THE SEQUENTIAL LITHIATION OF 1-PHENYL-1,2,4-TRIAZOLES

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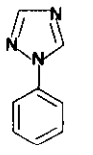
Abstract - 1-Phenyl-1,2,4-triazole is lithiated exclusively at the C-5 position. 5-Methyl-1-phenyl-1,2,4-triazole produces the 5-lithiomethyl derivative; while the 5-ethyl, 5-methoxymethyl, and 5-acetic acid derivatives of 1-phenyl-1,2,4-triazole undergo exclusive lithiation of the C-5-methylene group. 5-Thiomethyl-1-phenyl-1,2,4-triazole is lithiated on the C-5 thiomethyl group.

The sequential lithiation of 1-phenyl-1,2,4-triazole, 1, was investigated as part of our studies on the synthesis of biologically active compounds[1]. Raap has previously reported on the lithiation of 1-phenyl-1,2,3-triazole, 2, leading to the initial formation of the 5-lithio compound which is stable at low temperatures, but rapidly evolves nitrogen at 20 to 50°C to form the lithium phenylketenimine anion, 3[2].



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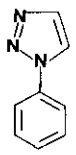

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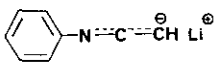

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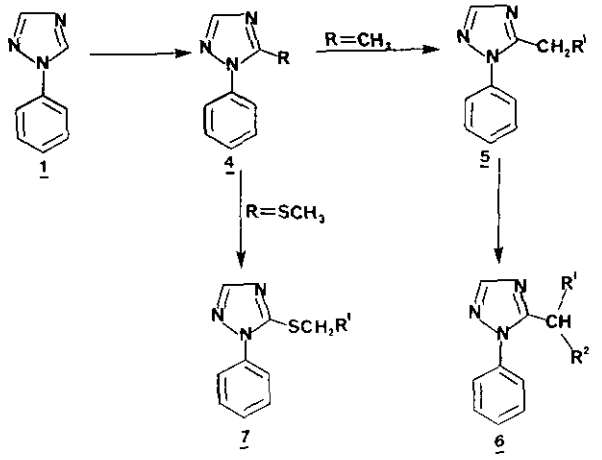
Lithiation studies on the 1,2,4-triazoles appear to have been neglected. The pattern of the sequential lithiation of 1-phenyl-1,2,4-triazole, 1, is quite different from that for 1-phenylpyrazole[3], but is similar to that for 1-phenylimidazole and is obviously a result of the influence of the 4-N of the triazole ring.

The initial lithiation of 1-phenyl-1,2,4-triazole, 1, as in the case of 1-phenylpyrazole, proceeds as expected at the C-5 position to give the 5-lithio-1-phenyl-1,2,4-triazole, 4 (R=Li). This compound on reaction with the appropriate reagent is converted to the 5-sub-

stituted 1-phenyl-1,2,4-triazoles, 4 (see Table 1). There is no evidence, in the nmr spectra of the crude products, of co-lithiation at any other site.



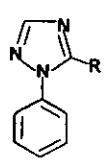
Treating 5-methyl-1-phenylpyrazole with n-butyllithium in THF results in exclusive lithiation of the phenyl group at the ortho-position[3]. By contrast, 5-methyl-1-phenyl-1,2,4-triazole, 4a ($R=CH_3$), undergoes exclusive lateral lithiation of the C-5 methyl group to form 5 (R^1=Li), reaction with methyl iodide or carbon dioxide providing 5 ($R=CH_3$ and COOH respectively). When the lithiation was repeated on compound 5a ($R^1=CH_3$), and 5b (R^1=COOLi), lithiation of the C-5 methylene group occurred, reaction with methyl iodide producing compounds 6a ($R^1=R^2=CH_3$), and 6b ($R^1=CH_3$, R^2=COOH) respectively. The site of lithiation and the structures of the products were readily determined from the nmr spectra of the products.

With 5-methoxymethyl-1-phenyl-1,2,4-triazole, 4e ($R=CH_2OCH_3$), lithiation occurred at the C-5-methylene group, reaction with carbon dioxide producing the 1-phenyl-1,2,4-triazole-5α-methoxyacetic acid, 6c ($R^1=OCH_3$, R^2=COOH).

In the case of 5-thiomethyl-1-phenylpyrazole, lithiation went exclusively at the ortho-position of the phenyl ring[3]. Again there was a significant difference in the behaviour of 5-thiomethyl-1-phenyl-1,2,4-triazole. Lithiation of the C-5 thiomethyl group to give 7 (R^1=Li) occurred readily, reaction with methyl iodide giving the compound 7 ($R^1=CH_3$) as was evident from the nmr spectrum of the compound.

The inductive effect of the 4-N is significant in this ring system, and directs the lithiation exclusively to the C-5 position of 1, the C-5 methyl group of 4a, the C-5 methylene group of 5, and the C-5 thiomethyl group of 4b.

Table 1. 5-Substituted 1-Phenyl-1,2,4-triazoles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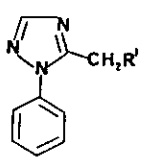
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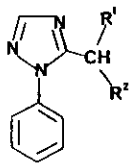
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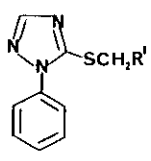
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No	$(R^1, R^2)^R$	Reagent Used	bp °C/mm (mp °C)	Yield %	NMR Spectrum 60 MHz, ($CDCl_3$), δ-values
1			88-90/0.4 (46-47)	67	7.36- 7.80(m,5H,$C_6\underline{H}_5$), 8.15(s,1H,5-H), 8.67(s,1H,3-H)
4a	CH_3	CH_3I	76-78/0.35	68	2.60(s,3H,$C\underline{H}_3$), 7.68(m,5H,$C_6\underline{H}_5$), 8.13 (s,1H,3-H)
4b	SCH_3	CH_3SSCH_3	102-103/0.45	55	2.76(s,3H,$SC\underline{H}_3$), 7.53(m,5H,$C_6\underline{H}_5$), 7.96 (s,1H,3-H)
4c	COOH	CO_2	(330) (lithium salt)[a]	95	7.50(s,5H,$C_6\underline{H}_5$), 8.05(s,1H,3-H) *
4d	SC_6H_5	$ClSC_6H_5$	157-158/0.45 (55-56)	79	7.38-7.55(m,10H,$C_6\underline{H}_5$), 8.01(s,1H,3-H)
4e	CH_2OCH_3	$ClCH_2OCH_3$	95-97/0.8	78	3.45(s,3H,$OC\underline{H}_3$), 4.55(s,2H,$C\underline{H}_2O$), 7.45 -7.73(m,5H,$C_6\underline{H}_5$), 8.03(s,1H,3-H)
4f	COC_6H_5	$C_6H_5CO_2CH_3$	158-160/0.5	50	7.46-7.56(m,10H,$C_6\underline{H}_5$), 8.15(s,1H,3-H)
5a	(CH_3)	4a, CH_3I or 1, C_2H_5I	85-86/0.5	75 88	1.43(t,3H,J=8.0Hz,$SCH_2C\underline{H}_3$), 3.33(q,2H J=8.0Hz,$SC\underline{H}_2CH_3$), 7.43-7.70(m,5H,$C_6\underline{H}_5$), 8.07(s,1H,3-H)
5b	(COOH)	4a, CO_2	(102-103)	70	4.00(s,2H,$C\underline{H}_2$), 7.60(s,5H,$C_6\underline{H}_5$), 8.37 (s,1H,3-H)
6a	(CH_3,CH_3)	5a, CH_3I	88/0.45	50	1.51(d,6H,J=7.0Hz,$CH(C\underline{H}_3)_2$), 3.32(hept, 1H,J=7.0Hz,$C\underline{H}(CH_3)_2$), 7.63(m,5H,$C_6\underline{H}_5$), 8.07(s,1H,3-H)
6b	(CH_3,CO_2H)	5b, CH_3I	(104-106)	62	1.61(d,3H,J=7.0Hz,$CHC\underline{H}_3$), 4.06(q,1H, J=7.0Hz,$C\underline{H}CH_3$), 7.56(s,5H,$C_6\underline{H}_5$),8.18 (s,1H,3-H), 12.83(s,1H,COOH)
6c	(OCH_3,CO_2H)	4e,CO_2	(272-275) (sodium salt)[a]	78	3.18(s,3H,$OC\underline{H}_3$), 4.81(s,1H,$C\underline{H}OCH_3$), 7.38-7.51(m,5H,$C_6\underline{H}_5$), 8.11(s,1H,3-H)*

Table 1 (contd.)

7	(CH_3)	4b, CH_3I	106-108/0.45	70	0.93(t,3H,J=7.0Hz,$SCH_2\underline{CH_3}$), 3.30(q,2H, J=7.0Hz,$S\underline{CH_2}CH_3$), 7.36-7.67(m,5H,$C_6\underline{H_5}$) 8.05(s,1H,3-H)

[a]This compound was isolated as the lithium salt. On conversion to the free acid, it rapidly decarboxylated to the starting compound.

*NMR data were obtained from the corresponding salts in D_2O, since acidification of the salts caused decarboxylation.

EXPERIMENTAL

Representative examples are described. Melting points were taken on a Thomas Hoover "UniMelt" capillary melting point apparatus, and are uncorrected. Nmr spectra were recorded on a Varian EM 360 spectrometer. Elemental analyses of all compounds were within accepted levels.

1-Phenyl-1,2,4-triazole, 1

A mixture of phenylhydrazine (259g, 1.9 mole) and formamide (259g, 5.7 mole) was stirred and heated under reflux in a nitrogen atmosphere in an oil bath at 135 to 140°C for 30 h. The reaction mixture was cooled, dissolved in methylene chloride (500 ml), washed with water (4 x 300 ml), dried ($MgSO_4$), filtered and concentrated to give 236g of a brown low melting solid. Distillation under reduced pressure gave 183g (67%) of 1-phenyl-1,2,4-triazole, bp 88-90°C/0.4 mm, as a clear oil that crystallised, mp 46-47°C.

5-Methyl-1-phenyl-1,2,4-triazole, 4a

n-Butyllithium (140 ml of a 1.6 molar solution in n-hexane, 0.22 mole) was added slowly (over 40 min) to a cooled (-70°C, dry ice-acetone bath), stirred solution of 1-phenyl-1,2,4-triazole (29g, 0.2 mole) in dry THF (1 l) in a nitrogen atmosphere. The reaction mixture was stirred at -70 to -75°C for an additional 1 h, and a solution of methyl iodide (31.2g, 0.22 mole) in THF (200 ml) added over 25 min at -70 to -75°C. The reaction mixture was stirred and allowed to reach ambient temperature over 2.5 h, and then concentrated under reduced pressure. The residue was taken up in methylene chloride (500 ml), washed with brine (3 x 300 ml), dried ($MgSO_4$), filtered and concentrated to give 30g of an orange oil. Distillation under reduced pressure gave 21.6g of a clear oil, bp 76-78°C/0.35 mm.

5-Thiomethyl-1-phenyl-1,2,4-triazole, 4b

n-Butyllithium (7 ml of a 1.6 molar solution in n-hexane, 0.011 mole) was added over 10 min to a cooled (-70°C), stirred solution of 1-phenyl-1,2,4-triazole (1.45g, 0.01 mole in dry THF (50 ml) in a nitrogen atmosphere. The reaction mixture was stirred for an additional 1.5 h at -70 to -75°C, and a solution of dimethyldisulfide (1.04g, 0.011 mole) in dry THF (15 ml) added over 10 min. The reaction mixture was stirred at -75°C for 2 h and allowed to reach room temperature. The mixture was concentrated under reduced pressure and the residue dissolved in methylene chloride (50 ml). This solution was washed with brine (3 x 50 ml), dried ($MgSO_4$), filtered and concentrated to give 1.8g of a colourless oil. Distillation under reduced pressure gave 1.05g (55%) of 5-thiomethyl-1-phenyl-1,2,4-triazole as a colourless oil, bp 102-103°C/0.45 mm.

1-Phenyl-1,2,4-triazole-5-carboxylic acid, 4c

n-Butyllithium (70 ml of a 1.6 molar solution in n-hexane, 0.11 mole) was added over 25 min to a cold (-75°C, dry ice-acetone bath), stirred solution of 1-phenyl-1,2,4-triazole (14.5g, 0.1 mole) in dry THF (500 ml), in a dry nitrogen atmosphere. The reaction mixture was stirred at -75°C for 1.5 h, and then poured with stirring on to excess (about 150 g) of well powdered dry ice. The mixture was stirred, allowed to reach room temperature, and stirred for an additional 1 h, and then concentrated under reduced pressure. The resulting solid (lithium salt), was stirred well with dry ether (300 ml), filtered, washed well with dry ether, and dried to give 19.6 g (100%) of a white powder, whose nmr spectrum (see Table 1) was consistent with the salt of 1-phenyl-1,2,4-triazole-5-carboxylate.
Attempts to prepare the free acid resulted in loss of carbon dioxide and isolation of the starting material, 1-phenyl-1,2,4-triazole, 1.

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