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PALLADIUM CATALYZED SELECTIVE MONOARYLATION OF 2-AMINOPYRIMIDINES AND 2-AMINOPYRAZINE WITH 1,2-DIBROMOBENZENE WITHOUT CYCLIZATION

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ABSTRACT:
A simple one-flask highly selective method for the Pd-catalyzed preparation of sterically hindered 2-(2-bromophenyl)pyrimidines.was elaborated. 2-(2-Bromophenyl)pyrimidines were isolated in 22-64% yields. Similarly was prepared 2-(2-bromophenyl)aminopyrazine.

Keywords: palladium catalysis, 2-aminopyrimidines, 1,2-dibromobenzene, 2-(2-bromophenyl)pyrimidines

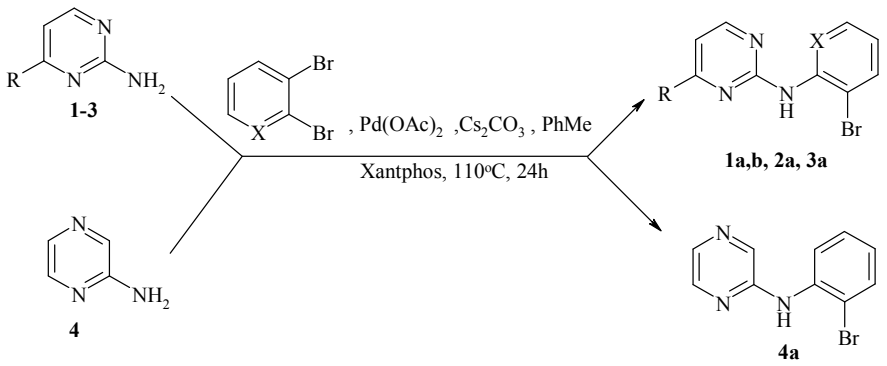
INTRODUCTION

Substituted 2-aminopyrimidines are of great interest as intermediates in the synthesis of organic compounds [I]. 2-Arylaminopyrimidines were prepared from 2-aminopyrimidines and bromobenzene or iodobenzene in the presence of CuI [II] or *t*-BuOK [III ,IV]. Second group of methods of synthesis of substituted 2-arylaminopyrimidines is based on the interaction of 2-chloropyrimidines with anilines in the presence of palladium [I, V] or cobalt [VI] catalysts or treatment of 2-bromopyrimidine with aniline under microwave irradiation. There are only one method for the synthesis of 2-(2-bromophenyl)aminopyrimidine based on the treatment of 2-chloropyrimidine with 2-bromoaniline in high temperatures [VII]. Beside this, cyclization of 2-(2-bromophenyl)aminopyrimidines or pyridines may form coresponding pyrimidobenzimidazoles or pyridobenzimidazoles. For example, 2-(2-bromophenyl)aminopyrimidines in the presence of copper catalyst afforded pyrimidobenzimidazoles in almost quantitative yield [VIII]. We have elaborated novel and selective Pd-catalyzed method for the preparation sterically hindered 2-(2-bromophenyl)pyrimidines. Beside this, formation of pyrimidobenzimidazoles does not occur in these cases.

RESULTS AND DISCUSSION

We have elaborated effective catalytic system for the selective preparation of 2-(2-bromophenyl)pyrimidnes **1-3a** from corresponding 2-aminopyrimidines **1-3**. Thus, amines **1-3** in the system 1,2-dibromobenzene / $Pd(OAc)_2$ / Xantphos / Cs_2CO_3 / PhMe afforded 2-(2-bromophenyl)pyrimidines **1-3a-c** in 22-64% yield (Scheme 1). Similarly was prepared 2-(3-bromopyridin-2-yl)aminopyrimidine (**1b**) (yield 52%) from amine **1** and 2,3-dibromopyridine. Reaction of 2-aminopyrazine **4** with 1,2-dibromobenzene leads to 2-(2-bromophenyl)aminopyrazine (**4a**) in 30% yield..

Scheme 1



R = H (**1**), R = Me (**2**), R = CF_3 (**3**); X = CH (**1a-c**), X = N (**1b**)

EXPERIMENTAL SECTION

^1H and ^{13}C NMR spectra were registered on Varian Mercury BB 400 MHz in $CDCl_3$. Mass-spectra were recorded on Alliance Waters 2695 instrument with Full scan POS NEG 16 detector. 2-Aminopyrimidines**,** 1,2-dibromobenzene, palladium acetate, Xantphos and cesium carbonate (all Acros) were used without purification. Melting points were detected on Boetius aparatos equipped with visual detector PHMH 05. HR-MS spectra were performed on Micromass *Q-TOF* Micro quadrupole-time of fight high resolution mass spectrometer. Leucine enkephalin was used as internal lock mass for accurate mass calculation.

General procedure for the synthesis of 2-(2-bromophenyl)aminopyrimidines 1-3a and 2-(3-Bromopyridin-2-yl)aminopyrimidine (1b). Solid Cs_2CO_3 (0.98 g, 3 mmol) was added to the solution of 2-aminopyrimidine **1-3** (1 mmol) and 1,2-dibromobenzene or 2,3-dibromopyridine (1 mmol), $Pd(OAc)_2$ (11 mg, 0.05 mmol), Xantphos (29 mg, 0.1 mmol) in dry toluene (2 ml) in a glass reactor (50 ml) under argon. The reaction mixture was stirred at 110°C (TLC-control) for 24 h under argon. The solvent was removed under reduced pressure and crude residue was chromatographed on silica using CH_2Cl_2 : ethyl acetate EtOH (10:3:0.4) as eluent.

2-(2-Bromophenyl)pyrimidine (1a) [VII]. Yield 62 %. M.p. 44-46°C. GH-MS: 250.0 (M^+, 11), 170.1 (100), 85.1 (12). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.70 (1H, t, *J* = 4.8 Hz, H-5 in pyrimidine); 6.91 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.33 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.56 (1H, d, *J* = 7.2 Hz, C_6H_4); 7.60 (1H, bs, NH); 8.46 (2H, , *J* = 4.8 Hz, H-4 and H-6 in pyrimidine); 8.51 (1H, d, *J* = 7.6 Hz, C_6H_4). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 113.31; 113.35; 120.65; 123.36; 128.02; 132.41; 137.15; 157.99; 159.76. Found, *m/z* (EI): 249.9968 $[M]^+$. $C_{10}H_8BrN_3$. Calculated, *m/z*: 249.9980.

4-Methyl-2-(2-bromophenyl)pyrimidine (2a). Yield 64 %. M.p. 55-57°C. GC-MS, 264.0 (M^+, 8), 184.1 (100), 92 (10). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.44 (3H, s, Me); 6.65 (1H, d, *J* = 5.2 Hz, H-5 in pyrimidine); 6.88 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.32 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.55 (1H, d, *J* = 7.2 Hz, C_6H_4); 7.56 (1H, bs, NH); 8.46 (1H, *J* = 5.2 Hz, H-6 in pyrimidine); 8.56 (1H, d, *J* = 7.6 Hz, C_6H_4). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 24.15; 112.96; 113.07; 120.44; 123,00; 127.98; 132.34; 137.40; 157.40; 159.55; 168.25. Found, *m/z* (EI): 264.0151 $[M]^+$. $C_{11}H_{11}BrN_3$. Calculated, *m/z* 264.0136.

4-Trifluoromethyl-2-(2-bromophenyl)pyrimidine (3a). Yield 22 %. M.p. 94-96°C. GC-MS, 318.0 (M^+, 10), 238.1 (100), 169.1 (9), 119.0 (10). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.96 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.08 (1H, d, *J* = 5.2 Hz, H-5 in pyrimidine); 7.36 (1H, t, *J* = 7.2 Hz, C_6H_4); 7.59 (1H, d, *J* = 7.2 Hz, C_6H_4); 7.82 (1H, bs, NH); 8.46 (1H, d, *J* = 7.6 Hz, C_6H_4); 8.67 (1H, d, *J* = 5.2 Hz, H-6 in pyrimidine). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 108.35; 113.62; 118.96; 120.90; 121.70; 124.18; 128.19; 132.50; 136.34; 156.27; 160.52. Found, *m/z* (EI): 317.9870 $[M]^+$. $C_{11}H_7BrF_3N_3$. Calculated, *m/z* 317.9854.

2-(3-Bromopyridin-2-yl)aminopyrimidine (1b). Yield 52 %. M.p. 154-156°C. GC-MS, 251.0 (M^+, 5), 171.1 (100), 144.1 (7), 79.1 (8). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.85 (1H, t, *J* = 4.8 Hz, H-5 in pyrimidine); 6.88 (1H, m, 5-H in pyridine); 7.85 (1H, d, *J* = 8.0 Hz, H-4 in pyridine); 7.92 (1H, bs, NH); 8.43 (1H, d, *J* = 4.0 Hz, H-6 in pyridine); 8.57 (2H, d, *J* = 4.8 Hz, H-4 and H-6 in pyrimidine). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 109.71; 114.60; 119.08; 141.01; 147.21; 149.55; 158.32; 158.92. Found, *m/z* (EI): 250.9917 $[M]^+$. $C_9H_7BrN_4$. Calculated, *m/z* 250.9932.

2-(2-Bromophenyl)aminopyrazine (4a). Yield 30 %. M.p. 77-79°C. GC-MS, 250.0 (M^+, 10), 170.1 (100), 143.0 (9), 85.0 (11), 68.1 (10). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 6.94 (1H, t, *J* = 7.6 Hz, C_6H_4); 6.95 (1H, bs, NH); 7.32 (1H, t, *J* = 7.6 Hz, C_6H_4); 7.58 (1H, d, *J* = 7.6 Hz, C_6H_4), 8.04 and 8.15 (2H, both d, *J* = 2.8 Hz, H-5 and H-6 in pyrazine); 8.27 (1H, d, *J* = 1.2 Hz, H-3 in pyrazine); 8.50 (d, *J* = 7.6 Hz, C_6H_4). ^{13}C NMR (100.58 MHz, $CDCl_3$) δ (ppm): 114.23; 120.30; 123.92; 128.24; 132.80; 134.08; 135.76; 137.18; 141.66. Found, *m/z* (EI): 250.0006 $[M]^+$. $C_{10}H_8BrN_3$. Calculated, *m/z* 249.9980.

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