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Synthesis of Functionalized Cyanopyrazoles via Magnesium Bases

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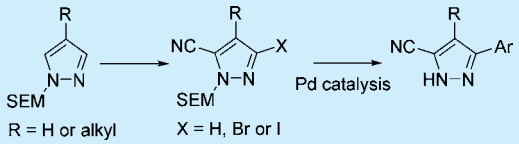
Supporting Information

ABSTRACT: 4-Alkyl- and 4-H-pyrazoles were sequentially metalated using TMPMgCl·LiCl, and their reaction with electrophiles afforded 3-aryl-4-alkyl-5-cyanopyrazoles.



In a recent drug discovery project, we became interested in the synthesis of a series of 3-cyano-4-methyl-5-arylpyrazoles (Figure 1). Our work has shown that the 3-cyano group is essential for biological activity, and the C4-methyl, as well as other C4-alkyl groups, is very interesting. Therefore, we wanted to develop a synthetic methodology that would allow late-stage variation of the C5-aryl ring, ideally where the 3-cyano-4-methyl substitution was pre-established or where the C4 substitution could also be varied.

Trisubstituted pyrazoles[1] are generally obtained either by the addition of hydrazines to 1,3-dicarbonyl compounds[1] or 1,3-dipolar cycloadditions.[2]

We anticipated that the pyrazole nonaflate **5** could undergo a metal-catalyzed cross-coupling with a range of organometallics to give the arylpyrazoles.[3] The nonaflate **5** could be prepared according to known procedures,[4a] and we were able to prepare multiple gram of the nonaflate **5** but via conditions that were not ideal. Treatment of the diester **1** with hydrazine gave the pyrazole **2** in 66% yield, and protection gave the ester **3** as a single regioisomeric *N*-protected THP ether. The conversion of the ester **3** to the nitrile **4** with lithium hexamethyldisilazide was only possible in sodium-distilled tetrahydrofuran under microwave irradation or in a sealed vessel at 140 °C and then only in 32% isolated yield.[5] The alcohol **4** was treated with sodium hydride and nonaflyl fluoride to give the nonaflate **5**.[4b]

However, the major disadvantages of this chemistry were the yields for the subsequent Suzuki coupling of the nonaflate **5** with arylboronic acids and esters. When the nonaflate **5** in dioxane containing the boronic acid, potassium carbonate, and tetrakis(triphenylphoshine)palladium (0) was heated at 120 °C for 30 min, the typical isolated yields for the arylpyrazoles **6** were in the 10−40% range after chromatography. An extensive catalyst and solvent screen only confirmed these to be the best coupling conditions. Given the limitation of the route in Scheme 1, we embarked on a reinvestigation of the synthetic protocols where we wished to address synthetic efficiency and scaleability.

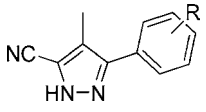


Figure 1. 3-Cyano-4-methyl-5-arylpyrazoles.

A timely addition to the literature[6] came from Knochel and co-workers, who demonstrated that substituted pyrazoles could be prepared via a deprotonation with the tetramethylpiperidinylmagnesium chloride lithium chloride (TMP-MgCl·LiCl) base **7** followed by reaction of the resultant magnesium anion with a range of electrophiles. The scope of this work was limited to 4-H-pyrazoles but offered the possibility to us of shorter routes to 4-methyl-5-cyanopyrazoles **9** (R = Me, R_1 = CN) as well as opening up the later investigation of differing substituents in the pyrazole 4-position **11** (Scheme 2). We reasoned that if we could develop Knochel's work to 4-alkylpyrazoles **8** (R = alkyl) then substitution into the 5-position of 4-alkylpyrazoles could be achieved via magnesiation to give compounds of type **9** (R = alkyl). This would be followed by 3-position magnesiation, transmetalation with zinc(II), and then cross-coupling to afford alkylpyrazoles **10** (R = alkyl) with suitably functionalized aryl groups at the 3-position. The single example of this deprotonation−Negishi protocol introduced an aromatic system into an unsubstituted pyrazole,[6] whereas we were looking to extend this chemistry to sterically and electronically complex pyrazoles. This approach would ensure that a range of substituted aryl groups could be introduced in the last step of the sequence, enabling us to synthesize a diverse range of medicinally important pyrazoles. We would have to demonstrate that the magnesiation chemistry could be advanced to include 4-alkylpyrazoles as well as develop a previously unreported magnesiation−Negishi coupling between aromatic sulfonamides and 4,5-disubstituted pyrazoles. To this end we set about developing a new synthetic route for the production of a range of 4-methylpyrazoles.

Commercially available 4-methylpyrazole **12** was treated with sodium hydride in *N*,*N*-dimethylformamide for 1 h and then was treated with silylethoxymethyl chloride to give the SEM-protected pyrazole **13** in 81% yield. The methylpyrazole **13** in tetrahydrofuran was magnesiated at position 5 with TMP−

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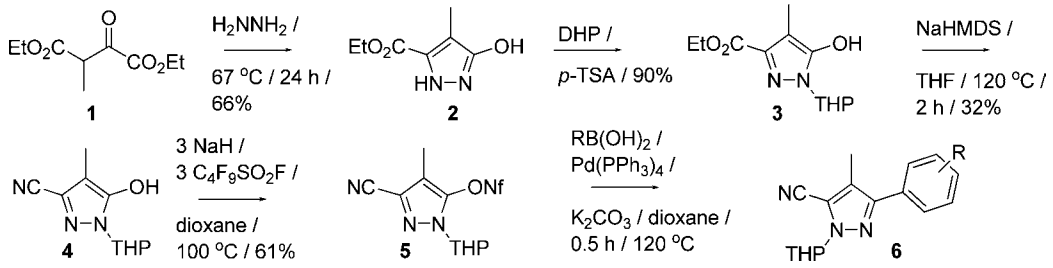
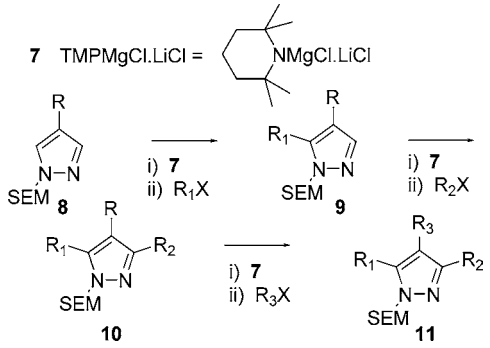
Scheme 1. Preparation and Coupling of the Pyrazole Nonaflate 5



Scheme 2. Successive Functionalization of Pyrazoles Using TMPMgCl·LiCl (Knochel[6])



Scheme 3. Successive Functionalisation of Pyrazoles Using TMPMgCl·LiCl 7

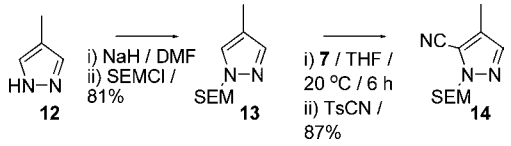
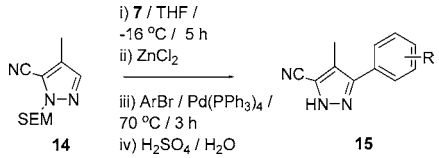
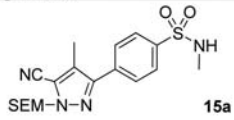
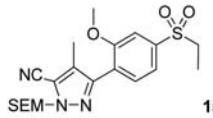
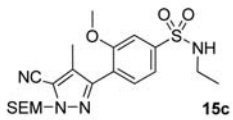
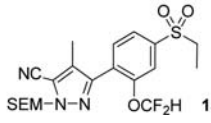
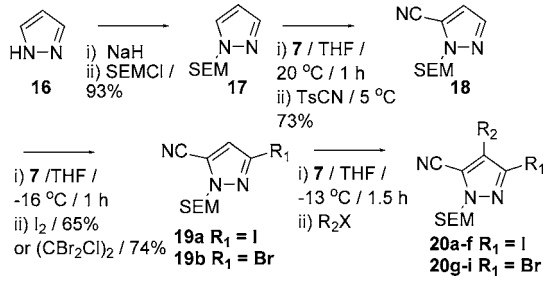


Table 1. Negishi Cross-Coupling of 4-Methylpyrazoles with Aryl Bromides



entry	product	yield
1	 **15a**	48%
2	 **15b**	78%
3	 **15c**	39%
4	 **15d**	92%

Scheme 4. 4-Alkylpyrazoles via Magnesiation



MgCl·LiCl at room temperature. The progress of deprotonation was followed by the iodination of a small aliquot of the reaction mixture and analysis by LCMS.[7] After 6 h, complete reaction was confirmed and the mixture was treated with phenylsulfonyl cyanide. The 2-cyano-3-methylpyrazole **14** was isolated in 87% yield after silica gel chromatography (Scheme 3).

With the cyanopyrazole **14** in hand, we were able to look at CH functionalization of the C5-position. We envisioned a Negishi cross-coupling may be applicable in this situation. When **14** was treated with base **7** in THF at −16 °C, full C5 magnesiation was observed after 5 h. Zinc chloride (1.0 M in diethyl ether) was added, the reaction mixture was allowed to warm to ambient temperature, and an aryl bromide in *N*,*N*-dimethylformamide followed by catalyst was added. The mixture was heated at 70 °C for 2 h, and following treatment of the crude product with aqueous sulfuric acid, we were pleased to isolate the arylpyrazole **15** after silica gel chromatography. Yields were generally good (Table 1); however, aryl sulfones (entries 2 and 4) were superior coupling partners compared to the aryl sulfonamides (entries 1 and 3) as it appears that an acidic N−H partially quenches the organometallic reagent to give recovery of starting material.

This reliable chemistry improved the preparation of pyrazole **15c** from a five-step 5% sequence via the nonaflate **5** to three steps in 57% via the magnesium base technology and represents the first application of this methodology to 4-alkylpyrazoles. Of particular note is the coupling of aryl sulfonamides; we were easily able to execute this chemistry on larger scale to prepare 13 g of the pyrazole **15a**.

We next wished to explore the SAR around 4-position alkyl groups in a cyanopyrazole, which necessitated the synthesis of 3-cyano-4-alkyl-5-arylpyrazoles. The absence of literature would indicate that preparation of these compounds is not trivial, and we were able to prepare only a limited number of 4-halo derivatives by established methods. Ideally, we required carbon substituents in the 4-position. Once again, we were able to apply sequential pyrazole deprotonation methodology to prepare this substitution pattern (Scheme 4).[6]

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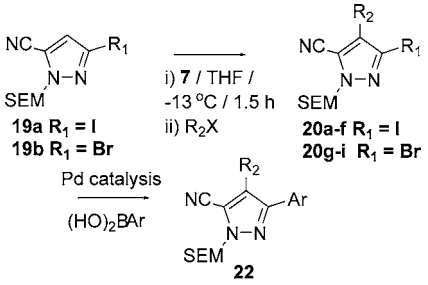
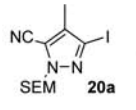
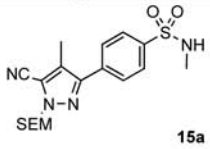
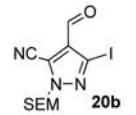
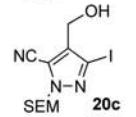
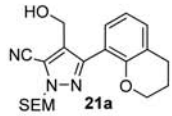
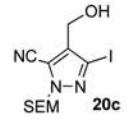
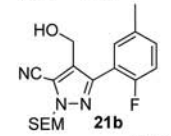
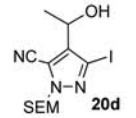
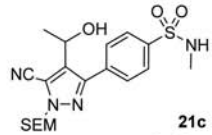
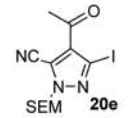
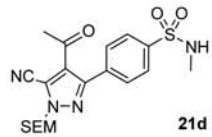
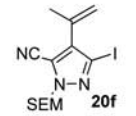
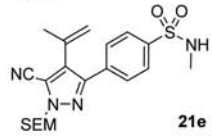
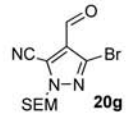
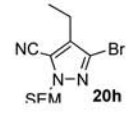
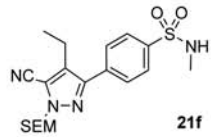
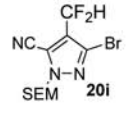
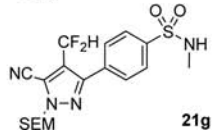
Table 2. Preparation of 4-Alkylpyrazoles and Coupling to Bromoarenes



entry	pyrazole	yield	product	yield
1	 **20a**	67%	 **15a**	88%
2	 **20b**	61%		
3	 **20c**	72%	 **21a**	83%
4	 **20c**	72%	 **21b**	88%
5	 **20d**	40%	 **21c**	56%
6	 **20e**	86%	 **21d**	77%
7	 **20f**	77%	 **21e**	72%
8	 **20g**	48%		
9	 **20h**	41%	 **21f**	67%
10	 **20i**	69%	 **21g**	76%

Pyrazole **16** in *N*,*N*-dimethylformamide was treated with sodium hydride and silylethoxymethyl chloride to give the SEM-protected pyrazole **17** in 86% yield. Magnesiation in the 5-position was achieved at 20 °C over 1 h with TMP−MgCl·LiCl **7**, and quenching with tosyl cyanide gave the nitrile **18** in 73% yield after silica gel chromatography. This material was subjected to the same base **7**, and the anion was quenched with either iodine or tetrabromodichloroethane to afford the 3-iodo-**19a** (65%) or 3-bromopyrazole **19b** (74%).

The literature observes that the third deprotonation in the 4-position of disubstituted pyrazoles requires the more basic $TMP_2Mg{\cdot}2LiCl$ unless substitution includes a carboxylate group.[6] We found that the weaker TMP−MgCl·LiCl **7** was capable of this deprotonation at −13 °C over 1.5 h, and we were able to quench the magnesium anion with electrophiles to afford a range of 4-alkyl-substituted pyrazoles **20** (entries 1, 2, and 8, Table 2). When iodide **19a** was metalated under these conditions and treated with excess iodomethane at 20 °C, the methylpyrazole **20a** was isolated in 67% yield (entry 1). The same metalated iodide **19a** also reacted with morpholine-4-carbaldehye to give the aldehyde **20b** in 61% yield (entry 2). The metalated bromide **19b** reacted with morpholine-4-carbaldehyde to give the aldehyde **20g** in 48% yield (entry 8).

While the scope of this reaction will be explored further with a wider range of electrophiles, we desired to elaborate further the existing 4-position substituents. The aldehyde **20b** could be reduced with sodium borohydride to the alcohol **20c** in 72% yield (entry 3) or reacted with methylmagnesium bromide (40%) to give the alcohol **20d** (entry 5). The bromoaldehyde **20g** gave the difluoromethylene pyrazole **20i** in 69% yield when treated with Deoxo-fluor (entry 10). The 4-ethylpyrazole **20h** was prepared in 41% from the aldehyde **20g** in two steps (Wittig methylenation followed by hydrogenation) (entry 9). The alcohol **20d** could be oxidized under Swern conditions to give the ketone **20e** (86%) (entry 6), which on methylenation via a Wittig reaction (77%) gave alkene **20f** (entry 7). With a range of 3-halo-4-alkylpyrazoles in hand, we were finally able to attempt aryl substitution at the 3-position (the aldehydes **20b** and **20g** were excluded from this coupling). Gratifyingly, the 3-halopyrazoles were coupled with a suitable boronic acid under palladium catalysis to afford the synthetically challenging 3-aryl-4-alkylpyrazoles **15a** and **21** in 56−88% yield. Removal of the SEM group was readily achieved by treatment with aqueous sulfuric acid or tetrabutylammonium fluoride.

In summary, we have prepared a range of 3-cyano-4-alkyl-5-arylpyrazoles via the application of regioselective magnesium amide base protocols and have demonstrated that this previously unknown biologically privileged structure is readily accessible to the medicinal chemist. In a significant advancement to the established methods, we have shown that 4-alkylpyrazoles can now be deprotonated with magnesium bases and that after deprotonation disubstituted pyrazoles can be readily functionalized with complex aromatic groups. The aryl group was introduced by either a Suzuki coupling or by a direct deprotonation−zincation Negishi reaction.

■ ASSOCIATED CONTENT

Supporting Information

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

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Notes

The authors declare no competing financial interest.

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(7) See the Supporting Information for a typical procedure.