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Direct C−H Arylation and Alkenylation of 1-Substituted Tetrazoles: Phosphine As Stabilizing Factor

Marcel Špulák, Richard Lubojacký, Petr Šenel, Jiří Kuneš, and Milan Pour*

Centre for New Antivirals and Antineoplastics, Department of Inorganic and Organic Chemistry, Charles University in Prague, Faculty of Pharmacy in Hradec Králové, Heyrovského 1203, CZ-500 03 Hradec Králové, Czech Republic

pour@faf.cuni.cz

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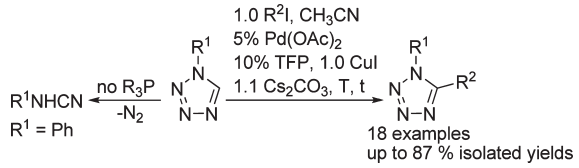

Direct arylation and alkenylation of 1-substituted tetrazoles was achieved via Pd catalysis in the presence of CuI and Cs_2CO_3. Unlike the related reactions of imidazoles and purines, phosphine ligand was necessary to prevent the intermediate tetrazolyl-Pd^{II} species from fragmentation into the corresponding cyanamide. Various 1,5-disubstituted tetrazoles were prepared with good to excellent isolated yields.

New heteroaryl compounds continuously emerge as lead structures for novel pharmaceuticals. Among them, 1,5-disubstituted tetrazoles occupy an important place because of being able to act as NAD(P)H oxidase inhibitors,[1] glucokinase activators,[2] hepatitis C virus (HCV) serine protease S3 inhibitors,[3] calcitonine gene-related peptide receptor antagonists, and antimigraine agents.[4] In addition, they also serve as synthetic intermediates[5] for the synthesis of energetic salts[6] and other useful compounds including natural products.[7] Their preparation from 5-substituted tetrazoles is accompanied by the formation of regioisomers which are often difficult to separate, while syntheses starting with acyclic precursors and using classical reagents suffer from long reaction times, high temperatures, low yields, difficult workup, and use of toxic and/or explosive reagents.[8,9] As regards metal-catalyzed reactions, Buchwald reported two examples of a successful Negishi[10] and Suzuki[11] coupling of 1-phenyl-5-chlorotetrazole, while the only systematic study[12] published thus far involved the Suzuki reaction of 1-benzyl-5-bromotetrazole with various boronic acid reagents. An unsuccessful attempt[13] to effect a Stille coupling between 1-phenyl-5-iodotetrazole and 5-ethyl-3-tributylstannyl-2,5-dihydrofuran-2-one[14] was also recently reported by us.

Thus, we became interested in exploring a more attractive possibility of a direct activation of the C5−H bond, since these reactions constitute an attractive alternative to traditional cross-couplings. Even though direct activation reactions[15] have been described for a variety of heteroarenes,[16] including the closely related triazoles,[17] there are, to the best of our knowledge, no reported examples of direct C−H arylation/alkenylation of tetrazoles. Since 1-substituted tetrazoles can be prepared in a one-pot process from primary amines, orthocarboxylic acid ester, and sodium azide,[18] subsequent C−H bond activation would enable a rapid entry into a range of 1,5-disubstituted tetrazoles from primary

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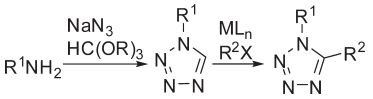
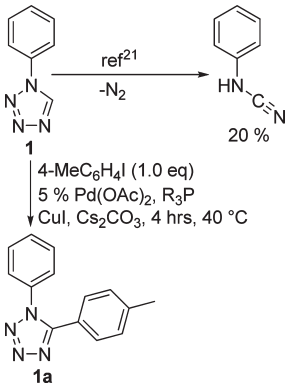
SCHEME 1. Proposed Sequence to 1,5-Disubstituted Tetrazoles



amines (Scheme 1). In fact, the preparation outlined in Scheme 1 would be more straightforward than the Suzuki or Negishi coupling of 1-substituted 5-halotetrazoles, since the necessity to prepare the halotetrazoles would add extra step(s) to the sequence, which would be less economic and would mean lower overall yields.

Similar to C2 in imidazoles and C8 in purines, tetrazole C5 is surrounded by two nitrogens. Hence, we assumed we could use the conditions[19] described for imidazoles[20] or purines[21] as the starting point. Our initial attempts were therefore based on an attractive phosphine-free protocol developed by Hocek et al.[21] for the intermolecular arylation of C8 in purines (Scheme 2). Using 1-phenyltetrazole as a model

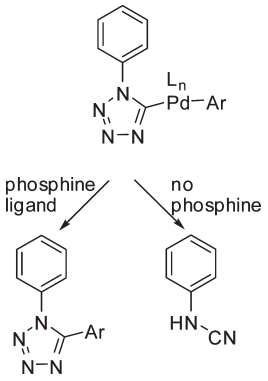
SCHEME 2. Model Reaction of Tetrazole 1 with Iodotoluene



compound, 4-iodotoluene as an electrophile, and the same conditions as Hocek et al. (entry 1, Table 1), however, gave just a trace amount of the desired 1-phenyl-5-*p*-tolyltetrazole **1a**, while phenylcyanamide arising from the fragmentation of the tetrazole ring was the only isolated product in 20% yield. Interestingly, the addition of a 10% molar amount of Ph_3P raised the isolated yield of **1a** to 59% (entry 2), with nearly the same yield (60%) having been obtained when Ph_3P was replaced with P(2-furyl)$_3$ (entry 3). Since these reactions required roughly 4 h for completion, the subsequent experiments were also allowed to run for 4 h. Further experiments showed that decreasing the amount of both CuI and the base down to 1 and 1.1 mol equiv, respectively, increased the yield to 69% (entry 4) and DMF could be replaced with the more user-friendly MeCN (entry 5). When Ph_3P was used under the same conditions (entry 6), the reaction rate slowed down.

Further variation of the ligand had negative influence (entries 7 and 8). The reaction in the absence of CuI furnished only traces again (entry 9). A possible explanation of the influence of the phosphine ligand is based on the relative stability of the putative intermediate Pd^{II} species (Scheme 3).

SCHEME 3. Reductive Elimination Vs. Decomposition of the Pd^{II} Species



As indicated by the isolation of phenylcyanamide as the only product under phosphine-free[21] conditions, collapse of the Pd^{II} intermediate into phenylcyanamide via ring fragmentation with concomitant release of nitrogen is the major reaction pathway in the absence of phosphine. On the other hand, the addition of a phosphine ligand gives rise to a more stable species[22] that has enough time to undergo reductive elimination.

With the optimized conditions in hand, the introduction of a variety of aryl and alkenyl groups into tetrazoles bearing both aromatic and aliphatic R^1 substituents was carried out with very good to excellent isolated yields (Scheme 4,

SCHEME 4. Preparation of the Title Tetrazoles

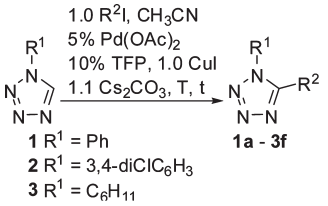


Table 2). The possibility of introduction of a highly functionalized alkene moiety (**1f**, **2f**, and **3f**) is particularly notable. On the other hand, somewhat lower yields obtained for **3b** and **3e** may indicate a lower stability of the corresponding Pd^{II} intermediates (see Scheme 3), which could be resolved by the use of a different phosphine. Studies in this direction are in progress, and will be reported in due course.

In conclusion, we have explored the conditions for the direct C–H arylation/alkenylation of 1-substituted tetrazoles, and developed a high-yielding and reliable protocol to achieve this transformation. Unlike the related reactions of purines and imidazoles, the process requires the presence

(19) These conditions were first used by Miura et al., see: Pivsa-Art, S.; Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1998**, *71*, 467.

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(22) Stable tetrazolyl-Pd^{II} or Pt^{II} complexes with Me_3P as ligand have been reported, see: (a) Kim, Y.-J.; Kim, D.-H.; Lee, J.-Y.; Lee, S.-W. *J. Organomet. Chem.* **1997**, *538*, 189. (b) Kim, Y.-J.; Kwak, Y.-S.; Lee, S.-W. *J. Organomet. Chem.* **2000**, *603*, 152. (c) Kim, Y.-J.; Lee, S.-H.; Jeon, S.-I.; Lim, M.-S.; Lee, S.-W. *Inorg. Chem. Acta* **2005**, *538*, 650. (d) Kim, Y.-J.; Kwak, Y.-S.; Joo, Y.-S.; Lee, S.-W. *J. Chem. Soc., Dalton Trans.* **2002**, 144. (e) Kim, Y.-J.; Joo, Y.-S.; Han, J.-T.; Han, W.-S.; Lee, S.-W. *J. Chem. Soc., Dalton Trans.* **2002**, 3611.

TABLE 1. Development of Reaction Conditions

entry	Cs_2CO_3 (equiv)	CuI (equiv)	$Pd(OAc)_2$ (equiv)	phosphine (0.1 equiv)	solvent	yield (%)
1	3	2.5	0.05	**none**	DMF	**traces**
2	3	2.5	0.05	Ph_3P	DMF	59
3	3	2.5	0.05	**TFP**[a]	DMF	**60**
4	**1.1**	**1**	**0.05**	TFP	**DMF**	**69**
5	**1.1**	**1**	**0.05**	TFP	**MeCN**	**69**
6	1.1	1	0.05	Ph_3P	MeCN	46[b]
7	1.1	1		PEPPSI-*i*Pr[c]	DMF	8.5
8	1.1	1	0.05	$(Cy)_2$(2-biphenyl)P	DMF	41
9	1.1	**0**	0.05	TFP	DMF	**traces**

[a]Tris(2-furyl)phoshine. [b]41% of starting material was recovered. [c][1,3-Bis(2,6-diisopropylphenyl)imidazol-2-ylidene](3-chloropyridyl)palladium(II) dichloride.

of a phosphine ligand to stabilize the intermediate Pd^{II} species. Even though TFP appeared as the ligand of choice, the cheaper Ph_3P can, in principle, also be used, but the reaction proceeds at a slower rate. The reaction is widely applicable and opens up a short and reliable route toward a range of 1,5-disubstituted tetrazoles.

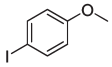
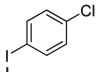
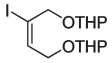
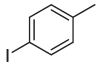
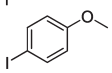
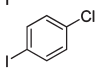
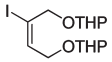
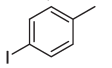
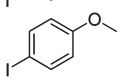
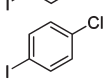
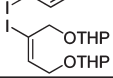
Experimental Section

General Procedure for Preparation of Compounds 1a−3f. A suspension of tetrazole **1**−**3** (1.00 mmol), aryl/alkenyl iodide (1.00 mmol), cesium carbonate (1.10 mmol), copper(I) iodide (1.00 mmol), palladium(II) acetate (0.05 mmol), and tris(2-furyl)phosphine (0.10 mmol) in dry acetonitrile (3 mL) was heated under argon atmosphere for 4−6 h (see Table 2). The resulting mixture was diluted with ethyl acetate (20 mL) and filtered quickly through Celite, then the solvents were removed under reduced pressure. The residues were purified by column chromatography (hexane: ethyl acetate 9:1) to afford the title tetrazoles **1a**−**3f**.

Synthesis of 5-(4-Chlorophenyl)-1-phenyl-1*H*-tetrazole[23] (1e). A suspension of tetrazole **1** (146.2 mg, 1.00 mmol), 1-chloro-4-iodobenzene (238.5 mg, 1.00 mmol), cesium carbonate (358.4 mg, 1.10 mmol), copper(I) iodide (190.4 mg, 1.00 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), and tris(2-furyl)-phosphine (23.2 mg, 0.10 mmol) in dry acetonitrile (3 mL) was heated at 40 °C under argon atmosphere for 4 h. The resulting mixture was diluted with ethyl acetate (20 mL) and filtered quickly through Celite, then the solvents were removed under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate 9:1) to afford tetrazole **1e** (222.9 mg, 87%). Colorless crystals, mp 157−158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.39 (5H, m), 7.34−7.25 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 137.4, 134.0, 130.4, 130.0, 129.8, 129.1, 125.1, 121.8; IR (ATR) ν_{max} 997, 1093, 1104, 1134, 1263, 1297, 1431, 1449, 1463, 1495, 1591, 1602, 2852, 2922, 2955, 3068 cm^{-1}; LRMS m/z (rel intensity) 257.1 $[M + H]^+$ (100), 249.0 (6), 229.4 (8), 216.1 (5), 195.3 (5), 161.2 (2), 119.1 (5). Anal. Calcd for $C_{13}H_9ClN_4$: C, 60.83; H, 3.53; N, 21.83. Found: C, 60.98; H, 3.62; N, 22.00.

Synthesis of 1-Cyclohexyl-5-phenyl-1*H*-tetrazole[24] (3c). A suspension of tetrazole **3** (152.2 mg, 1.00 mmol), iodobenzene (204.0 mg, 1.00 mmol), cesium carbonate (358.4 mg, 1.10 mmol), copper(I) iodide (190.4 mg, 1.00 mmol), palladium(II) acetate (11.2 mg, 0.05 mmol), and tris(2-furyl)phosphine (23.2 mg, 0.10 mmol) in dry acetonitrile (3 mL) was heated at 60 °C under argon atmosphere for 6 h. The resulting mixture was diluted with ethyl acetate (20 mL) and filtered quickly through Celite, then the solvents were removed under reduced pressure. The residue was purified by column chromatography (hexane:ethyl acetate 9:1) to afford tetrazole **3c** (150.8 mg, 66%). White crystals, mp 131−133 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62−7.54 (5H, m), 4.39−4.25 (1H, m), 2.20−1.90 (6H, m), 1.77−1.72 (1H, m), 1.41−1.29 (3H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 131.1, 129.3, 128.9, 124.5, 58.2, 33.2, 25.3, 24.8;

TABLE 2. Overview of the Prepared Derivatives

Tetrazole	Iodide	Reaction time (h)	T (°C)	Product	Yield (%)
1		4	40	**1a**	69
1		6	40	**1b**	49
1		5	40	**1c**	85
1		4	40	**1d**	76
1		4	40	**1e**	87
1		4	40	**1f**	56
2		4	40	**2a**	73
2		5	40	**2b**	57
2		4	40	**2c**	66
2		4	40	**2d**	79
2		4	40	**2e**	53
2		4	40	**2f**	59
3		5	40	**3a**	69
3		6	60	**3b**	26
3		6	60	**3c**	66
3		5	60	**3d**	54
3		5	60	**3e**	35
3		4	60	**3f**	63

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IR (ATR) ν_{max} 1007, 1078, 1100, 1162, 1244, 1278, 1335, 1378, 1394, 1454, 1468, 1532, 2861, 2946 cm^{-1}; LRMS *m*/*z* (rel intensity) 229.1 $[M + H]^+$ (100), 218.9 (2), 195.1 (3), 165.3 (2), 147.1 (19). Anal. Calcd for $C_{13}H_{16}N_4$: C, 68.39; H, 7.06; N, 24.54. Found: C, 68.58; H, 7.27; N, 24.42.

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Supporting Information Available: General experimental procedures, characterization data (^1H, ^{13}C NMR, IR, LR-MS, and elemental analysis), and copies of ^1H and ^{13}C NMR spectra for compounds **1a**−**3f**. This material is available free of charge via the Internet at http://pubs.acs.org.