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Synthesis of Fully Substituted Pyrazoles via Regio- and Chemoselective Metalations

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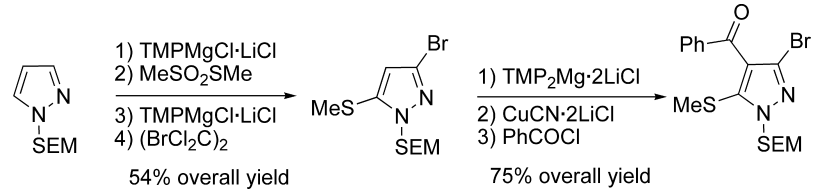
ABSTRACT



The full functionalization of the pyrazole ring was achieved by successive regioselective metalations using TMPMgCl·LiCl and $TMP_2Mg·2LiCl$. Trapping with various electrophiles led to trisubstituted pyrazoles. An application to the synthesis of the acaricide Tebufenpyrad is reported.

Pyrazole derivatives display a broad spectrum of biological activities and are used as cholesterol-lowering,[1] anti-inflammatory,[2] anticancer,[3] antidepressant, and antipsychotic[4] agents. They are therefore attractive building blocks for pharmaceutical research, and pyrazoles are present in leading pharmaceuticals (e.g., Celebrex,[2] Viagra[5]). These heterocycles have also found applications in the agrochemical industry and recently in the field of photoprotectors, ultraviolet stabilizers, and energetic materials.[6]

As a result, there is a constant striving to develop new methods for the synthesis of highly substituted pyrazoles. So far, the main access to fully functionalized pyrazoles involves condensation reactions between hydrazines and 1,3-dicarbonyl compounds and their derivatives[7] or 1,3-dipolar cycloadditions.[8] However, some limitations of these methods are the poor regioselectivity, multistep synthesis of the starting materials, and the harsh conditions often used.[9]

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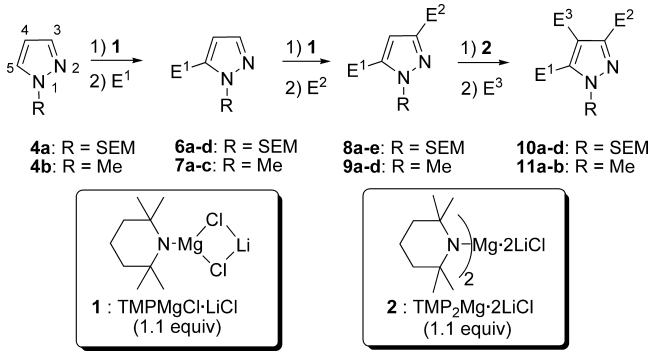
Deprotonation reactions on the pyrazole ring were until now limited to lithiations at very low temperatures on the most acidic C5 position.[10] Functionalization at the C3 position of the pyrazole core was only possible through a protecting group switch, while the C4 position was accessed through electrophilic substitutions.[11] Recently, we reported the new mixed Li/Mg bases TMPMgCl·LiCl (**1**; TMP = 2,2,6,6-tetramethyl- piperidyl)[12] and the more reactive TMP_2Mg·2LiCl (**2**),[13] which allow the magnesiation of functionalized arenes and heteroarenes. Sensitive substrates can be efficiently metalated using the milder base TMP_2Zn·$2MgCl_2$·2LiCl (**3**).[14]

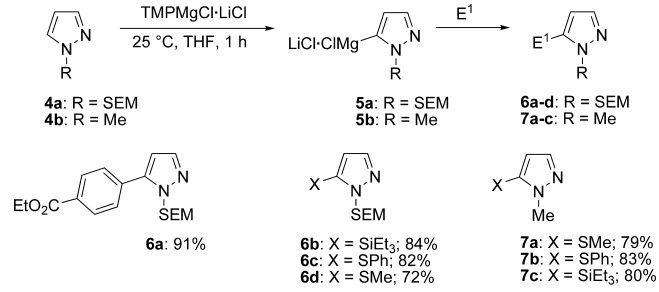
Herein, we report a new regio- and chemoselective synthesis of fully substituted pyrazoles through successive metalations on easily accessible pyrazoles (Scheme 1).

Scheme 1. Full Functionalization of Pyrazoles through Successive Metallations using TMPMgCl·LiCl (**1**) and TMP_2Mg·2LiCl (**2**)



Starting from the SEM-protected pyrazole[15] **4a** or the commercially available 1-methyl-1*H*-pyrazole (**4b**), magnesiation of the C5 position could be achieved using TMPMgCl·LiCl[12] (**1**; 1.1 equiv, 25 °C, THF, 1 h). The resulting magnesiated pyrazole **5a** successfully undergoes, after transmetalation with $ZnCl_2$, a Negishi[16] cross-coupling furnishing the expected product **6a** in 91% yield. Trapping of **5a** with various electrophiles such as Et_3SiCl, $PhSO_2SPh$, and $MeSO_2SMe$[17] gave the corresponding 5-substituted pyrazoles **6b**−**d** in 72−84% yield. Similarly, the 5-magnesiated *N*-methylpyrazole **5b** provides after reaction with $MeSO_2SMe$, $PhSO_2SPh$, and Et_3SiCl the new substituted pyrazole derivatives **7a**−**c** in 79−83% yields (Scheme 2).

Scheme 2. Magnesiation of Pyrazole Derivatives of Type **4** at Position 5 using TMPMgCl·LiCl (**1**)



A subsequent deprotonation at position 3 is readily achieved by adding TMPMgCl·LiCl (**1**) to various 5-substituted pyrazoles of type **6** and **7**. Thus, treatment of the SEM-protected pyrazoles **6c** and **6d** with TMPMgCl·LiCl (**1**; 1.1 equiv, −15 °C, 10 h) and subsequent quenching with TsCN, $NCCO_2Et$, FCl_2CCClF_2,[18] $(BrCl_2C)_2$, and DMF furnished the 3,5-disubstituted pyrazoles **8a**−**e** in 65−76% yield (entries 1−5 of Table 1).

Similarly, the *N*-methylated pyrazoles **7a** and **7b** were magnesiated under the same conditions. Metalation of **7a** using TMPMgCl·LiCl (**1**) followed by the transmetalation with CuCN·2LiCl[19] and addition of benzoyl chloride gave the expected ketone **9a** in 78% yield (entry 6). Magnesiation of the pyrazole **7b** gave after chlorination with FCl_2CCClF_2[18] (−15 to 25 °C, 5 h) the chloro derivative **9b** in 69% yield (entry 7). In the presence of CuCN·2LiCl[19] an allylation with allyl bromide furnished the pyrazole **9c** in 78% yield, after magnesiation with TMPMgCl·LiCl (**1**) (entry 8). The 5-si-

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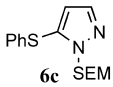
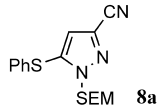
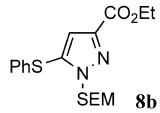
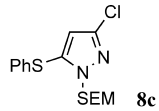
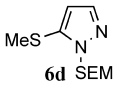
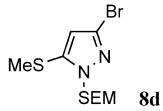
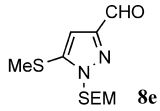
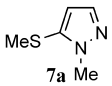
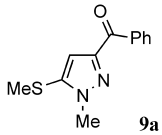
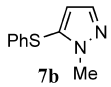
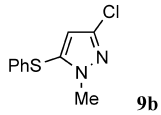
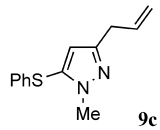
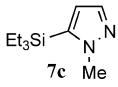
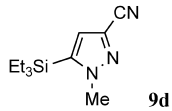
Table 1. Disubstituted Pyrazoles of Type **8** and **9** Obtained by Regioselective Magnesiation of Pyrazoles of Type **6** and **7** with TMPMgCl·LiCl (**1**) and Quenching with Electrophiles

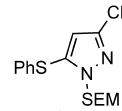
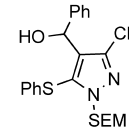
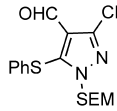
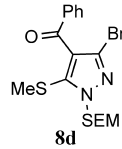
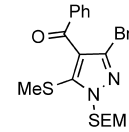
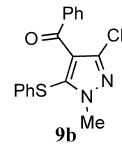
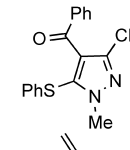
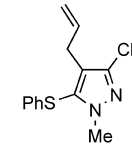
entry	substrate	electrophile	product	yield (%)[a]
1	 **6c**	TsCN	 **8a**	68[b]
2	**6c**	$NCCO_2Et$	 **8b**	71[b]
3	**6c**	FCl_2CCClF_2	 **8c**	65[b]
4	 **6d**	$(BrCl_2C)_2$	 **8d**	75[b]
5	**6d**	DMF	 **8e**	76[b]
6	 **7a**	PhCOCl	 **9a**	78[b,c]
7	 **7b**	FCl_2CCClF_2	 **9b**	69[b]
8	**7b**		 **9c**	78[b,d]
9	 **7c**	TsCN	 **9d**	61[e]

[a] Isolated, analytically pure product. [b] Deprotonation conditions: TMPMgCl·LiCl (**1**; 1.1 equiv), −15 °C, 10 h. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl. [d] Catalyzed with 5 mol % of CuCN·2LiCl. [e] Deprotonation conditions: TMPMgCl·LiCl (**1**; 1.1 equiv), 25 °C, 2 h.

lylated pyrazole **7c** was deprotonated using TMPMgCl·LiCl (**1**; 1.1 equiv, 25 °C, 2 h). Subsequent reaction with TsCN afforded the corresponding nitrile **9d** in 61% yield (entry 9).

The remaining position 4 of the pyrazole core was smoothly magnesiated using the stronger base TMP_2Mg·2LiCl[13] (**2**; 1.1 equiv, −20 °C, 4 h). Thus, the disubstituted pyrazole **8c** was deprotonated at position 4 and treated with benzaldehyde or DMF giving the corresponding alcohol **10a** in 71% yield or aldehyde **10b** in 67% yield (entries 1 and 2 of Table 2). The deprotonation of **8d** under the same conditions gave after transmetalation with CuCN·2LiCl[19] the

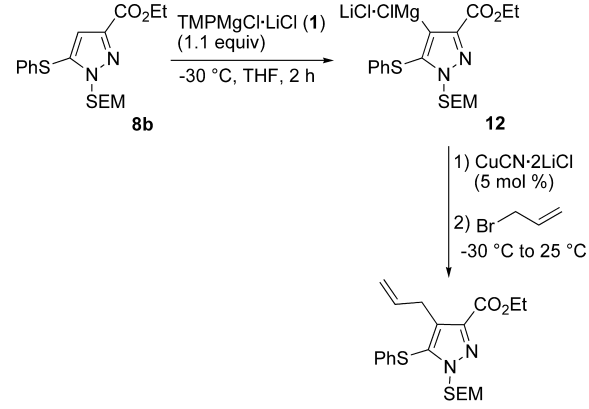
Table 2. Trisubstituted Pyrazoles of Type **10** and **11** Obtained by Regioselective Magnesiation of Pyrazoles of Type **8** and **9** with TMP_2Mg·2LiCl (**2**) and Quenching with Electrophiles

entry	substrate	electrophile	product	yield (%)[a,b]
1	 **8c**	PhCOH	 **10a**	71
2	**8c**	DMF	 **10b**	67
3	 **8d**	PhCOCl	 **10c**	75[c]
4	 **9b**	PhCOCl	 **11a**	76[c]
5	**9b**		 **11b**	70[d]

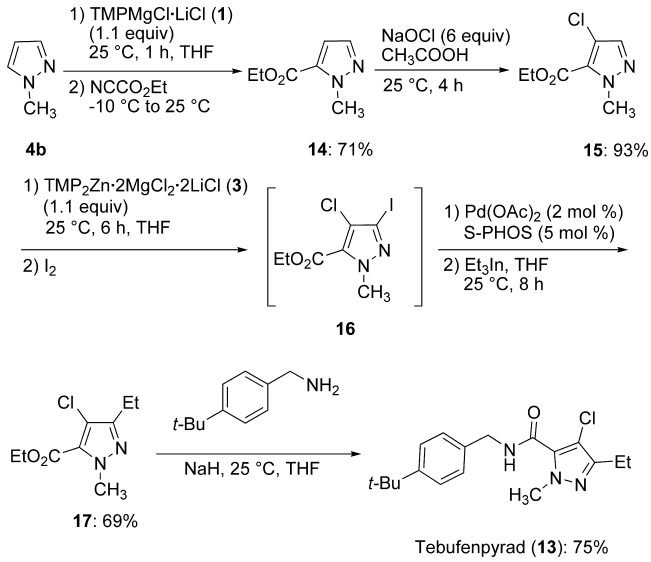
[a] Isolated, analytically pure product. [b] Deprotonation conditions: TMP_2Mg·2LiCl (**2**; 1.1 equiv), −20 °C, 4 h. [c] Transmetalation with 1.1 equiv of CuCN·2LiCl. [d] Catalyzed with 5 mol % of CuCN·2LiCl.

expected ketone **10c** in 75% yield (entry 3). Similarly, *N*-methylpyrazole **9b** was magnesiated and transmetalated with CuCN·2LiCl,[19] leading after reaction with benzoyl chloride and allyl bromide to the trisubstituted pyrazoles **11a** and **11b** in 70−76% yield (entries 4 and 5). Interestingly, pyrazole **8b** bearing an ester moiety at the C3 position could

Scheme 3. Magnesiation of Pyrazole **8b** at Position C4 using TMPMgCl·LiCl (**1**)



Scheme 4. Synthesis of the Acaricide Tebufenpyrad (**13**) through Successive Regio- and Chemoselective Metallations



be deprotonated with the milder base TMPMgCl·LiCl (**1**; 1.1 equiv, −30 °C, 2 h). Quenching of the resulting magnesium reagent **12** in the presence of CuCN·2LiCl[19] with allyl bromide afforded the allylated pyrazole **10d** in 75% yield (Scheme 3).

This functionalization of the pyrazole core was applied to the synthesis of the acaricide Tebufenpyrad (**13**).[20] *N*-Methylpyrazole **4b** was treated with TMPMgCl·LiCl (**1**; 1.1 equiv, 25 °C, 1 h) and quenched with $NCCO_2Et$, providing the expected ester **14**. Position 4 was then chlorinated via an electrophilic substitution reaction,[20b,c] furnishing **15** in 93% yield. The chlorine serves to activate the position C3, so that it could be metalated using the milder base $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[15] (**3**). Pyrazole **15** was treated with $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$[15] (**3**; 1.1 equiv, 25 °C, 6 h), and subsequent addition of I_2 furnished the iodopyrazole **16**. This iodide **16** undergoes a one-pot cross-coupling reaction with Et_3In generated by the reaction of EtMgCl (1.5 equiv) with $InCl_3$ (0.5 equiv),[21] affording the Tebufenpyrad precursor **17** in 69% yield. Reaction with 4-*tert*-butyl- benzylamine yielded Tebufenpyrad (**13**) in 75% yield (Scheme 4).

In conclusion, we have developed a new general method for regio- and chemoselective metalations of pyrazoles via successive deprotonation reactions using TMPMgCl·LiCl (**1**), $TMP_2Mg{\cdot}2LiCl$ (**2**), or $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**3**) leading to a variety of functionalized pyrazole derivatives with a regiocontrolled introduction of all substituents. Further applications to the preparation of more complex pyrazoles are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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