# Brief Communications

## Homocoupling of bromotriazole derivatives on metal complex catalysts

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Homocoupling of 4-bromo-1,2,3-triazoles upon treatment with stoichiometric amount of bis(pinacolato)diboron on a palladium catalyst gives 4,4´-bi-1,2,3-triazoles in up to 95% yields.

**Key words:** 1,2,3-triazoles, bi-1,2,3-triazoles, Suzuki—Miyaura reaction, homocoupling.

The 1,2,3- and 1,2,4-triazole fragments are structural parts of various natural compounds and medicines such as antimicrobial, antiinflammatory, antitumor, antiepileptic, antiviral, antihistamine, and other agent. 1,2,3-Triazoles are also widely used as dyes, optical illuminators, polymer photostabilizers, corrosion inhibitors, electrographic photoreceptors.[1,2] In this connection, the studies of new transformations of 1,2,3-triazoles, including their coupling reactions, become a relevant issue. By now, several narrowly specialized examples of triazole coupling are known: first of all, this is a modified alkyne-azide cycloaddition, the yields in which vary from 23 to 87% (see Ref. 3), the Stille reaction which uses tin-substituted triazoles,[4] a coupling on a rhodium catalyst,[5] a coupling of triazoles bound by a sulfide bridge,[6] a coupling on a palladium catalyst.[7] Nonetheless, the development of truly preparative method for the coupling of triazoles remains an important problem. In the present work, we suggest a new method for the homocoupling of available halo derivatives of 1,2,3-triazoles.

### Results and Discussion

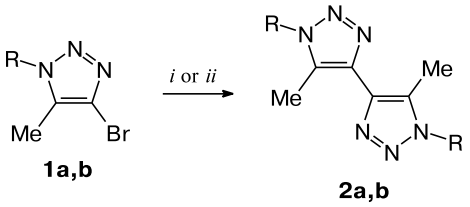
We found that 1-benzyl-4-bromo-5-methyl-1*H*-1,2,3-triazole (**1a**) treated with $Ni(PPh_3)_4$ generated *in situ* gave bitriazole derivative **2a** in 44% yield with a 90% conversion (Scheme 1).

The variation of the reaction conditions, including replacement of the triphenylphosphine ligand with cyclooctadiene and *N*,*N*´-ethane-1,2-diylidenebis(*tert*-butylamine), did not increase the product yield.

We also showed that the application of the Suzuki—Miyaura reaction conditions[8] (a solvent-free procedure[9]) instead of the nickel reagent smoothly led to the expected dimers **2a** and **2b** in 94—95% yields (see Scheme 1).

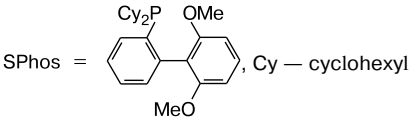
Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 6, pp. 1470—1472, June, 2015.

**Scheme 1**




R = Bn (**1a**, **2a**), Ph (**1b**, **2b**)

**Reagents and conditions:** *i*. $NiCl_2$, $PPh_3$, Zn, THF, 50 °C, 7 h; *ii*. bis(pinacolato)diboron $(pinB)_2$, $Pd(OAc)_2$, SPhos, KOH, 120 °C, 12—14 h.




In conclusion, a suggested new preparative method for the homocoupling of 1,2,3-triazole monohalo derivatives makes it possible to synthesize 4,4′-bitriazoles in quantitative yields. This synthetic method is favorably distinguished from the known analogs by the use of readily available starting compounds and a simplicity of the experimental procedure, which does not require an inert atmosphere or a solvent. We currently investigate a possibility of the extension of this method on other bromotriazoles.

## Experimental

$^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AC-300 spectrometer (400.13 MHz). Mass spectra were recorded on a Finnigan MATINCOSSO mass spectrometer (electron impact (70 eV), direct injection). LC HRMS spectra were recorded on a LTQ Orbitrek mass spectrometer (ESI, eluent MeCN—HCOOH, 99 : 1). Elemental analysis was carried out on a Carbo-Erba CHN-analyzer. Chromatography was performed using Merck Kieselgel silica gel (40/60). 2-Dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (SPhos) was commercially available from Sigma-Aldrich. Nickel chloride was dried by reflux in $SOCl_2$; THF was dried using the sodium—benzophenone system.

The starting ethyl 1-benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylate and ethyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate were synthesized according to the improved by us procedures.[10,11] .

**1-Benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid.**[11] A mixture of ethyl 1-benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylate (10 g, 0.04 mol), potassium hydroxide (3.4 g, 0.06 mol) and water (100 mL) was heated with stirring until all the compounds were dissolved. Then, the solution was cooled, hydrochloric acid was added to weakly acidify the medium. A white precipitate formed was filtered. The yield was 8.0 g (92%); m.p. 169—170 °C (*cf.* data in Ref. 11: m.p. 168—169 °C).

**1-Benzyl-4-bromo-5-methyl-1*H*-1,2,3-triazole (1a).** 1-Benzyl-5-methyl-1*H*-1,2,3-triazole-4-carboxylic acid (2 g, 9.2 mmol) was dissolved in aqueous KOH (0.6 g, 11.0 mmol of KOH in 25 mL of water). Bromine (0.6 mL, 11.0 mmol) was added dropwise to the solution with continuous stirring, which was accompanied by the gas evolution. The stirring was continued for more 3 h at room temperature. A precipitate formed was filtered. The yield of the product was 2.2 g (96%), m.p. 127—128 °C (methanol). Found (%): C, 47.37; H, 3.99; N, 16.70. $C_{10}H_{10}BrN_3$. Calculated (%): C, 47.64; H, 4.00; N, 16.67. $^1H$ NMR ($CDCl_3$), δ: 7.19—7.36 (m, 5 H, Ph); 5.50 (s, 2 H $CH_2$); 2.15 (s, 3 H, $CH_3$). $^{13}C$ NMR ($CDCl_3$), δ: 133.98, 131.84, 129.12, 128.63, 127.31, 120.86, 53.05, 8.30.

**4-Bromo-1-phenyl-5-methyl-1*H*-1,2,3-triazole (1b) was** synthesized similarly. The yield on two steps starting from ethyl 5-methyl-1-phenyl-1*H*-1,2,3-triazole-4-carboxylate was 86%, m.p. 67—69 °C. Found (%): C, 45.45; H, 3.42; N, 17.57. $C_{10}H_{10}BrN_3$. Calculated (%): C, 45.40; H, 3.39; N, 17.65. $^1H$ NMR ($CDCl_3$), δ: 7.55—7.60 (m, 3 H, Ph); 7.46—7.48 (m, 2 H, Ph); 2,35 (s, 3 H, $CH_3$). $^{13}C$ NMR ($CDCl_3$), δ: 136.28, 132.32, 129.91, 129.68, 124.73, 121.12, 9.29.

**5,5′-Dimethyl-1,1′-dibenzyl-1*H*,1′*H*-4,4′-bi-1,2,3-triazole (2a).** ***A.*** Anhydrous $NiCl_2$ (0.52 g, 4.0 mmol) and $Ph_3P$ (4.2 g, 16.0 mmol) were placed into a Schlenk flask equipped with a magnetic stirrer. Tetrahydrofuran (20 mL) was added through a septum under argon. Zinc dust (0.26 g, 4.0 mmol) was added to the resulting mixture at 50 °C. The solution acquired brown red color. After stirring for more 1 h, 1-benzyl-4-bromo-5-methyl-1*H*-1,2,3-triazole (**1a**) (1 g, 4.0 mmol) was added and the mixture was stirred for more 3 h and poured into aqueous ammonia (80 mL). The mixture was extracted with chloroform (3×50 mL), the chloroform extract was washed with water (3×50 mL), dried with anhydrous $Na_2SO_4$, the solvent was evaporated on a rotary evaporator. The residue was purified from $Ph_3P$ by flash-chromatography on silica gel (eluent light petroleum ether). The residual compound was finally eluted with light petroleum ether—ethyl acetate (2 : 1) mixture. The yield of **2a** was 0.6 g (44%); m.p. 172—173 °C. Found (%): C, 69.86; H, 5.80; N, 24.30. $C_{20}H_{20}N_6$. Calculated (%): C, 69.75; H, 5.85; N, 24.40. $^1H$ NMR ($CDCl_3$), δ: 7.19—7.34 (m, 10 H, Ph); 5.55 (s, 4 H, $CH_2$); 2.57 (s, 6 H, $CH_3$). $^{13}C$ NMR ($CDCl_3$), δ: 138.14, 134.63, 131.07, 128.99, 128.31, 127.22, 51.84, 9.21. MS, *m/z*: 344 $[M]^+$ (30), 91 $[C_7H_7]^+$ (100).

***B.*** 1-Benzyl-4-bromo-5-methyl-1*H*-1,2,3-triazole (**1a**) (251 mg, 1 mmol), bis(pinacolato)diboron (152 mg, 0.6 mmol), melted potassium hydroxide (168 mg, 3 mmol), palladium acetate (2.24 mg, 1 mol.%), and ligand SPhos (8.21 mg, 2 mol.%) were placed into a Schlenk flask equipped with a magnetic stirrer. The resulting mixture was heated in an oil bath to 120 °C and allowed to stand at this temperature for 12 h. The melt obtained was cooled to room temperature, the product was dissolved in dichloromethane and purified by column chromatography on silica gel (eluent light petroleum ether—ethyl acetate, 2 : 1). The yield of **2a** was 161 mg (94%).

**5,5′-Dimethyl-1,1′-diphenyl-1*H*,1′*H*-4,4′-bi-1,2,3-triazole (2b).** 4-Bromo-5-methyl-1-phenyl-1*H*-1,2,3-triazole (**1b**) (237 mg, 1 mmol), bis(pinacolato)diboron (152 mg, 0.6 mmol), melted potassium hydroxide (168 mg, 3 mmol), palladium acetate (2.24 mg, 1 mol.%), and ligand SPhos (8.21 mg, 2 mol.%) were placed into a Schlenk flask equipped with a magnetic stirrer. The mixture was heated in an oil bath to 120 °C for 14 h. The melt obtained was cooled to room temperature, the product was dissolved in dichloromethane and purified by column chromatography on silica gel (eluent light petroleum ether—ethyl acetate, 2 : 1). The

yield of product **2b** was 150 mg (95%), m.p. 195—196 °C. $^1$H NMR (400 MHz, $CDCl_3$), δ: 7.5—7.6 (m, 10 H, Ph); 2.74 (s, 6 H, $CH_3$). $^{13}$C NMR (400 MHz, $CDCl_3$), δ: 137.67, 136.16, 133.22, 131.69, 129.42, 125.00, 10.06. HRMS (ESI): 317.1524 $[M + H]^+$, 339.1342 $[M + Na]^+$, 355.1083 $[M + K]^+$. Calculated: for $[C_{18}H_{17}N_6]^+$ 317.1515 $[M + H]^+$; for $[C_{18}H_{16}N_6Na]^+$ 339.1334 $[M + Na]^+$; for $[C_{18}H_{16}N_6K]^+$ 355.1073 $[M + K]^+$.

This work was financially supported by the Russian Foundation for Basic Research (Project No. 14-03-00712) and the President of the Russian Federation Council for Grants (Program for State Support of Leading Scientific Schools of the Russian Federation, Grant NSh-5130.2014.3).

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*Received February 2, 2015;*
*in revised form March 30, 2015*