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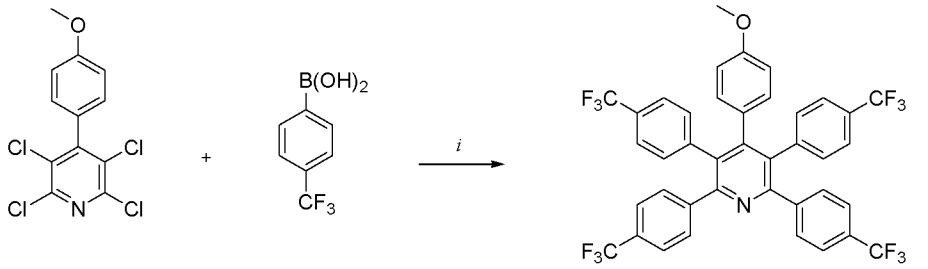
SYNTHESIS OF 2,3,5,6-TETRAKIS[4-(TRIFLUOROMETHYL)PHENYL]-4-(4-METHOXYPHENYL)PYRIDINE BY SUZUKI-MIYAURA REACTION

Pyridine ring is among one of the most essential structures widespread in various natural products, pharmaceuticals and compounds which are used in supramolecular chemistry or in transition metal catalysis [1-4]. Therefore, the synthesis of functionalized pyridines, in particular highly substituted derivatives, is of great interest.

Palladium-catalyzed cross-coupling reactions provide an elegant way for successive introduction of the desired substituents in the pyridine ring. In particular, Suzuki-Miyaura reaction is often a method of choice for the construction of biaryl motifs [5].

In this report, the synthesis of pentaarylsubstituted pyridine **3** from corresponding tetrachloropyridine **1** and boronic acid **2** is shown. At first, the starting material **1** containing 4-methoxyphenyl substituent located at position 4, was synthesized from pentachloropyridine according to a known procedure [6]. Afterwards, starting material **1** was used in the tertafold cross-coupling reaction with 4-(trifluoromethyl)phenylboronic acid. Due to the optimal conditions, reaction proceeds smoothly and provides desired product in 81 % yield. The used catalytic system consisting of $PdCl_2(CH_3CN)_2$ and sophisticated biarylphosphine ligand SPhos developed by Buchwald *et al.* proved to be very efficient [7].



1 **2** **3**

Scheme. Synthesis of 3; conditions: *i:* $PdCl_2(CH_3CN)_2$ (5 mol.%), SPhos (10 mol.%), K_3PO_4, Toluene, 100°C, 20 *h*.

In conclusion, a straightforward one stage synthesis of polyaryl substituted pyridine **3** was carried out. The desired product was conveniently prepared in high yield via tetrafold Suzuki-Miyaura reaction of the initial tetrachloropyridine (**1**). This reaction can be applied to obtain similar pyridines with a variety of other substitution patterns.

Experimental part

The reaction was carried out in oven-dried pressure tube under argon atmosphere. Unless otherwise mentioned, all chemicals are commercially available and were used without further purification. Column chromatography was performed using Merck Silicagel 60 (0.043-0.06 *mm*). NMR data were recorded on Bruker ARX 300 spectrometer (at 300 *MHz* for ^{1}H, 75 *MHz* for ^{13}C and 282 *MHz* for ^{19}F) using $CDCl_3$ as solvent. NMR ^{13}C and ^{1}H spectra were referenced to signals of deuterated solvent and residual protonated solvent, respectively. Infrared Spectrum was recorded on Nicolet 550 FT-IR spectrometer with ATR sampling technique. Mass analysis was carried out on Agilent HP-5890 device with an Agilent HP-5973 Mass Selective Detector (EI) and HP-5 capillary column using helium carrier gas. Elemental analysis (EA) was performed with a LecoMikroanalysator - TrueSpec CHNS Micro. Melting point was determined on a Micro-Hot-Stage GalenTM III Cambridge Instrument.

Synthesis of 2,3,5,6-tetrakis[4-(trifluoromethyl)phenyl]-4-(4-methoxyphenyl) pyridine. An argon-flushed glass pressure tube was charged with 2,3,5,6-tetrachloro-4-(4-methoxyphenyl)pyridine **1** (97 *mg*, 0.3 *mmol*), $PdCl_2(CH_3CN)_2$ (3.9 *mg*, 5.0 *mol.*%), SPhos (12,3 *mg*, 10.0 mol.%), boronic acid **2** (455 *mg*, 2.4 *mmol*), K_3PO_4 (509 *mg*, 2.4 *mmol*) and anhydrous toluene (6 *ml*). The tube was sealed with a teflon cap and the reaction mixture was stirred at 100 °C for 20 *hours*. Resulting mixture was cooled down to room temperature, diluted with water and extracted with dichloromethane. The combined organic layers were dried over Na_2SO_4, filtered and the solvent was evaporated. Then, the crude residue was purified by column chromatography on silica gel using a mixture of hexane and dichloromethane as eluent.

The product was isolated as a white solid (81 %); mp. = 240*242°C. NMR ^{1}H (300 *MHz*, $CDCl_3$): δ = 3.65 (s, 3H, OCH_3), 6.47 - 6.52 (m, 2H, CH), 6.56 - 6.61 (m, 2H, CH), 7.00 (d, 4H, ^{3}J = 8.1 *Hz*, CH), 7.32 (d, 4H, ^{3}J = 8.1 *Hz*, CH), 7.41 - 7.47 (m, 8H, CH). NMR ^{13}C (75 MHz, $CDCl_3$): δ = 55.0 (OCH_3), 113.1 (CH), 123.8 (q, $^{1}J_{C-F}$ = 272.3 *Hz*, CF_3), 123.9 (q, $^{1}J_{C-F}$ = 272.1 *Hz*, CF_3), 124.8 (q, $^{3}J_{C-F}$ = 3.8 *Hz*, CH), 128.3 (CH), 129.5 (q, $^{2}J_{C-F}$ = 32.9 *Hz*, C), 130.3, 131.2, 131.4 (CH), 133.5, 141.4, 143.4, 150.5, 155.7, 158.4 (C). NMR ^{19}F (282 *MHz*, $CDCl_3$): δ = -62.1 (s, 3F, CF_3), -62.2 (s, 3F, CF_3). IR (ATR, cm^{-1}): $\tilde{\nu}$ = 2936 (w), 1616 (m), 1516 (m), 1321 (s), 1163 (s), 1106 (s), 1065 (s), 1015 (s), 853 (s), 833 (s), 669 (m). MS (EI, 70 eV): m/z (%) = 760 (M^+, 100), 742 (5), 716 (10), 381 (5). HRMS (EI, 70 eV): calcd. for $C_{40}H_{22}F_{12}NO$: 760.15043; Found: 760.14943. EA: Calcd. for $C_{40}H_{23}F_{12}NO$ (761.60): C 63.08; H 3.04; N 1.84; Found: C 63.34; H 3.36; N 1.85.

2,3,5,6-ՏԵՏՐԱՔԻՍ[4-(ՏՐԻՖՏՈՐՄԵԹԻԼ) ՖԵՆԻԼ]-4-(4-ՄԵԹՕՔՍԻՖԵՆԻԼ)ՊԻՐԻԴԻՆԻ ՍԻՆԹԵԶԸ ՍՈՒԶՈՒԿԻ-ՄԻՅԱՈՒՐԱ ՌԵԱԿՑԻԱՅՈՎ

Ա. Մ. ՊԵՏՐՈՍՅԱՆ

Իրականացվել է 2,3,5,6-տետրաքիս[4-(տրիֆտորմեթիլ)ֆենիլ]-4-(4-մեթօքսիֆենիլ)պիրիդինի սինթեզը պալադիում-կատալիզվող Սուզուկի-Միյաուրա քրոսհամակցման ռեակցիայով: Օգտագործվել է ժամանակակից ֆոսֆինային լիգանդ պարունակող ակտիվ կատալիտիկ համակարգ, որը ցուցաբերել է բարձր արդյունավետություն՝ ապահովելով վերջնանյութի բարձր ելքը: Ռեակցիան կարելի է օգտագործել նաև այլ տեղակալված պիրիդինների միափուլ սինթեզի համար:

СИНТЕЗ 2,3,5,6-ТЕТРАКИС[4-(ТРИФТОРМЕТИЛ)ФЕНИЛ]-4-(4-МЕТОКСИФЕНИЛ)ПИРИДИНА РЕАКЦИЕЙ СУЗУКИ-МИЯУРЫ

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Осуществлен синтез 2,3,5,6-тетракис[4-(трифторметил)фенил]-4-(4-метоксифенил)пиридина реакцией кросс-сочетания Сузуки-Мияуры. Каталитическая система, состоящая из лиганда SPhos и прекурсора $PdCl_2(CH_3CN)_2$, проявила высокую активность, тем самым обеспечивая высокий выход конечного продукта. Описанной реакцией возможен синтез аналогичных полиарилзамещенных пиридинов.

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