

Directed *ortho* Lithiation in the Reactions of 3,5-Dimethyl- and
5-Trifluoromethyl-1-phenylpyrazoles with Butyllithium

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Lithiation of 3,5-dimethyl- and 5-trifluoromethyl-1-phenylpyrazoles with butyllithium is found to be directed to an *ortho* position. The *ortho* direction is ascribed to coordination of lithium with pyrazole 2-nitrogen or 5-trifluoromethyl group, respectively.

Metalation of azoles followed by electrophilic substitution is well recognized as the synthetic method providing a wide variety of substituted azoles.¹⁾ In a previous paper, we reported the reactivity of 5-lithio-4-trifluoromethylthiazoles which were applied on synthesis of the photochromic bis(4-trifluoromethylthiazolyl)ethene derivatives.²⁾ As a part of our study on metalation of the fluorinated azoles, we now wish to demonstrate the novel *ortho* directing ability of 5-trifluoromethyl- and 3,5-dimethylpyrazolyl groups, which is disclosed in lithiation of 1-phenylpyrazoles.³⁾

1-Phenylpyrazoles **1a-d**, prepared from phenylhydrazine and acetyl-acetones,⁴⁾ were lithiated with butyllithium in dry tetrahydrofuran to produce the corresponding lithium salts which were trapped by trimethylsilyl chloride (TMSCl). Reaction conditions and products are summarized in Table 1.

Inspection of the results thus obtained reveals some regiospecific features. (A) 1-Phenyl-3,5-bis(trifluoromethyl)pyrazole **1a** gave 4-TMS-pyrazole **2a** in good yield, as expected (Entry 1).⁵⁾ Surprisingly, however, treatment with an excess butyllithium yielded bis(TMS)pyrazole **5a**,⁶⁾ pointing

out that the second lithiation took place regioselectively on the *ortho* position of the phenyl group (Entry 2). (B) 3,5-Dimethylpyrazole **1b** was exclusively lithiated on the *ortho* position to give **3b** even on treatment with an excess butyllithium (Entry 3). (C) 5-Methyl-3-trifluoromethylpyrazole **1c** was trimethylsilylated at 5-methyl group to afford **4c** as a major product and 1-(*o*-TMS-phenyl)-5-(TMS-methyl)pyrazole **7c** as a minor product (Entry 4). (D) In contrast, 3-methyl-5-trifluoromethylpyrazole **1d** mainly gave *o*-TMS-phenylpyrazole **3d** together with a small amount of 4-TMS-pyrazole **2d**. When treated with an excess butyllithium, **1d** produced 1-(*o*-TMS-phenyl)-4-TMS-pyrazole **5d** as a major product. These results indicate that the first lithiation occurs on the *ortho* position predominantly (Entries 5 and 6).

The remarkable *ortho* directing ability of 3,5-dimethyl- and 5-trifluoromethylpyrazoles could be rationalized in terms of coordination between pyrazole 2-nitrogen and lithium (2-N-Li) or between 5-trifluoromethyl group and lithium (5-CF₃-Li).⁷⁾ Thus in the case of dimethylpyrazole **1b**, the exclusive formation of *o*-lithiated product **3b** could be interpreted by the strong coordination between 2-N-Li. 3-Trifluoromethylpyrazole **1c**, however, resulted in lithiation at 5-methyl group and this is ascribed to the reduced ability for coordination between 2-N-Li, because of the presence of electron-withdrawing 3-trifluoromethyl group. Most interestingly, in spite of the attachment of the electron-withdrawing 5-trifluoromethyl group in the pyrazole ring, the first lithiation of **1d** and the second lithiation of **1a** still occur on the *ortho* position predominantly. These results suggest that lithiation might be accelerated by coordination between 5-CF₃-Li or 2-N-Li. Thus, in order to evaluate which coordination is more effective, we carried out the AM 1 calculation of the heat of formation of the lithiated pyrazoles.⁸⁾ The calculation of two reasonable conformational isomers **3d'** and **3d''** indicates that **3d'** is more stable than **3d''**, the difference of 5.85 kcal/mol being estimated. This calculation suggests coordination between 5-CF₃-Li plays an important role in the *ortho* directed lithiation.⁹⁾ Furthermore, according to the calculation of **3d'**, it should be noted that lithium atom is located between two fluorine atoms, as depicted in Fig. 1.

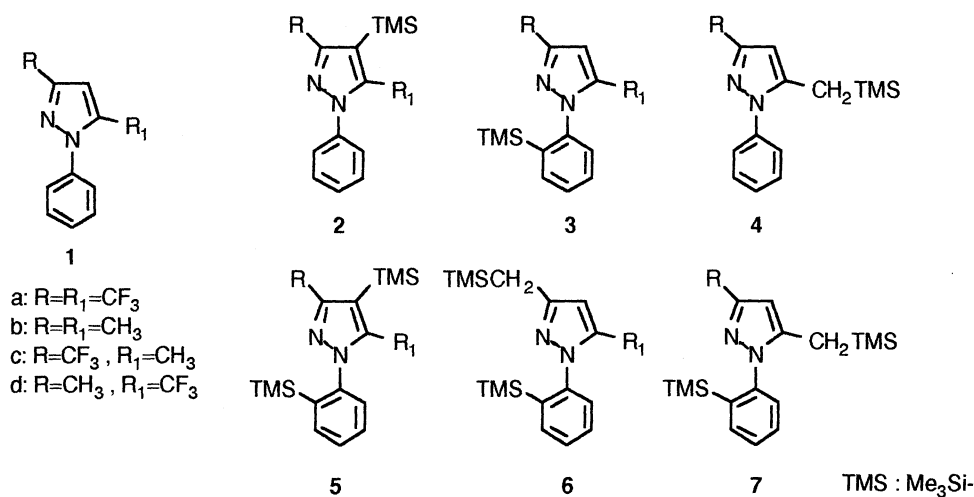


Table 1. Lithiation - Electrophilic Substitution with Trimethylsilyl Chloride

Entry	Compounds	BuLi (equiv.)	Conditions		Yields of products ^{a)}					
			Temp /°C	Time /h	2	3	4	5	6	7
1	1a	1.2	0	0.5	95	0	--	0	--	--
2	1a	3.0	0	1	0	0	--	93	--	--
3	1b	3.0	0	1	0	78	0	0	0	0
4	1c	3.0	-70 ^{b)}	3	0	0	37	0	--	7
5	1d	1.2	0	2.5	11	32	--	0	0	-- ^{c)}
6	1d	3.0	0	1	0	0	--	76	8	--

a) Isolated yield.

b) The formed lithium salt is so unstable as to decompose at 0 °C.

c) Starting compound (34%) was recovered.

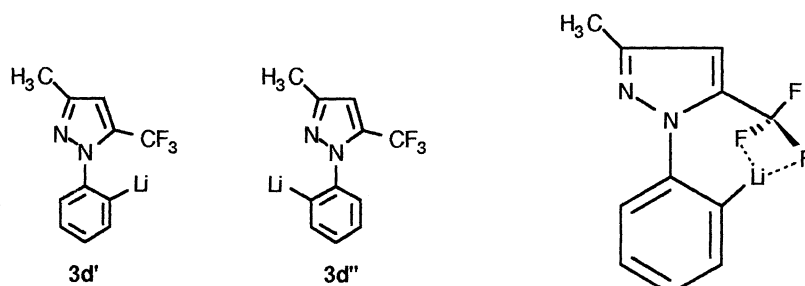


Fig. 1. Coordination between lithium atom and trifluoromethyl group.

In conclusion, the *ortho* lithiation of 1-phenylpyrazoles is accelerated by pyrazole 2-nitrogen and this coordinational ability is weakened by the electron-withdrawing group substituted at the pyrazole ring. Furthermore, the *ortho* directing ability of 5-trifluoromethyl group on the pyrazole ring is suggested by the AM 1 calculation.

References

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- 6) Substituted positions in all products 2-7 were determined by ^1H -NMR analysis. For example ^1H -NMR data of 5a are as follows; δ 0.01 (s, o-TMS, 9H), 0.39 (s, 4-TMS, 9H), 7.22 (dm, $J=7.6$ Hz, 1H), 7.44 (ddd, $J=1.7$, 7.3, 7.3 Hz, 1H), 7.50 (ddd, $J=1.7$, 7.3, 7.6 Hz, 1H), 7.67 (dd, $J=1.7$, 7.3 Hz, 1H).
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- 9) The similar stabilization by 5-trifluoromethyl group is estimated for 4-lithio-1-(o-lithiophenyl)-3,5-bis(trifluoromethyl)pyrazole from 1a and the difference being 10.91 kcal/mole.

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