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Effect of lithiation on the reactivity of diazo derivatives with sulfonylalkynes: application to the synthesis of three isomeric trisubstituted pyrazoles.

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Abstract: The difference in reactivity of diazo derivatives *versus* their lithium salts allowed the synthesis of different regioisomeric funtionalized pyrazoles. © 1999 Elsevier Science Ltd. All rights reserved.

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Due to their 1,3-dipolar structure, diazoalkanes (RR'CN_2) have been extensively used for the synthesis of various five-membered heterocycles.[1,2] In this field, metalated diazo derivatives [R(CN_2)M] have been used as *activated* diazoalkanes and for instance, numerous azoles have been prepared by reacting the lithium salt of the trimethylsilyldiazomethane [$Me_3Si(CN_2)Li$] with nitriles,[3,4] carboxylic esters,[5] carbamoyl- and thiocarbamoylchlorides.[6] It is noteworthy that we have demonstrated that metalation of diazo derivatives affords ambident and highly functionalized nucleophiles that can react either *via* the carbon atom leading to new diazo derivatives or *via* the terminal nitrogen giving nitrile-imines.[7] Here we report for the first time that lithiation of diazo derivatives can dramatically modify the course of their reaction with electron-poor alkynes.

Reaction of the phosphinodiazomethane derivative **1a-H**[8] with one equivalent of the trimethylsilylsulfonylalkyne **2**[9,10] at room temperature for two hours afforded the trisubstituted pyrazole **3a** in 75% yield (Equation 1). After treatment with elemental sulfur, the corresponding thioxophosphoranylpyrazole **4a** was obtained in 93% yield. We then investigated the reaction of the corresponding lithium salts **1a,b-Li** with one equivalent of the trimethylsilylsulfonylalkyne **2**. The reaction was complete after a few minutes at -78°C,

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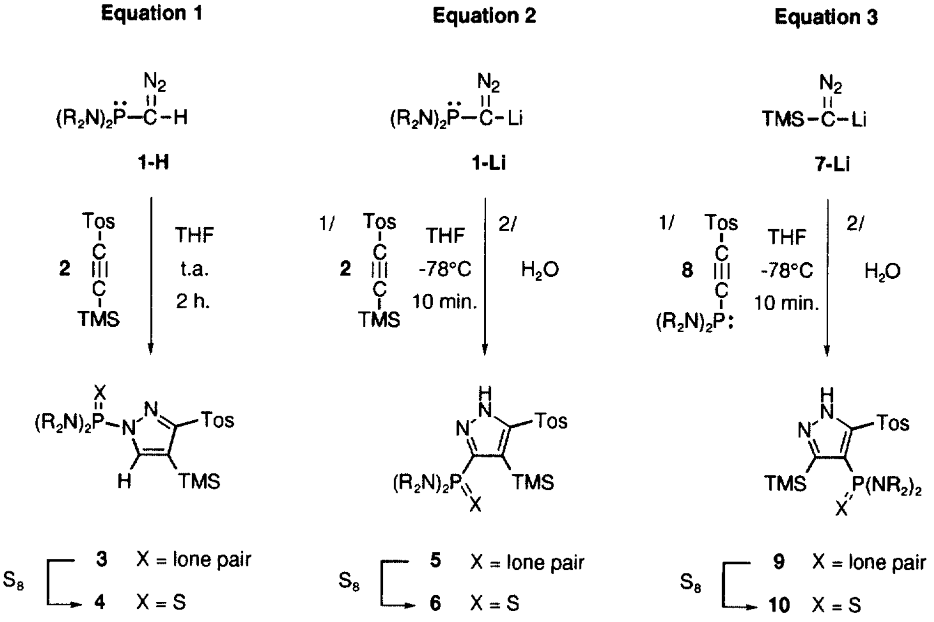
giving rise to the trisubstituted pyrazoles **5a,b**. The corresponding thioxophosphoranylpyrazoles **6a,b** were isolated in 65 and 75% yield, respectively, after sulfuration (Equation 2). It is clear that lithiation of the diazo moiety increases the reactivity of the 1,3-dipole and results in a dramatic alteration in the nature of the cycloadduct. Lastly, we tried to introduce the phosphino group in the 4-position of the pyrazole ring by reacting a trimethylsilyldiazo derivative with the phosphino-sulfonyl-alkyne **8**, which was easily prepared in two steps from trimethylsilylacetylene, chlorophosphine and *p*-toluenesulfonylanhydride (Equation 4). While the trimethylsilyldiazomethane **7-H** appeared to be unreactive towards **8**, its lithium salt **7-Li** cleanly reacted with **8**, leading to the pyrazole **9a** which was isolated after sulfuration as **10a** (45% yield) (Equation 3).

The products **3-10** were fully characterized by multinuclear NMR spectroscopies and mass spectrometry.[11] In addition, the structures of **4a**, **6a,b** and **10a** were confirmed by single crystal X-ray diffraction studies.[12]



$$\mathrm{LiC{\equiv}CSiMe_3} \xrightarrow{\mathrm{(R_2N)_2\ddot{P}Cl}} \mathrm{(R_2N)_2\ddot{P}C{\equiv}CSiMe_3} \xrightarrow[\text{2/ Tos}_2\text{O}]{\text{1/ MeLi}} \underset{\mathbf{8}}{\mathrm{(R_2N)_2\ddot{P}C{\equiv}CTos}}$$

Equation 4

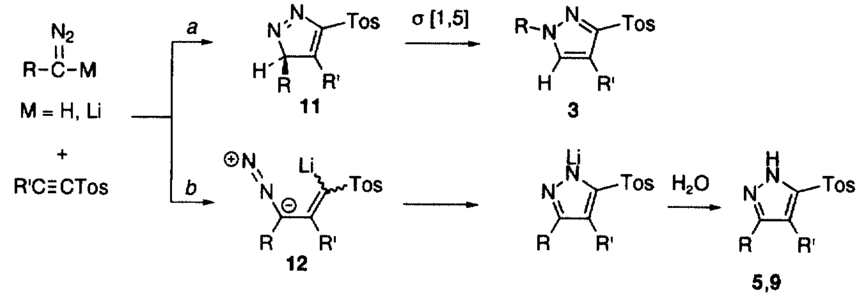
a R = *i*-Pr Tos = p-$CH_3C_6H_4$
b R = *c*-Hex TMS = $SiMe_3$

From a mechanistic point of vue, the formation of **3a** clearly results from a concerted [3+2]-dipolar cycloaddition followed by a 1,5-migration of the phosphino substituent[13] (Scheme 1, route a). Therefore, in this reaction the α-phosphino diazo derivative **1-H** simply behaves as a 1,3-dipole, and not as a 1,4-dipole as previously observed,[14] the regiochemistry of the cycloaddition being probably governed by electronic factors.

Even though a concerted cycloaddition reaction cannot be excluded for the formation of **5**, the reaction probably proceeds *via* nucleophilic addition of the metalated diazo derivative **1-Li** to the alkyne, followed by cyclization (Scheme 1, route b). In this case, the regiochemistry of the product is governed by the sulfonyl group which stabilizes the negative charge of the transient adduct **12**. Note that all the results reported so far[15] indicate that the reaction of electron-poor alkynes with nucleophiles involve such a Michael addition.

By analogy, the formation of **9** probably results from a step-by-step process (Scheme 1, route b), the regiochemistry and thus the position of the phosphino group again being governed by the presence of the sulfonyl substituent.

Scheme 1



In summary, three different regioisomeric trisubstituted pyrazoles have been prepared in good yields by playing with the nature of both the diazo derivatives and the electron-poor alkynes. These results demonstrate that the lithiation of diazo compounds can be very useful in improving their reactivity and in controlling the regiochemistry of the cycloaddition process. Moreover, since both silyl and sulfonyl[16,17] groups may be removed from these trisubstituted derivatives, they may serve as useful precursors for a wide variety of pyrazoles.[18]

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[11] Selected data: **3a**: δ_P 91.8; δ_H 8.10 (d, J(P,H)=2.7, 1H, CH); δ_C 137.8 (d, J(P,C)=20.5, CH), 133.8 (d, J(P,C)=23.9, CSO_2), 106.7 (s, CSi). CIMS (NH_3) m/z 525 (M+1). **4a**: δ_P 58.6; δ_H 9.00 (d, J(P,H)=2.4, 1H, CH); δ_C 142.5 (d, J(P,C)=14.2, CH), 138.7 (d, J(P,C)=13.9, CSO_2), 107.2 (d, ^2J(P,C)=4.6, CSi). CIMS (NH_3) m/z 557 (M+1). $C_{25}H_{45}N_4O_2PS_2Si$: calcd C 53.93, H 8.15, N 10.06; found C 53.98, H 8.23, N 9.95. **5a**: δ_P 34.0; δ_C 164.2 (d, J(P,C)=10.1, CSO_2), 150.0 (d, ^1J(P,C)=14.2, CP), 115.1 (d, J(P,C)=54,3, CSi). **6a**: mp 188°C; δ_P 64.1; δ_H 10.25 (s, 1H, NH); δ_C 160.5 (d, J(P,C)=17.6, CSO_2), 146.7 (d, ^1J(P,C)=137.7, CP), 119.6 (d, J(P,C)=24.5, CSi). CIMS (NH_3) m/z 557 (M+1). $C_{25}H_{45}N_4O_2PS_2Si$: calcd C 53.93, H 8.15, N 10.06; found C 54.07, H 7.82, N 9.88. **5b**: δ_P 38.0. **6b**: mp 160°C; δ_P 64.4; δ_H 10.57 (s, 1H, NH); δ_C 147.8 (d, ^1J(P,C)=137.2, CP), 120.7 (d, J(P,C)=24.2, CSi), the CSO_2 carbon was not observed. CIMS (NH_3) m/z 717 (M+1). $C_{37}H_{61}N_4O_2PS_2Si$: calcd C 61.97, H 8.58, N 7.81; found C 61.88, H 8.22, N 7.18. **8**: δ_P 28.8; δ_C 100.1 (d, ^2J(P,C)=1.0, CSO_2), 100.0 (d, ^1J(P,C)=34.7, CP). CIMS (NH_3) m/z 411 (M+1). **9a**: δ_P 53.4. **10a**: δ_P 64.9; δ_H 10.33 (s, 1H, NH); δ_C 153.5 (d, J(P,C)=35.0, CSi or CSO_2), 153.0 (d, J(P,C)=8.6, CSi or CSO_2), 125.4 (d, ^1J(P,C)=43.5, CP). CIMS (NH_3) m/z 557 (M+1).

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