# SYNTHESES OF 5-ARYLPYRAZOLE DERIVATIVES *VIA* PALLADIUM-CATALYZED CROSS-COUPLING REACTIONS

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**Abstract** - The first examples of a direct introduction of an aryl group onto a pyrazole ring *via* palladium-catalyzed cross-coupling reactions are reported. It was found that substituents at 1-position on the pyrazole ring affected the yields, and dimethylsulfamoyl group, as an electron-withdrawing group, gave highest yield.

Recently, considerable attention is being paid to the direct introduction of an aryl group onto nitrogen-containing heteroaromatics, such as pyridine,[1-3] pyrimidine[4] and imidazole,[5,6] as a method for construction of natural products[3,5] or pharmaceuticals.[2,6] The key reactions to build up these molecules are palladium-catalyzed cross-coupling reactions.[7]

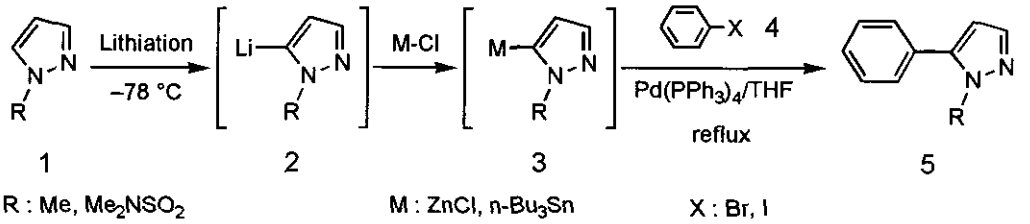
In nitrogen-containing heteroaromatics, pyrazole is a major moiety of biologically active compounds, especially in the field of agricultural chemicals.[8] Although a number of synthetic methods have been developed to construct pyrazole, possessing an aryl group on the ring,[8b,8c,9] many of these methods are based on time-consuming multi-step procedures or structure-limited ring transformation reactions. Hence, a widely applicable, operationally simple methodology to construct pyrazole-containing molecules has been sought as a route to discovery of new biological activities. To our knowledge, however, direct introduction of an aryl group onto the pyrazole nucleus *via* a palladium-catalyzed cross-coupling reaction has not been published yet.

In connection with our investigation of substances with biological activities, and from the viewpont of new pyrazole chemistry as well, we searched for a facile synthetic method to construct novel pyrazole derivatives.

Here we now wish to report the first successful examples of our attempts for the direct introduction of an aryl group onto the pyrazole ring *via* palladium-catalyzed cross-coupling reactions and a preliminary biological evaluation of the coupling product.

Firstly, reactions between 1-substituted *1H*-pyrazoles (**1**) and halobenzenes were examined in the presence of 5 mol% of tetrakis(triphenylphosphine)palladium(0) as a catalyst in accordance with the method reported in the literature[6] (Scheme 1).

**Scheme 1**




The reactions proceeded smoothly and gave coupling products as a first examples of the palladium catalyzed cross-coupling reaction on the pyrazole nucleus.

Thus, the reactions between 1 eq. of 1-substituted *1H*-pyrazole-5-zinc chlorides or -5-tri-n-butylstannanes (**3**), prepared from 1-substituted *1H*-pyrazoles (**1**) *via* lithiation and transmetallation with zinc chloride or tri-n-butylstannyl chloride at 5-position, and halobenzenes (**4**), gave 1-substituted 5-phenyl-*1H*-pyrazoles (**5**). The results were shown in Table.

Table. Reactions of 1-substituted *1H*-pyrazoles (**1**) with halobenzenes (**4**).

| Run | R | Base | M-Cl | X | Time (h) | Yield (%) |
|---|---|---|---|---|---|---|
| 1 | Me | n-BuLi | $ZnCl_2$ | Br | 4.5 | 9 |
| 2 | Me | n-BuLi | $ZnCl_2$ | I | 4.5 | 19 |
| 3 | Me | n-BuLi | $n\text{-}Bu_3SnCl$ | Br | 4.5 | 16 |
| 4 | Me | n-BuLi | $n\text{-}Bu_3SnCl$ | I | 4.5 | 22 |
| 5 | Me | LDA | $ZnCl_2$ | I | 4.5 | 57 |
| 6 | $Me_2NSO_2$ | LDA | $ZnCl_2$ | Br | 6.5 | 75 |

In the reactions of 1-methylpyrazole (**1**, R=Me) with halobenzenes (**4**) using n-BuLi as the lithiation reagent (Runs 1-4), iodobenzene (**4**, X=I) gave better results compared to that of bromobenzene (**4**, X=Br) and the yields of **5** (R=Me) were practically same; *ca.* 20 %. As to the metal on the pyrazole, both of stannane and zinc exibited similar effects.

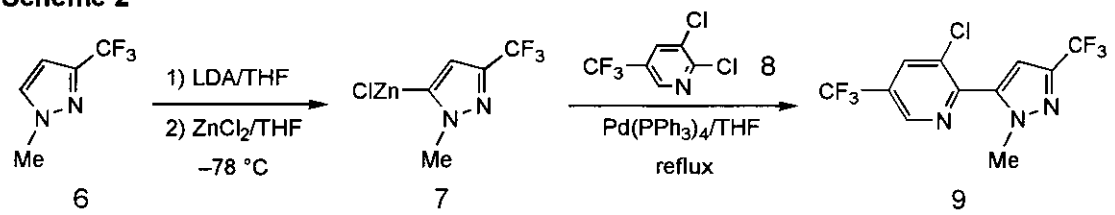
It was found that the yield was significantly increased by an exchange of the lithiation reagent, from n-BuLi to LDA, to 57 % (Run 5).

Substitutents at 1-position on the pyrazole ring also affected to the yield of **5**. Substitution of dimethylsulfamoyl group, as an electron-withdrawing group, instead of methyl group led further

improvement concerning the yield of **5** ($R=Me_2NSO_2$) to 75 % (Run 6).

Secondly, extending this cross-coupling reaction and in expectation of biological activities, a reaction between 1-methyl-3-trifluoromethyl-*1H*-pyrazole (**6**) and 2,3-dichloro-5-trifluoromethylpyridine (**8**)[10] *via* 3-trifluoromethyl-*1H*-pyrazole-5-zinc chloride (**7**) was carried out under the similar conditions as mentioned above (Scheme 2). Both of the heterocycles have a trifluoromethyl group on the rings, which is greatly of interest in biological activity.

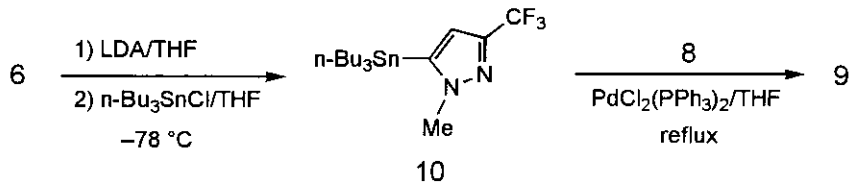
**Scheme 2**




The reaction proceeded expectedly to furnish the desired 5-(3-chloro-5-trifluoromethyl-2-pyridyl)-1-methyl-3-trifluoromethyl-*1H*-pyrazole (**9**).[11] However, the yield of **9** was low; *ca.* 20 %.

To optimise the yield of **9**, the cross-coupling reaction using stannane instead of zinc as the metal for the transmetallation on the pyrazole nucleus, in combination with dichlorobis(triphenylphosphine)palladium as the catalyst, was also examined[12] (Scheme 3).

**Scheme 3**




Quenching the lithium derivative with tri-n-butyltin chloride gave the 5-tri-n-butyltin-*1H*-pyrazole (**10**) in 63% yield, which enabled the cross-coupling reaction with the pyridine (**8**) to give **9** in 56% yield. Although the route was a two-step reaction, the total yield of **9** from the starting pyrazole (**6**) was significantly improved.

The coupling product (**9**) was subjected to biological assay to evaluate its potential as a pesticide. Insecticidal activity was successfully found against cucurbit leaf beetle, *Aulacophora femoralis*, which cause a damage to the root of cucurbitaceous plant, at 500 ppm.

Considering the results obtained in this study, the palladium-catalyzed cross-coupling reaction was proved as a promising method to introduce an aryl group onto the pyrazole nucleus as a key step to construct biologically active compounds and more complicated molecules efficiently.

Further investigation concerning the cross-coupling reaction on the pyrazole nucleus and substitution reaction on the compound (**9**) as well as biological evaluations, are now in progress.

## REFERENCES AND NOTES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11 Satisfactory spectral data of **9** was obtained as follows : $n_D^{21}$ =1.4874; $^1$H-NMR ($CDCl_3$) δ 4.08(3H, s), 7.07(1H, s), 8.13(1H, s), 8.90(1H, s); $^{13}$C-NMR($CDCl_3$) δ 39.6, 107.8 ($J_{C\text{-}C\text{-}C\text{-}F}$=2.1 Hz), 121.1($J_{C\text{-}F}$=268.8 Hz), 122.4($J_{C\text{-}F}$=273.2 Hz), 127.3($J_{C\text{-}C\text{-}F}$=34.6 Hz), 131.4, 135. 8($J_{C\text{-}C\text{-}C\text{-}F}$=3.6 Hz), 138.4, 141.0($J_{C\text{-}C\text{-}F}$=39.0 Hz), 144.2($J_{C\text{-}C\text{-}C\text{-}F}$=3.6 Hz), 149.6; $^{19}$F-NMR($CDCl_3$) δ -16.7, -16.3; Anal. Calcd for $C_{11}H_5N_3Cl_2F_6$: C, 40.33; H, 2.15; N, 12.44. Found: C, 40.51; H, 2.16; N,12.50.

12 A synthetic procedure :

A solution of 4.0 g (39.6 mmol) of diisopropylamine in 50 mL of THF was cooled to -78 °C in a dry-ice/acetone bath and treated with 24.7 mL (40.0 mmol) of 1.62M n-butyllithium in hexane and stirred for 15 min. A solution of 5.0 g (33.3 mmol) of 1-methyl-3-trifluoromethyl-*1H*-pyrazole (**6**) in 30 mL of THF was added and stirring was continued for an additional 0.5 h. To this solution, a solution of 13.0 g (39.9 mmol) of tributyltin chloride in 30 mL of THF was added and stirred at -78 °C for 3 h and at rt. over night. The resulting mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with aqueous sodium bicarbonate and dried over sodium sulfate. Removal of the solvent gave 9.2 g (63 %) of 1-methyl-5-tributylstannyl-3-trifluoromethyl-*1H*-pyrazole (**10**) as an oil.

A mixture of 150 mg (0.34 mmol) of **10**, 81 mg (0.38 mmol) of 2,3-dichloro-5-trifluoromethylpyridine, 2.2 mg of dichlorobis(triphenylphosphine)palladium and 3 mL of THF was refluxed overnight. The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate. After removal of the solvent, the residue was purified by preparative TLC (benzene) to afford the desired 5-(3-chloro-5-trifluoromethylpyridyl)-1-methyl-3-trifluoromethyl-*1H*-pyrazole (**9**) as an oil, 63 mg (56 %).


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