Lithiation of 1-Alkyl-1*H*-1,2,4-triazol-5-yl Phosphonic Acid Esters: Novel Anion-mediated Carbon-to-Carbon Phosphonate Migrations

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The lithiation chemistry of 1-alkyl-1*H*-1,2,4-triazol-5-yl phosphonic acid esters **3** has been investigated. Lithiation occurs exclusively on the 1-alkyl group, α to nitrogen, to give carbanionic intermediates **10**. No evidence was found for any lithiation at the 3-position of the triazole ring. On warming, intermediates **10** undergo an unusual anion-mediated phosphonate migration, giving rise to 1*H*-1,2,4-triazol-1-yl-methylphosphonates **14**.

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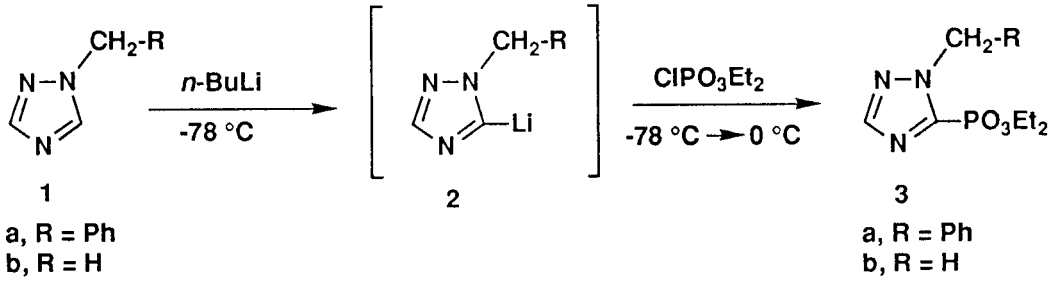
Electrophilic substitution of lithiated 1-alkyl-1*H*-1,2,4-triazoles **1** is known to be a general route to 5-substituted-1*H*-1,2,4-triazoles [1-3]. The first examples of 5-phosphono-1*H*-1,2,4-triazoles **3** were synthesized *via* this methodology (Scheme I) [2]. There are few reported methods [4] for bisfunctionalization, at positions 3 and 5, of 1-alkyl-1,2,4-triazoles. Therefore, a method based on sequential lithiation/substitution appeared to be an attractive route to triazoles of general formula **5** (Scheme II). While the initial lithiation, **1a** to **2a**, is known to be both thermodynamically and kinetically favored [2,5], a small amount of benzylic lithiation product **7** is also present at low temperature. In fact, with certain electrophiles (benzyl halides), the isolated products **8** are formed exclusively *via* **7** (Scheme III) [6]. In contrast, there have been no reports to indicate that lithiation at C-3 of the 1,2,4-triazole ring is a viable process. This suggested that **4** might not be a viable intermediate, with lithiation of the 1-alkyl group (α to nitrogen) being the more energetically favored reaction path. An investigation of the lithiation chemistry of **3** was therefore undertaken.

1-Benzyl-1*H*-1,2,4-triazol-5-yl phosphonic acid diethyl ester (**3a**) was chosen for the initial studies. Since the phosphonate group of **3a** was not stable to alkyllithiums, LDA was utilized as the lithiating reagent. Treatment of **3a** with LDA at -78° for several hours, followed by deuterium quenching (perdeuteriomethanol) did not give the desired **9**. The major product **11** indicated that the benzylic position, α to nitrogen, was the preferred site for lithiation (Scheme IV). A minor product **14**, resulting from phosphonate migration, was also isolated. There was no evidence that any **4a** had formed. Allowing the reaction mixture to warm to 0° before quenching, resulted in **14** becoming the major product with a small amount of de-

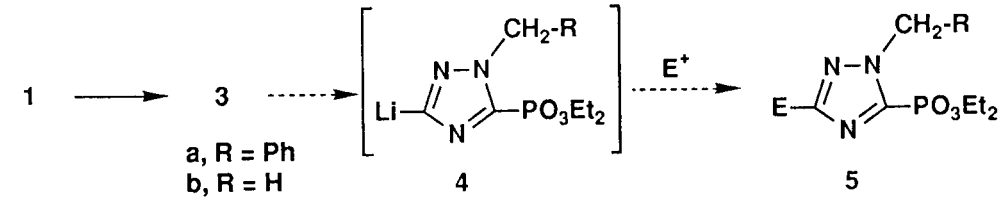
Scheme I



1 2 3

a, R = Ph
b, R = H

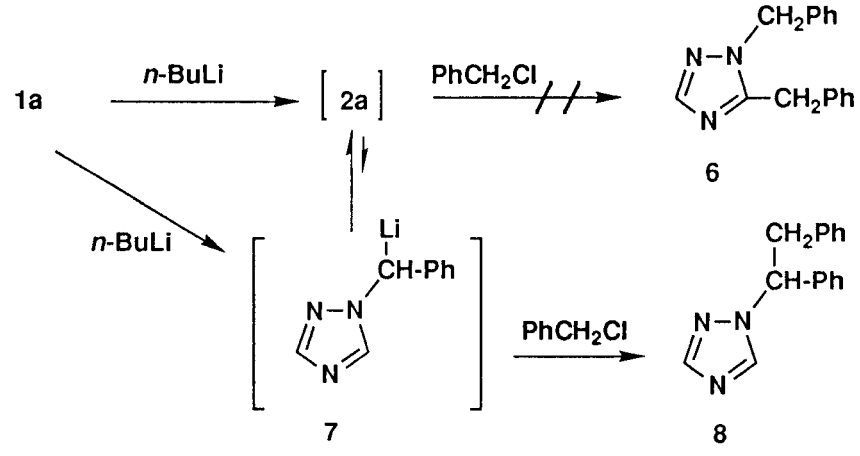
Scheme II



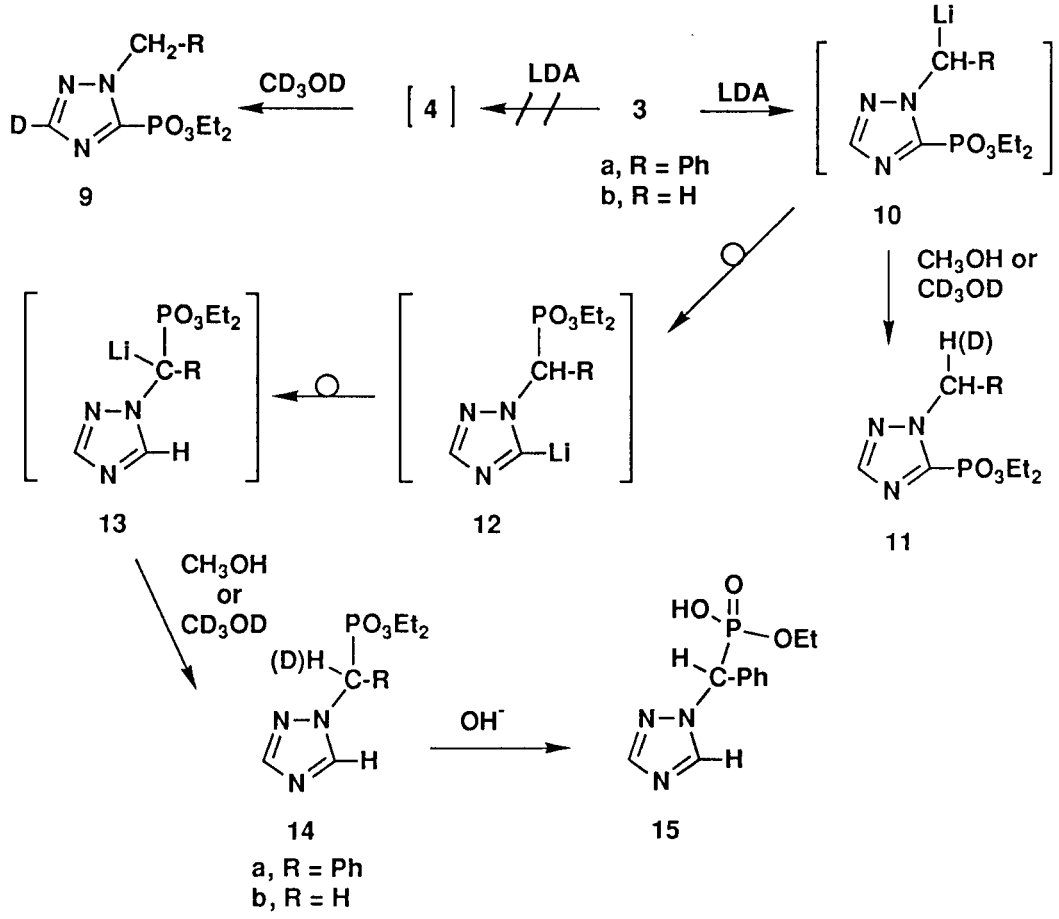
a, R = Ph
b, R = H

4 5

Scheme III [5,6]



Scheme IV



phosphorylated starting material, **1a**, also present. Again there was no evidence that any **4a** had been formed. The ^{1}H-nmr analysis of the crude product mixture showed a clean 3:1 mixture of **14a** and **1a**, respectively. The structure of **14a** was determined spectroscopically. Mass spectral analysis indicated that **14a** was isomeric with starting **3a**. The ^{1}H-nmr analysis indicated that the benzylic methylene protons of **3a** (5.65 ppm, 2H, s) had been replaced by a single methine proton, geminally coupled to phosphorus (5.7 ppm, 1H, d, J_{PCH} = 22 Hz). Furthermore, a proton was

now present at the 5-position on the triazole ring (8.5 ppm, 1H, s). The ^{13}C and ^{31}P-nmr spectra also supported this structural assignment.

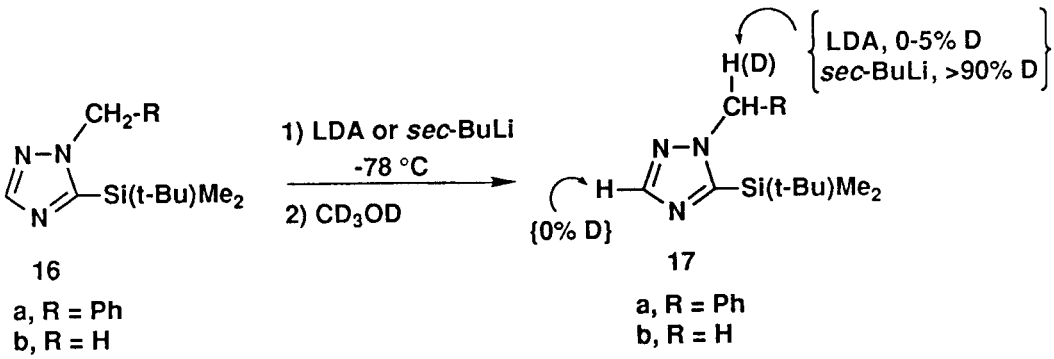
It was not possible, however, to isolate **14a** in yields higher than 25-40%. Phosphonate **14a** undergoes a facile hydrolysis to hemiester **15a**, making isolation of pure **14a** difficult. When the crude product mixture was treated with dilute caustic followed by filtration through cation exchange resin, pure **15a** could be isolated in reasonable yields (50-60%). No attempt was made to optimize the isolated yields of phosphonate **14a**.

The driving force for the phosphonate migration is undoubtedly formation of the more stable lithiated triazoles **12a** and **13a** from the lithiated benzyl intermediate **10a**. Whether the migration is an intramolecular or intermolecular process was not determined, but the former seems most likely. Several related carbanion-mediated, phosphate-to-phosphonate (oxygen to carbon) rearrangements have been previously reported [7], but carbon-to-carbon migrations of phosphorus are, to our knowledge, unprecedented.

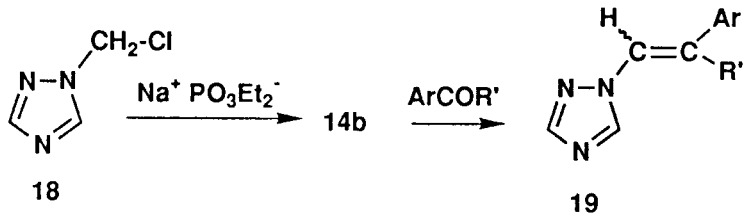
Initially, the total predominance of lithiation of the 1-alkyl methylene group over lithiation at the 3-position of the triazole ring was believed to be due to several additional "activating" factors. First, *N*-benzyl groups are known to be significantly easier to lithiate than the corresponding *N*-methyl groups. Therefore, with phosphonate **3a** it may have been benzylic activation that resulted in selective lithiation at the 1-alkyl position. However, when the *N*-methyl derivative **3b** was lithiated under the same conditions, identical results were obtained. Lithiation occurred exclusively on the 1-methyl group leading to **14b** as the major product. Second, the selective lithiation of the 1-alkyl groups may have been due to the "directing" effect of the adjacent phosphonate group. Phosphorus containing groups, especially phosphates, are known to be excellent activators for lithiations [7,8]. To gain further insight into the effect of phosphonate activation on the selectivity of these lithiations, silyl triazole **16a** was lithiated under the same reaction conditions (Scheme V). With LDA only very low levels of lithiation were attained. Stirring for several hours at -78° before quenching typically gave less than 5% deuterium incorporation into the 1-benzyl group [9]. In contrast, *sec*-butyllithium at -78° and deuterium quenching gave greater than 90% deuterium incorporation on the 1-benzyl group. In both cases, however, there was no deuterium incorporation at the 3-position of the triazole ring. Identical results were obtained with lithiation/deuteration of **16b**. These results suggest that the phosphonate group of **3** does increase the acidity of the protons (α to nitrogen) on the adjacent 1-alkyl group, but this increased acidity does not appear to be responsible for the selectivity of the lithiations. That is, lithiation occurs α to nitrogen on the 1-alkyl group even in the absence of a directing group at the 5-position. Furthermore, in no instance was any lithiation of the 3-position of the triazole ring observed.

1*H*-1,2,4-Triazol-1-ylmethylphosphonate (**14b**) is a

Scheme V



Scheme VI [10]



known compound previously prepared from 1-chloromethyl-1*H*-1,2,4-triazole (**18**) *via* a Michaelis-Becker reaction with sodium diethyl phosphite (Scheme VI) [10]. Triazole **14b** was subsequently utilized to prepare olefinically substituted triazoles **19** *via* the Wittig-Horner reaction. Our attempts to prepare **14a** by an analogous approach failed. It appears that only the parent compound **14b**, with no additional substituents on the methylene group, can be prepared by the Michaelis-Becker reaction. Our attempts, and others [10], to prepare these systems under Mannich reaction conditions (1,2,4-triazole/RCHO/dialkyl phosphite) also failed. This suggests that this anion-mediated phosphonate migration approach to substituted systems, such as **14a**, might have considerable synthetic utility.

In summary, lithiation of 1-alkyl-1*H*-1,2,4-triazol-5-yl phosphonates **3** occurs specifically on the 1-alkyl (methyl or benzyl) group, α to nitrogen. When warmed above -78° the lithiated adducts **10** undergo an anion-mediated phosphonate migration, giving rise to 1*H*-1,2,4-triazol-1-ylmethylphosphonates **14**. No evidence of any lithiation having occurred at the 3-position of the triazole ring was found.

EXPERIMENTAL

The ^{1}H and ^{13}C-nmr spectra were recorded at 60 MHz and 75 MHz, respectively, using TMS as an internal standard. The ^{31}P-nmr spectra were recorded at 40.5 MHz with chemical shifts reported in ppm relative to phosphoric acid (external coaxial standard). Melting points were determined on a Mel-Temp (Laboratory Devices, Inc.) apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Inc. Perdeuteriomethanol utilized in the deuterium quenching experiments was obtained from Aldrich Chemical Co. (99.96% D).

Compounds **3a**, **3b** and **16a** were prepared as previously described [2]. Compound **16b** was prepared from **1b** utilizing a procedure identical to that described for **16a** in the aforementioned reference [2]. Spectral data for **16b** is given below.

Phenyl(1*H*-1,2,4-triazol-1-yl)methylphosphonic Acid Diethyl Ester (**14a**).

A solution of anhydrous diisopropylamine (5.1 g, 51 mmoles) in 100 ml of anhydrous THF was cooled to -78° under nitrogen and treated with *n*-butyllithium (16.2 ml of a 2.3 *M* solution in hexane, 37 mmoles) *via* syringe. The solution was stirred for 30 minutes then treated with a solution of **3a** (10 g, 34 mmoles) in 100 ml of anhydrous THF, dropwise over a 20 minute period. The reaction temperature was maintained below -70° throughout the addition. After 1 hour at -78° the reaction was allowed to slowly warm to 0°. The reaction was stirred for 15 minutes at 0°, then quenched with methanol (perdeuteriomethanol in the deuterium trapping experiments). The reaction was concentrated *in vacuo*, and the residue was extracted into methylene chloride. The organic layer was dried over sodium sulfate and concentrated to yield 5.7 g of an orange oil which was a 3:1 mixture of **14a** and **1a**, respectively. Multiple recrystallizations from dichloromethane/ether gave 4.0 g (40%) of **14a** as a white solid, mp 77-79°; ^{1}H-nmr (deuteriochloroform): 8.5 (1 H, s), 7.8 (1 H, s), 7.1-7.5 (5 H, m), 5.7 (1 H, d, J_{PCH} = 22 Hz), 3.6-4.3 (4 H, unresolved m), 1.1 and 1.2 (6 H, overlapping t, J = 7 Hz) ppm; ^{31}P-nmr (deuteriochloroform, proton decoupled): +16.1 ppm; ^{13}C-nmr (deuteriochloroform, decoupled): 151.7, 143.5 (J_{PC} = 2 Hz), 132.3 (J_{PC} = 2 Hz), 129.0 (J_{PC} = 2 Hz), 128.8, 128.3, 63.8 (J_{PC} = 20 Hz), 63.7 (J_{PC} = 20 Hz), 61.7 (J_{PC} = 154 Hz), 16.1, 16.0 ppm.

Anal. Calcd. for $C_{13}H_{18}N_3O_3P$: C, 52.88; H, 6.14; N, 14.23; P, 10.49. Found: C, 52.77; H, 6.32; N, 14.19; P, 10.61.

1*H*-1,2,4-Triazol-1-ylphosphonic Acid Diethyl Ester (**14b**).

Compound **14b** was prepared from **3b** in 60-70% yield utilizing an identical procedure to that described for **14a** above. This material had identical spectral properties to a sample of **14b** prepared as described in reference [10].

Phenyl(1*H*-1,2,4-triazol-1-yl)methyl Phosphonic Acid Monoethyl Ester (**15**).

Crude **14a**, prepared as described above, was dissolved in a 1:1 mixture of 10% aqueous sodium hydroxide and ethanol (100 ml). After stirring 1 hour at room temperature, the ethanol was removed *in vacuo* and the aqueous residue was washed with an equal volume of dichloromethane to remove **1a**. The aqueous layer was then passed through a column of cation exchange resin (Bio-Rad AG® 50W-X8, 200-400 mesh, 130 x 6 cm) with additional water as the eluant. Concentration of the final eluant yielded 5.2 g of **15** as a white solid, mp 195-198°; ^{1}H-nmr (DMSO-d_6): 8.7 (1 H, s), 8.0 (1 H, s), 7.2-7.7 (5 H, m), 6.05 (1 H, d, J_{PCH} = 21 Hz, overlapped by broad s), 5.7-6.30 (H_2O, broad s), 3.8 (2 H, dq, J = 7 Hz, appears as pentuplet), 1.0 (3 H, t, J = 7 Hz) ppm; ^{31}P-nmr (ethanol, decoupled): +9.61 ppm.

Anal. Calcd. for $C_{11}H_{14}N_3O_3P \cdot 0.2H_2O$: C, 48.78; H, 5.36; P, 11.44. Found: C, 48.60; H, 5.38; P, 11.60.

Dimethyl(1,1-dimethylethyl)(1-methyl-1*H*-1,2,4-triazol-5-yl)silane (**16b**).

Compound **16b** was purified by Kügelrohr distillation at 40° (0.5 mm Hg) to give a white solid, mp 47-50°; ^{1}H-nmr (deuteriochloroform): 8.0 (1 H, s), 3.9 (3 H, s), 0.9 (9 H, s), 0.3 (6 H, s).

Anal. Calcd. for $C_9H_{19}N_3Si$: C, 54.77; H, 9.70; N, 21.29. Found: C, 54.69; H, 9.76; N, 21.24.

REFERENCES AND NOTES

[1] For an excellent review of heteroatom-facilitated lithiations, see: H. W. Gschwend and H. R. Rodriguez, *Org. React.*, **26**, 1 (1979).

[2] D. K. Anderson, J. A. Sikorski, D. B. Reitz, and L. T. Pilla, *J. Heterocyclic Chem.*, **23**, 1257 (1986).

[3] P. Jutzi and U. Gilge, *Organomet. Chem.*, **246**, 163 (1983).

[4] The only reported methods for this type of bis-functionalization are halogenations. For examples see: C. Temple Jr., 1,2,4 Triazoles, John Wiley and Sons, Inc., New York, NY, 1981, pp 288-296.

[5] M. Moreno-Mañas, J. Bassa, N. Lladó, and R. Pleixats, *J. Heterocyclic Chem.*, **27**, 673 (1990).

[6] M. R. Cuberes, M. Moreno-Mañas, and A. Trius, *Synthesis*, 302 (1985).

[7] For examples, see: [a] G. B. Hammond, T. Calogeropoulou, and D. F. Wiemer, *Tetrahedron Letters*, 4265 (1986); [b] B. Dhawan and D. Redmore, *J. Org. Chem.*, **49**, 4018 (1984).

[8] For an additional example, see: J. P. Lampin and F. Mathey, *J. Organomet. Chem.*, **71**, 239 (1974).

[9] The lithiation/deuteration of **16a** and **16b** was considerably more complex if warmed to 0° before quenching. The higher temperature resulted in silyl migration and/or desilylation to give complex product mixtures. There was, however, no deuterium incorporation at the 3-position of the triazole ring in any of the other products. A manuscript describing the results of lithiation studies on silyltriazoles is currently in preparation.

[10] L. Maier, W. Kunz, and G. Rist, *Phosphorus Sulfur*, **33**, 41 (1987).