04 (CH_2); 28.73 (CH_2); 25.50 (CH_2); 24.10 (CH_2).

General procedure for ring opening reactions of triazolopyridines 1a,b with H_2SO_4
A solution of the triazolopyridine **1a** (0.2g, 0.84mmol) or **1b** (0.2g, 0.75mmol) in aqueous sulfuric acid (10mL, 2.5M) was heated to reflux for 5h with **1a** and 12h with **1b**. The solution was neutralized with a saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The organic solvent was dried, and evaporated. The residue was purified by silica chromatography.

6-[(1*E*,3*E*)-4-(2*H*-[1,2,3]-Triazol-4-yl)-1,3-butadienyl]-2-pyridylmethanol (8a). Elution with CH_2Cl_2/AcOEt (1:1) gave a yellow oil characterized as **8a** (153mg; 80%). Exact mass calcd. for ($C_{12}H_{12}N_4O$): 228.1011; found 228.1010. MS (EI) m/z (%) 228 (34); 227 (6); 199 (17); 181 (20); 160 (14); 146 (100); 130 (7); 117 (10); 91 (7). ^{13}C NMR δ (CD_3OD) 162.15 (C); 156.02 (C); 138.84 (CH); 138.60 (C); 134.16 (2CH); 133.81 (CH); 132.73 (CH); 124.37 (CH); 121.34 (CH); 120.26 (CH); 65.60 (CH_2).

1-{6-[(1*E*,3*E*)-4-(5-Methyl)-2*H*-[1,2,3]triazol-4-yl]-1,3-butadienyl]-2-pyridyl}-1-ethanol (8b). Elution with AcOEt/hexane (2:1) gave a white solid characterized as **8b**, (102mg; 53%), mp 117-119ºC (methanol). Exact mass calcd. for $C_{14}H_{16}N_4O$: 256.1325; found 256.1333. MS (EI) m/z (%) 256 (27); 241 (6); 209 (18); 193 (10); 175 (3); 160 (100); 154 (10); 106 (9) 77 (5). ^{13}C NMR δ ($CDCl_3$) 162.31 (C); 153.50 (C); 137.61 (CH); 137.40 (C); 135.10 (C); 133.30 (CH); 131.87 (CH); 130.75 (CH); 122.09 (CH); 120.75 (CH); 118.33 (CH); 68.41 (CH); 24.13 (CH_3); 10.11 (CH_3).

General procedure for ring opening reactions of triazolopyridines 1a,b with AcOH

A solution of the triazolopyridine **1a** (0.2g, 0.84mmol) or **1b** (0.2g, 0.75mmol) in glacial acetic acid (10mL) was heated to reflux for 10h with **1a** and 12h with **1b**. The solution was neutralized with saturated aqueous solution of sodium bicarbonate and extracted with dichloromethane. The organic solvent was dried, and evaporated. The residue was purified by silica chromatography.

6-[(1*E*,3*E*)-4-(2*H*-[1,2,3]triazol-4-yl)-1,3-butadienyl]-2-pyridylmethyl acetate (9a). Elution with AcOEt/ hexane (3:1) gave a white solid characterized as **9a**, (147mg; 65%), mp 125-128ºC (ethyl acetate). Exact mass calcd. for $C_{14}H_{14}N_4O_2$: 270.1116; found 270.1114. MS (EI) m/z (%) 270 (54); 241 (6); 227 (100); 199 (29); 181 (36); 146 (36); 130 (13); 92 (10). ^{13}C NMR δ ($CDCl_3$) 170.86 (CO); 155.51 (C); 155.10 (C); 144.38 (C); 137.31 (CH); 132.90 (CH); 132.83 (CH); 131.64 (CH); 129.75 (CH); 122.23 (CH); 120.96 (CH); 120.18 (CH); 66.79 (CH_2); 20.94 (CH_3).

1-{6-[(1*E*,3*E*)-4-(5-methyl-2*H*-[1,2,3]triazol-4-yl)-1,3-butadienyl]-2-pyridyl}ethyl acetate (9b). Elution with AcOEt/ hexane (1:1) gave a white solid characterized as **9b**, (163mg; 73%), mp 108-110ºC (ethyl acetate). Exact mass calcd. for $C_{16}H_{18}N_4O_2$: 298.1429; found 298.1419. MS (EI) m/z (%) 298 (25); 256 (20); 255 (100); 239 (29); 213 (29); 192 (20); 176 (39); 150 (47); 134 (37); 104 (35); 78 (17). ^{13}C NMR δ ($CDCl_3$) 170.58 (CO); 160.14 (C); 154.95 (C); 140.82 (C); 137.80 (C); 137.20 (CH); 133.08 (CH); 132.75 (CH); 130.85 (CH); 121.60 (CH); 120.69 (CH); 118.14 (CH); 73.31 (CH); 21.28 (CH_3); 20.77 (CH_3); 9.99 (CH_3).

Ring opening reaction of triazolopyridine 1b with SeO_2

A suspension of triazolopyridine **1b** (0.2g, 0.75mmol) and selenium dioxide (2 equivalents) in dioxane (10mL) was heated at 80ºC for 7h. The mixture was filtered and the filtrate neutralized with a saturated aqueous solution of sodium hydrogencarbonate and extracted with dichloromethane. The organic solvent was dried, and evaporated. The residue was purified by silica chromatography. Elution with AcOEt/ hexane (2:1) gave a white solid characterized as **1-**

{6-[(1*E*,3*E*)-4-(5-Methyl-2*H*-[1,2,3]triazol-4-yl)-1,3-butadienyl]-2-pyridyl}-1-ethanone (10b). (41mg; 21%). mp. 138-140ºC (ethanol). Exact mass calcd. for $C_{14}H_{14}N_4O$: 254.1167; found 254.1166. MS (EI) m/z (%) 254 (59); 226 (10); 211 (100); 184 (7); 172 (23); 142 (12); 106 (13); 78 (7). ^{13}C NMR δ ($CDCl_3$) 200.61 (CO); 171.09 (C); 154.74 (C); 153.37 (C); 141.99 (C); 137.32 (CH); 133.56 (CH); 132.16 (CH); 130.90 (CH); 125.38 (CH); 122.50 (CH); 119.79 (CH); 25.73 (CH_3); 10.29 (CH_3).

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