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SYNTHESIS OF 4-ARYLPYRAZOLES VIA $PdCl_2$(dppf)-CATALYZED CROSS COUPLING REACTION WITH GRIGNARD REAGENTS

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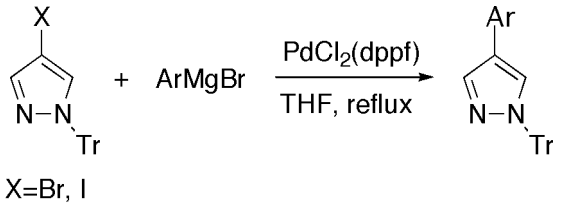
Abstract – 4-Aryl-1-tritylpyrazoles were prepared from the cross coupling reaction of aryl Grignard reagents with 4-bromo-1-tritylpyrazoles in the presence of 0.2 mol% $PdCl_2$(dppf) as catalyst. To deprotect the trityl group, 4-phenyl-1-tritylpyrazole was reacted with TFA to produce 4-arylpyrazole in quantitative yield.

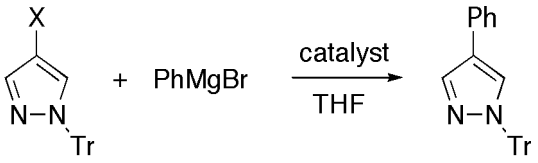
Heteroaromatic compounds have attracted considerable attention in the design of biologically active molecules and advanced organic materials. In particular, five-membered heterocyclic compounds such as pyrazoles[1] have been utilized in the development of new pharmaceutical compounds, for instance, molecular chaperone Hsp90 inhibitors, cyclooxygenase-2 (COX-2) inhibitors, and so on.[2] Hence, there is much interest in the development of a practical method for the preparation of pyrazoles in synthetic organic chemistry. The route to substituted pyrazoles has been established; it involves the 1,3-dipolar cycloaddition reaction of hydrazine with β-dicarbonyl compounds.[1] Therefore, the synthesis of 4-monosubstituted pyrazole requires a β-dialdehyde, specifically, a malonodialdehyde derivative.[3] The malonodialdehyde is, however, more unstable than a β-diketone[4] and the synthesis of malonodialdehydes having various substituents requires many steps. On the other hand, the direct synthesis of 4-substituted pyrazoles has been reported[5,6], including the Stille and Suzuki cross coupling route. However, there remain issues to be resolved in these cross coupling syntheses, namely, the Stille coupling route was low yield and impracticality and the Suzuki coupling route was low yield and required high reaction temperature. For these reasons, synthetic organic chemists have embarked on finding a new route for the synthesis of 4-substituted pyrazoles. Herein we report the synthesis of 4-arylpyrazoles via 0.2 mol% palladium catalyzed cross coupling reaction of 4-bromo-1-tritylpyrazole with various aryl Grignard reagents (Scheme 1).



Scheme 1

4-Halo-1-tritylpyrazole was reacted with phenylmagnesium bromide in the presence of various catalysts (Table 1). Nickel catalysts are widely used for the cross coupling reaction of Grignard reagents with a variety of heterocycles.[7] However, the nickel-complex-catalyzed cross coupling reactions proceeded in low yields to obtain coupled pyrazoles (Entries 1-4). $PdCl_2(PPh_3)_2$ also catalyzed the coupling reaction of bromopyrazoles with phenylmagnesium bromide in low yield (Entry 5). By contrast, when $PdCl_2$(dppf) was used to catalyze the reaction of Grignard reagent with iodopyrazole at 0 °C for 36 h, the coupled product was obtained in excellent yield (Entry 6). When the bromopyrazole (**1b**) was reacted with phenylmagnesium bromide under 0 °C for 30 hours, the coupling products were gave only 8% yields (Entry 7) and biphenyl, which was Wultz coupling products, was detected as a byproduct. However, the

Table 1. Coupling reaction of phenylmagnesium bromide with 4-bromo-1-tritylpyrazoles in the presence of various catalysts.[a]



1a: X=I, **1b**: X=Br **2**

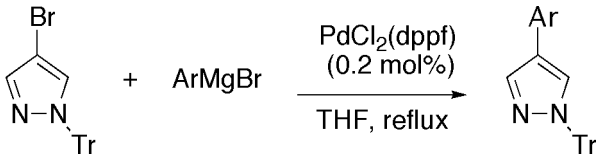
Entry	Substrate	Catalyst, (mol%)	Condition	Yield (%)[b]
1	**1a**	$NiCl_2$(dppp), 5	0 °C, 36 h	19[c]
2	**1a**	$NiCl_2$(dppp), 10	RT, 24 h	26[c]
3	**1b**	$NiCl_2$(dppe), 17	reflux, 3 h	26
4	**1b**	$NiCl_2$(dppp), 10	reflux, 2 h	31
5	**1b**	$PdCl_2(PPh_3)_2$, 1	reflux, 2 h	25
6	**1a**	$PdCl_2$(dppf), 5	0 °C, 36 h	96[c]
7	**1b**	$PdCl_2$(dppf), 5	0 °C, 30 h	8[c]
8	**1b**	$PdCl_2$(dppf), 1	RT, 24 h	90[d]
9	**1b**	$PdCl_2$(dppf), 0.2	reflux, 4 h	99

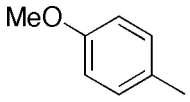
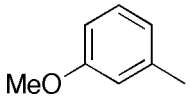
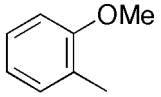
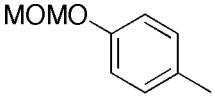
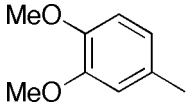
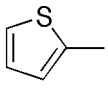
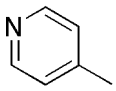
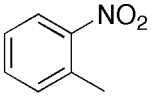
[a]Reaction conditions: **1** (1.0 mmol), phenylmagnesium bromide (1.1 equiv), catalyst in THF under N_2. Substrate concentration is 0.25 M. [b]Isolated yield. [c]Substrate concentration is 0.1 M. [d]Substrate concentration is 0.5 M.

use of high substrate concentration (0.25 M) and high reaction temperature shortened the reaction time and reduced the amount of catalyst required by the coupling reaction (Entry 8). Finally, 0.2 mol% $PdCl_2$(dppf) was found to catalyze the cross coupling reaction of 4-bromo-1-tritylpyrazole with phenylmagnesium bromide in quantitative yield (Entry 9).[8]

Additionally, 4-substituted pyrazoles were prepared by reacting various aryl Grignard reagents with 4-bromo-1-tritylpyrazoles (Table 2).[9] Coupled pyrazoles with *m*- and *p*-methoxyphenylmagnesium bromide were prepared in excellent yields and 4-(2'-methoxyphenyl)pyrazole was also obtained in good yield (Entries 1-3). 4-Methoxymethylphenylpyrazole is easily accessible to a variety of ether derivatives

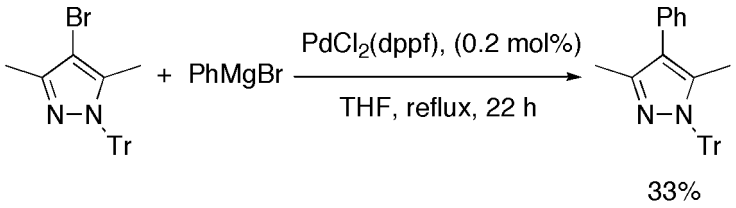
Table 2. 0.2 mol% $PdCl_2$(dppf) catalyzed cross coupling reaction of 4-bromo-1-tritylpyrazole with various aryl Grignard reagents.



Entry	Ar	Time (h)	Yield (%)[a]
1		2	92
2		2	93
3		4	70[b]
4		2	86
5		4	60[b]
6		4	76
7		4	n.r.[c]
8		3	n.r.[c]

[a]Isolated yield. [b]Arylmagnesium bromide (1.5 equiv). [c]n.r. = no reaction

because of bearing protected the hydroxyl group (Entry 4). By contrast, a moderate yield of 3',4'-dimethoxyphenylpyrazole was obtained in the reaction with 1.5 equiv of 3,4-dimethoxyphenylmagnesium bromide (Entry 5). It is noteworthy that 2'-thienylpyrazole was afforded in good yield from 2'-thienylmagnesium bromide and bromopyrazole (Entry 6). Unfortunately, no pyridyl- or nitrophenylpyrazoles were obtained from 4-pyridylmagnesium bromide[10] or 2-nitrophenylmagnesium bromide[11] (Entries 7 and 8). In addition, 4-bromo-3,5-dimethyl-1-tritylpyrazole was reacted with phenylmagnesium bromide in the presence of 0.2 mol% $PdCl_2$(dppf) to obtain the 3,5-dimethyl-4-phenyl-1-tritylpyrazole in 33% yield (Scheme 2).[12] It can be seen that the dimethyl groups sterically hindered the cross coupling reaction.



Scheme 2

Finally, to deprotect the trityl group, 4-phenyl-1-tritylpyrazole was reacted with trifluoroacetic acid (TFA) and 4-phenylpyrazole was obtained in quantitative yield.

In summary, we have achieved the 0.2 mol% palladium catalyzed cross coupling reaction of aryl Grignard reagents with 4-bromo-1-tritylpyrazole to yield 4-aryl-1-tritylpyrazole quantitatively. Deprotection of 4-phenyl-1-tritylpyrazole was achieved with TFA to obtain 4-phenylpyrazole in excellent yield.

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This paper is dedicated to the memory of the late Emeritus Professor Itsuo Mori of Osaka University of Pharmaceutical Sciences.

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8. Typical experiment procedure is as follows. To a solution of 4-halo-1-tritylpyrazole (1.0 mmol) and $PdCl_2$(dppf) (0.2 mol%) in freshly dried THF under N_2 at 0 °C was added ArMgBr (1.1 mmol). The reaction mixture was refluxed for the desired time until pyrazole was completely consumed as monitored by TLC. After the reaction mixture was quenched with saturated NH_4Cl solution and extracted with EtOAc, the organic layer was washed with brine and dried over $MgSO_4$. After filtration of the organic layer and evaporation of the solvent, the crude products were purified by silica gel column chromatography (hexane/EtOAc = 20/1 as an eluent) to afford the corresponding coupled products. **4-phenyl-1-tritylpyrazole:** mp 149 °C; IR (KBr) 1488, 2359, 3055 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.14−7.44 (20H, m, Ph and Tr), 7.61 (1H, m, pyrazole), 7.93 (1H, m, pyrazole); ^{13}C NMR ($CDCl_3$) δ 121.3, 125.2, 126.0, 126.9, 127.4, 127.5, 128.4, 128.7, 129.8, 132.1, 136.8, 142.6; HRMS Calcd for $C_{28}H_{22}N_2$: 386.1783 (M^+). Found: 386.1779 (M^+).
9. **4-(4'-methoxyphenyl)-1-tritylpyrazole:** mp 191 °C; IR (KBr) 1246, 1506, 2359, 3057 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.85 (3H, s, OCH_3), 6.84−7.36 (19H, m, Ar and Tr), 7.52 (1H, s, pyrazole), 7.86

(1H, s, pyrazole); ^{13}C NMR ($CDCl_3$) δ 55.4, 78.7, 113.9, 121.0, 124.9, 126.3, 127.3, 127.5, 128.1, 129.7, 136.5, 142.7, 157.7; HRMS Calcd for $C_{29}H_{24}N_2O$: 416.1889 (M^+). Found: 416.1883 (M^+). **4-(3'-methoxyphenyl)-1-tritylpyrazole:** mp 105 °C; IR (KBr) 1227, 1490, 2359, 3059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s, OCH_3), 6.70−7.34 (19H, m, Ar and Tr), 7.61 (1H, m, pyrazole), 7.83 (1H, s, pyrazole); ^{13}C NMR ($CDCl_3$) δ 55.4, 78.8, 111.0, 111.2, 117.7, 121.1, 127.3, 127.5, 128.8, 129.4, 129.7, 133.5, 136.8, 142.5 159.3; HRMS Calcd for $C_{29}H_{24}N_2O$: 416.1889 (M^+). Found: 416.1890 (M^+). **4-(2'-methoxyphenyl)-1-tritylpyrazole:** mp 124 °C; IR (KBr) 1249, 1493, 2362, 2998 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (3H, s, OCH_3), 6.84−7.49 (19H, m, Ar and Tr), 7.84 (1H, s, pyrazole), 8.06 (1H, s, pyrazole); ^{13}C NMR ($CDCl_3$) δ 55.4, 78.6, 111.0, 116.7, 120.4, 121.0, 126.8, 126.9, 127.3, 127.5, 129.8, 131.2, 138.1, 142.7, 155.1; HRMS Calcd for $C_{29}H_{24}N_2O$: 416.1889 (M^+). Found: 416.1892 (M^+). **4-(4'-methoxymethoxylphenyl)-1-tritylpyrazole:** mp 151 °C; IR (KBr) 1152, 1238, 1506 (C=C), 2955 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.45 (3H, s, OCH_3), 5.15 (2H, s, OCH_2), 6.96-7.36 (19H, m, Ar and Tr), 7.53 (1H, m, pyrazole), 7.87 (1H, m, pyrazole); ^{13}C NMR ($CDCl_3$) δ 56.0, 78.7, 94.3, 116.3, 120.9, 126.1, 126.3, 127.3, 127.5, 128.2, 129.7, 136.5, 142.6, 155.2; HRMS Calcd for $C_{30}H_{26}N_2O_2$: 446.1994 (M^+). Found: 446.1978 (M^+). **4-(3', 4'-dimethoxyphenyl)-1-tritylpyrazole:** mp 154 °C; IR (KBr) 1249, 1514, 2997 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.85 (6H, m, OCH_3), 6.79−7.35 (18H, m, Ar and Tr), 7.55 (1H, s, pyrazole), 7.87 (1H, s, pyrazole); ^{13}C NMR ($CDCl_3$) δ 56.0, 56.1, 78.7, 109.0, 111.3, 117.7, 121.2, 125.2, 127.3, 127.4, 128.1, 129.7, 136.5, 142.6, 147.3, 148.6; HRMS Calcd for $C_{30}H_{26}N_2O_2$: 446.1994 (M^+). Found: 446.1996 (M^+). **4-(2'-thienyl)-1-tritylpyrazole:** mp 120 °C; IR (KBr) 1037, 1490, 2359, 3065 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.94−7.34 (18H, m, thienyl and Tr), 7.53 (1H, m, pyrazole), 7.82 (1H, m, pyrazole); ^{13}C NMR ($CDCl_3$) δ 78.8, 115.4, 122.2, 122.6, 127.1, 127.4, 127.5, 128.6, 129.7, 134.6, 137.0, 142.4; HRMS Calcd for $C_{26}H_{20}N_2S$: 392.1347 (M^+). Found: 392.1348 (M^+).

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11. I. Sapountzis, H. Dube, R. Lewis, N. Gommermann, and P. Knochel, *J. Org. Chem.*, 2005, **70**, 2445.
12. **4-bromo-3,5-dimethyl-1-tritylpyrazole:** mp 168 °C; IR (KBr) 1443, 2364, 3051 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, s, CH_3), 2.20 (3H, s, CH_3), 7.05−7.32 (15H, m, Tr); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.2, 77.2, 126.9, 127.1, 127.5, 129.9, 139.0, 142.2, 143.7; HRMS Calcd for $C_{24}H_{21}N_2{}^{79}Br$: 416.0888 (M^+). Found: 416.0886 (M^+). **3,5-dimethyl-4-phenyl-1-tritylpyrazole:** mp 211 °C; IR (KBr) 1444, 2362, 3060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.48 (3H, s, CH_3), 2.22 (3H, s, CH_3), 7.11−7.39 (20H, m, Ph and Tr); ^{13}C NMR ($CDCl_3$) δ 13.4, 14.1, 77.2, 78.2, 125.7, 126.7, 127.0, 127.8 129.4, 130.0, 130.0, 138.1, 142.9, 143.1; HRMS Calcd for $C_{30}H_{26}N_2$: 414.2096 (M^+). Found: 414.2098 (M^+).