Functionalised Pyrazoles through a Facile One-Pot Procedure from N-Tosyl-N-propargylhydrazine and Aryl Iodides or Vinyl Triflates

Sandro Cacchi,* Giancarlo Fabrizi, Antonella Carangio

Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, Università "La Sapienza", P.le A. Moro 5, 00185 Roma, Italy

Fax: + 39 (6) 4991.2780; e-mail: cacchi@axrma.uniroma1.it

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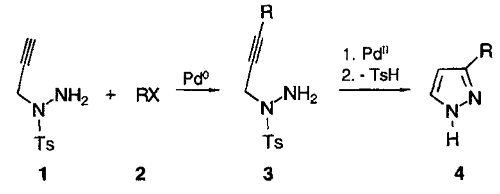
Abstract. Functionalised pyrazoles have been prepared in good overall yield through a facile one-pot procedure. The synthesis includes the palladium-catalysed coupling of the readily available N-tosyl-N-propargylhydrazine with aryl iodides or vinyl triflates, the palladium-catalysed annulation of the resulting N-tosyl-N-(1-aryl/vinyl-1-propyn-3-yl)hydrazine and exposure of the reaction mixture arising from the annulation step to KOBu^t.

The pyrazole nucleus is present in a wide variety of compounds with biological activity. Pyrazole derivatives have been shown to exhibit antihyperglycemic,[1] analgesic,[2] antiinflammatory,[2] antipyretic,[2] antibacterial,[2] hypoglycemic[3] sedative-hypnotic[4] activity and this justifies continuous efforts in developing more general and versatile synthetic methodologies to this class of compounds. Usually they are prepared following classical methods, the most important of which are based on the reaction of hydrazines with 1,3-dicarbonyls and on 1,3-dipolar cycloadditions.[5]

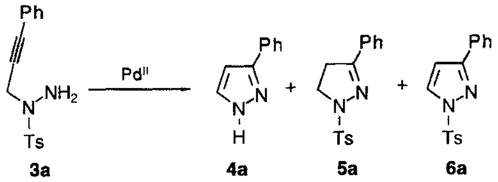
Our interest in the construction of heterocyclic rings through palladium-catalysed annulations lured us to investigate the possible development of a new strategy to functionalised pyrazoles **4** (hereafter represented, for the sake of simplicity, as one tautomer) based upon the concept of palladium-catalysed coupling/annulation.[6] Therefore, we turned our attention to the palladium-catalysed coupling of the readily available N-tosyl-N-propargylhydrazine **1**[7] with aryl halides or triflates, followed by the palladium-catalysed annulation of the resulting coupling product **3** and the elimination of *p*-toluenesulfinic acid[9] (Scheme 1).



R = aryl, vinyl; X = I, OTf

Scheme 1

Our initial attempts explored the reaction of **1** with 1.5 equiv. of phenyl iodide in the presence of 2 mol % of $Pd(OAc)_2(PPh_3)_2$, 4 mol % of CuI, 2 equiv. of Et_3N in DMF at room temperature for 24 h. Under these conditions, however, a typical preparation afforded the coupling derivative **3a** in a sparing 37% yield. Furthermore, the synthesis appeared to suffer from some irreproducibility, and work-up and purification seemed to be crucial. Nonetheless, to get an idea of the feasibility of the process, we decided to investigate the subsequent palladium-catalysed annulation step. Therefore, we subjected **3a** both to classical Utimoto's conditions[9] and to our acidic two-phase conditions,[10] and found that the reaction[11] gave rise to the formation of a mixture of the cyclic derivatives **4a**,[12] **5a** and **6a** (the latter most probably arising from a palladium-catalysed oxidation of **5a**) (Scheme 2).



Scheme 2

Attempts were made to channel the reaction towards the formation of **4a** by prolonging the reaction time or/and increasing the temperature to favour the elimination of TsH from **5a** or possibly the substitution of the nitrogen-sulfur bond in **6a** with the nitrogen-hydrogen bond. Relative ratios changed to some extent but no significant increase of the yield of **4a** was observed. Some representative results are summarised in Table 1.

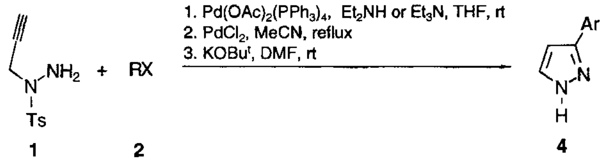
Table 1. Palladium-Catalysed Annulation of **3a**

entry	reaction conditions	reaction temperature	reaction time (h)	**4a** yield (%)[a]	**5a** yield (%)	**6a** yield (%)[a]
1	$PdCl_2$, MeCN[b]	rt	2	-	51	15
2	"	reflux	2	27	53	19
3	"	reflux	8	13	37	14
4	$PdCl_2$, n-Bu_4NCl, HCl 2N, CH_2Cl_2[c]	rt	24	30	39	12

[a] Yields refer to single runs, are given for isolated products and are calculated on **3a**. [b] Carried out on a 0.5 mmol scale in the presence of 5 mol % of $PdCl_2$ (MeCN: 2.5 mL). [c] Carried out on a 0.5 mmol scale in a two-phase system (2 mL of HCl 2N and 2 mL of CH_2Cl_2) in the presence of 5 mol % of $PdCl_2$ and 10 mol % of n-Bu_4NCl.

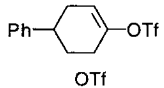
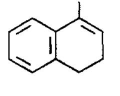
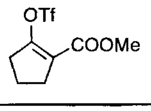
Having established that **5a** and **6a** cannot be converted into **4a** in good yield under the conditions employed for the palladium-catalysed annulation, we searched for conditions allowing this conversion to take place on the isolated products. Subjection of **5a** (5 min) and **6a** (1 h) to 3 equiv. of KOBu^t in DMF at room temperature proved to serve the purpose: **4a** was isolated in 85% and almost quantitative yield, respectively. In order to prepare the pyrazole derivative omitting the time consuming and troublesome isolation and purification of reaction intermediates, we subsequently exposed the reaction mixture resulting from the palladium-catalysed annulation to 3 equiv. of KOBu^t at room temperature, overnight. Under these conditions **4a** was isolated in 60% yield. The best result was obtained by adding KOBu^t and DMF to the mixture arising from the annulation reaction after evaporation of the solvent: **4a** was in this case isolated in 78% yield after 1 h at room temperature.

The success in the conversion of the reaction mixture resulting from the annulation of **3a** and the uncertain results obtained when its isolation was attempted persuaded us to examine a different approach for the transformation of **1** into **4**, based on a one-pot procedure avoiding both the isolation of the intermediates **5** and **6**, and that of **3**. To this end, the coupling step was carried out in THF (room temperature; 6 h)[14,15] so as to make it possible to obtain a crude reaction mixture and to subject it to annulation conditions simply by evaporating the solvent and triethylamine under mild conditions. Subsequently, MeCN and $PdCl_2$ were added to the crude mixture resulting from the coupling step and the reaction was refluxed for 6 h (after which the annulation reached completion). Then, the solvent was evaporated, DMF and $KOBu^t$ were added and, after 1 h at room temperature, the reaction was worked-up and **4a** was isolated in a satisfactory 46% overall yield. These conditions have been successfully applied to a variety of aryl halides.[16] With the vinyl triflates we tested the best results have been obtained using diethylamine in the coupling step. Our results are summarised in Table 2.



Scheme 3

Table 2. One-pot Synthesis of 3-Substituted-pyrazoles [a]

entry	aryl halide or vinyl triflate **2**	reaction time (h)[b]			**4** yield (%)[c,d]
1	PhI **a**	9	2.5	1	46
2	*p*-O_2N-C_6H_4-I **b**	5.25	1.5	2.5	63
3	*m*-O_2N-C_6H_4-I **c**	1.25	3.5	2.25	69
4	*p*-MeCO-C_6H_4-I **d**	2	2	0.75	60
5	*m*-CF_3-C_6H_4-I **e**	1.25	1.5	1.5	66
6	*p*-EtOOC-C_6H_4-I **f**	1.25	16	1	50
7	*m*-EtOOC-C_6H_4-I **g**	3.25	4.25	2	40
8	*o*-F-C_6H_4-I **h**	9	2.25	2.5	28
9	*m*-F-C_6H_4-I **i**	2.25	1.5	1	56
10	*p*-Me-C_6H_4-I **j**	2.5	4	1	38
11	*m*-$HOCH_2$-C_6H_4-I **k**	3.5	3	2	44
12	*p*-MeO-C_6H_4-I **l**	4.5	2	2	33
13	*m*-MeCONH-C_6H_4-I **m**	6	3	0.75	34
14	*p*-MeCONH-C_6H_4-I **n**	4	3.5	4.5	52
15	 **o**	1	6	2.5	45[e]
16	 **p**	2	2	0.75	30[e]
17	 **q**	0.75	3	1	23[e]

[a]With aryl halides, reactions have been carried out using a **1**:**2** = 1:1.5 molar ratio while with vinyl triflates a **1**:**2** = 1.5:1 molar ratio has been used. [b]Reaction times refer to the palladium-catalysed coupling, palladium-catalysed annulation, and basic treatment of the reaction mixture resulting from the annulation step, respectively. [c]Yields refer to single runs, are given for isolated products and, unless otherwise stated, are calculated on **1**. [d]All compounds had satisfactory elemental analysis and spectral data were consistent with postulated structures. [e]Calculated on the vinyl triflate.

In summary, this report discloses a new, simple approach to the synthesis of functionalised pyrazoles based on the use of a readily available building block. The process is extremely versatile and accommodates considerable functionality. Although yields are sometimes moderate, they represent *overall* yields for three steps in the reaction sequence.

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7 Preparation of N-tosyl-N-propargylhydrazine **1**: a solution of tosylhydrazine (1.00 g, 5.37 mmol) in anhydrous DMF (10 mL) was added dropwise to NaH (0.258 g, 6.44 mmol) freed of oil with pentane.[8] The resulting mixture was stirred at 40 °C for 0.5 h (vigorous hydrogen evolution was observed) and then allowed to cool to room temperature. Propargyl bromide (0.718 mL, 6.44 mmol) was added with stirring and the reaction mixture was stirred for additional 2 h at room temperature. Ethyl acetate was added and the resulting solution was washed with a saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane/ethyl acetate 70/30 v/v) to give **1** (0.976 g, 80% yield): mp 77-9 °C; IR 3362, 3271, 1338, 1163, 754 cm^{-1}; ^1H NMR δ 7.80 (d, 2H, J = 8.2 Hz), 7.35 (d, 2H, J = 8.2 Hz), 4.20 (d, 2H, J = 2.4 Hz), 3.83 (bs, 2H), 2.45 (s, 3H), 2.08 (t, 1H, J = 2.4 Hz); ^{13}C NMR δ 144.7, 131.7, 129.6, 129.1, 75.6, 74.7, 42.7, 21.7; MS *m/e* (relative intensity) 224 (M^+, 1), 91 (100).
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9 Utimoto, K., Miwa, H., Nozaki, H. *Tetrahedron Lett.* **1981**, *22*, 4277.
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11. Palladium-catalysed annulation of N-tosyl-N-(1-phenyl-1-propyn-3-yl)hydrazine **3a**: to a stirred solution of **3a** (0.150 g, 0.5 mmol) in MeCN (2.5 mL), was added $PdCl_2$ (0.004 g, 0.025 mmol). The reaction mixture was refluxed for 2 h under argon. Ethyl acetate was added and the resultant solution was washed with a saturated NaCl solution, dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane/ethyl acetate 75/25 v/v) to give **4a** (0.020 g, 27% yield), **5a** (0.079, 53% yield) and **6a** (0.030, 19% yield); **4a**: mp 63-66 °C; IR 3165, 1540, 753, 695 cm^{-1}; ^1H NMR δ 10.93 (bs, 1H), 7.89–7.84 (m, 2H), 7.67 (bs, 1H), 7.52–7.40 (m, 3H), 6.70 (bs, 1H); ^{13}C NMR δ 149.2, 133.3, 132.2, 128.8, 128.1, 125.9, 102,7; MS *m/e* (relative intensity) 144 (M^+, 100), 117 (17). **5a**: mp 118-120 °C; IR 1450, 1352, 1163, 843 cm^{-1}; ^1H NMR δ 7.81 (d, 2H, J

= 8.2 Hz), 7.69-7.64 (m, 2H), 7.39-7.26 (m, 5H), 3.66 (t, 2H, J = 9.6 Hz), 3.05 (t, 2H, J = 9.6 Hz), 2.38 (s, 3H); ^{13}C NMR δ 158.3, 144.3, 131.3, 130.9, 130.5, 129.5, 128.8, 128.6, 126.9, 48.7, 32.8, 21.6; MS *m/e* (relative intensity) 300 (M^+, 15), 145 (100). **6a**: mp 58-60 °C; IR 1376, 1146, 761, 671 cm^{-1}; ^{1}H NMR δ 8.12 (d, 1H, J = 2.8 Hz), 7.93 (d, 2H, J = 8.4 Hz), 7.80 (d, 2H, J = 8.4 Hz), 7.39-7.29 (m, 5H), 6.69 (d, 1H, J = 2.8 Hz), 2.40 (s, 3H); ^{13}C NMR δ 157.0, 145.8, 134.3, 132.6, 131.5, 130.0, 129.2, 128.7, 128.2, 126.5, 106.5, 21.7; MS *m/e* (relative intensity) 298 (M^+, 37), 234 (100).

12. According to literature data,[13] suggesting that the N-protons of dissolved pyrazoles undergo rapid intermolecular exchange, compounds **4** appear to exist as mixtures of interconverting tautomers. For example, the NMR spectrum of **4d** at ambient probe temperature (29 °C), in DMSO-d_6, shows the carbons C-4 and C-5 and the protons at C-4 and C-5 (width at half height are 6.4 and 9.6 Hz, respectively) as broad signals, suggesting the existence of slowly equilibrating tautomeric forms. In addition, the proton pattern depends on concentration. No coupling constants are discernible for the protons at C-4 and C-5 in the NMR spectrum, recorded at 29 °C, of a sample prepared by dissolving about 100 mg of **4d** in 0.5 mL of DMSO-d_6 (1.0 M). A more diluted sample (10 mg/0.5 mL; 0.1 M) shows the coupling constant $J_{4\text{-}5}$ (2.5 Hz) only for the proton at C-4. Replacement of hydrogen with methyl at the nitrogen atom of **4d** (methylation of **4b** affords the corresponding 1-N-methyl derivative in 64% yield) leads to a fixed structure whose protons at C-4 and C-5 appear as doublets (J = 2.2 Hz) at δ 6.15 and 7.41.
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14. Preparation of **3a**: *bis*(triphenylphosphine)palladium(II) diacetate (0.013 g, 0.0178 mmol) and copper(I) iodide (0.007 g, 0.0356 mmol) were added successively, under argon, to a stirred solution of **1** (0.200 g, 0.89 mmol) and Et_3N (0.25 mL, 1.78 mmol) in THF (3.5 mL). The resulting mixture was stirred at room temperature for 6 h under argon and worked-up as described for the preparation of **1**. Purification by chromatography (*n*-hexane/ethyl acetate 70/30 v/v) gave **3a** (0.160 g, 60% yield): mp 82-84 °C; IR 3458, 3366, 1348, 1164, 772 cm^{-1}; ^{1}H NMR δ 7.82 (d, 2H, J = 8.2 Hz), 7.20-7.28 (m, 5H), 7.05 (d, 2H, J = 8.2 Hz), 4.43 (s, 2H), 3.29 (bs, 2H), 2.31 (s, 3H); ^{13}C NMR δ 144.4, 131.9, 131.5, 129.5, 129.0, 128.5, 128.1, 121.8, 86.6, 80.4, 43.3, 21.4; MS *m/e* (relative intensity) 300 (M^+, 8), 145 (92), 115 (100).
15. Even under these conditions some irreproducibility was observed when the isolation of the coupling derivative was attempted. An apparently identical preparation gave **3a** in 30% yield.
16. A typical one-pot preparation of 3-substituted-pyrazoles **4** is as follows: to a stirred solution of **1** (0.250 g, 1.12 mmol) in THF (3 mL), were added *p*-nitrophenyl iodide (0.417 g, 1.67 mmol), Et_3N (0.31 mL, 2.23 mmol), $Pd(OAc)_2(PPh_3)_2$ (0.017 g, 0.022 mmol), and CuI (0.008 g, 0.045 mol). The reaction mixture was stirred at room temperature for 5 h under argon. Then, THF and Et_3N were evaporated under vacuum and MeCN (4 mL) and $PdCl_2$ (0.01 g, 0.0059 mmol) were added to the residue. The resulting suspension was refluxed for 1.5 h under argon. After removal of the solvent, anhydrous DMF and, at 0 °C, $KOBu^t$ (0.376 g, 3.35 mmol) were added. The reaction mixture was stirred for 2.5 h at room temperature. Ethyl acetate and a saturated NaCl solution were added, the organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; *n*-hexane/ethyl acetate 65/35 v/v) to give **4b** (0.133, 63% yield): mp 184-6 °C; IR 3296, 1606, 1516, 1335, 752, cm^{-1}; ^{1}H NMR δ 13.18 (bs, 1H), 8.26 (d, 2H, J = 8.9 Hz), 8.07 (d, 2H, J = 8.9 Hz), 7.84 (bs, 1H), 6.91 (d, 1H, J = 2.1 Hz); ^{13}C NMR δ 148.2, 146.3, 140.3, 130.6, 125.8, 124.1, 103.4; MS *m/e* (relative intensity) 189 (M^+, 40), 159 (100).