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Direct amination of pyrimidin-2-yl tosylates with aqueous ammonia under metal-free and mild conditions

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ABSTRACT

A metal-free synthesis of pyrimidine functionalized primary amines *via* direct amination of pyrimidin-2-yl tosylate with aqueous ammonia has been developed under mild conditions. The desired products pyrimidin-2-amines can be generated in excellent yields in PEG-400, without any catalysts or other additives.

1. Introduction

Primary (hetero)aryl amines are widely used in the synthesis of natural products, pharmaceuticals, agrochemicals as well as polymers and materials [1]. The common methods for preparation of primary amines include coupling of aryl halides with ammonia [2], reductive amination of carbonyl compounds [3], and hydroamination of alkenes [4–6]. Recently, ammonia, as one of the most attractive sources of nitrogen, has attracted a lot of attentions due to its great abundance and extremely low cost [7,8]. Very recently, a few methodological advancements for coupling aryl halides with aqueous ammonia to deliver aryl primary amines under mild conditions have been developed [9,10].

Aryl sulfonates that are easily prepared, usually crystalline, and lower toxicity, are with potential values to investigate as better materials to synthesize primary amines. Despite great progress toward the preparation of primary amines has been made, selective synthesis of primary amines from ammonia still encounters challenges, *i.e.* requirement of transition-metal, overreactions of primary amines with ammonia. Hence, further efforts were needed to developing a metal-free, mild method for the selective synthesis of primary amines directly from aqueous ammonia.

3,4-Dihydropyrimidinones and their derivatives have consequently been extensively used as a drug-like scaffold [11] and utilization as important precursors in the synthesis of pyrimidine bases [12]. In continuation of our ongoing interest in the synthesis of 3,4-dihydropyrimidinone derivatives [13], we are recently interesting in the synthesis of 2-aminopyrimidines.

2-Aminopyrimidines show interesting biological activities such as inhibitors of rhoassociated protein kinase [14,15], glycogen synthase kinase 3 (GSK3) [16], and of *N*-type calcium channels [17]. Notably, the 2-amino-4-arylpyrimidine heterocycle is also found in important drugs such as the hypocholesterolemic agent rosuvastatin [18,19] and the potent anticancer drug Gleevec [20].

Usually, 2-aminopyrimidine subunits are constructed by condensation reactions of enones with corresponding guanidine or nitrogen-containing building blocks [21]. In 2007, Kappe *et al.* [22] have described a three-step procedure to convert Biginelli DHPMs to 2-methylsulfonyl-pyrimidines, which subsequently converted to 2-aminopyrimidine by the substitution of the reactive sulfonyl group with ammonium acetate as substitute for NH_3 (Scheme 1, Method A).

Herein we developed a metal-free approach for the synthesis of 2-aminopyrimidines directly from pyrimidin-2-yl tosylates with aqueous ammonia under mild conditions in PEG medium (Scheme 1, Method B).

2. Experimental

Commercially available reagents were used without further purification unless otherwise stated. Melting points were measured on a XT-4 apparatus and are uncorrected. NMR spectra were

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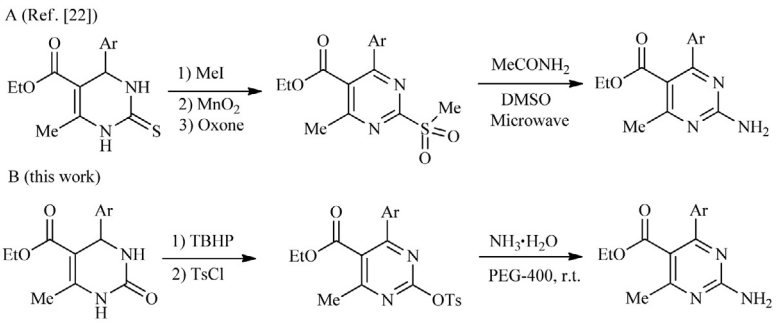

Scheme 1. Synthesis of the 2-aminopyrimidines starting from 3,4-dihydropyrimidinones.

recorded at 400 MHz (^{1}H) and 100 MHz (^{13}C), respectively, on a Varian Mercury plus-400 instrument using $CDCl_3$ as solvent and TMS as internal standard. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEX II 47e mass spectrometer. Column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections were on silica gel GF254 plates.

2.1. General procedure for the synthesis of 2-amino pyrimidines (**2a**–**2n**)

The pyrimidin-2-yl tosylate (**1**, 1.0 mmol), PEG-400 (2 mL) and ammonia water (10 mmol) were added into a test tube. The tube was then sealed with a balloon, and the mixture was stirred at r.t. for 24 h. Then the mixture was poured into water to precipitate the product. Crude product was obtained by means of vacuum filtration, and was further purified by column chromatography on silica gel with petroleum ether/ethyl acetate (3:1) and (1:1) to give the corresponding products **2a**–**i** and **2j**–**n**, respectively.

Ethyl 2-amino-4-methyl-6-phenylpyrimidine-5-carboxylate (**2a**): White solid, mp 132–133 °C [22]. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H), 7.41 (d, 3H, J = 5.2 Hz), 5.82 (s, 2H), 4.05 (q, 2H, J = 7.2 Hz), 2.48 (s, 3H), 0.94 (t, 3H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.31, 167.48, 166.47, 161.98, 138.60, 129.35, 128.15, 127.63, 115.95, 61.00, 22.58, 13.40.

Ethyl 2-amino-4-(4-fluorophenyl)-6-methylpyrimidine-5-carboxylate (**2b**): White solid, mp 167–168 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.53–7.49 (m, 2H), 7.08 (t, 2H, J = 8.6 Hz), 5.82 (d, 2H, J = 10.0 Hz), 4.07 (q, 2H, J = 7.2 Hz), 2.48–2.40 (m, 3H), 1.00 (t, 3H, J = 7.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.30, 167.60, 164.98 (d, J = 38.0 Hz), 162.31, 161.92, 134.70, 129.84 (d, J = 8.0 Hz), 116.14, 115.27 (d, J = 22.0 Hz), 61.16, 22.65, 13.58; HRMS: calcd. for $C_{14}H_{15}FN_3O_2$ $[M+H]^+$: 276.1143; found 276.1147.

Ethyl 2-amino-4-(4-chlorophenyl)-6-methylpyrimidine-5-carboxylate (**2c**): White solid, mp 164–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (d, 2H, J = 8.4 Hz), 7.38 (d, 2H, J = 8.4 Hz), 5.74 (s, 2H), 4.08 (q, 2H, J = 7.2 Hz), 2.46 (s, 3H), 1.01 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.11, 167.71, 165.07, 161.83, 137.00, 135.66, 129.16, 128.41, 116.09, 61.17, 22.67, 13.53; HRMS: calcd. for $C_{14}H_{15}ClN_3O_2$ $[M+H]^+$: 293.0847; found 293.0851.

Ethyl 2-amino-4-(4-bromophenyl)-6-methylpyrimidine-5-carboxylate (**2d**): White solid, mp 138–139 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (d, 2H, J = 8.4 Hz), 7.36 (d, 2H, J = 8.4 Hz), 5.88 (s, 2H), 4.08–4.03 (m, 2H), 2.43 (s, 3H), 0.98 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.09, 167.78, 165.19, 161.92, 137.49, 131.39, 129.42, 123.95, 116.11, 61.22, 22.70, 13.56; HRMS: calcd. for $C_{14}H_{15}BrN_3O_2$ $[M+H]^+$: 336.0342; found 336.0345.

Ethyl 2-amino-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate (**2e**): White solid, mp 151–153 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (d, 2H, J = 7.6 Hz), 7.20 (d, 2H, J = 7.6 Hz), 5.87 (s, 2H), 4.08 (q, 2H, J = 6.8 Hz), 2.45 (s, 3H), 2.37 (s, 3H), 0.99 (t, 3H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.62, 167.23, 166.30, 161.96, 139.60, 135.66, 128.91, 127.70, 116.12, 61.09, 22.62, 21.27, 13.55; HRMS: calcd. for $C_{15}H_{18}N_3O_2$ $[M+H]^+$: 272.1394; found 272.1400.

Ethyl 2-amino-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate (**2f**): White solid, mp 128–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, 2H, J = 8.0 Hz), 6.91 (d, 2H, J = 8.0 Hz), 5.95 (d, 2H, J = 29.2 Hz), 4.10 (q, 2H, J = 7.2 Hz), 3.81 (s, 3H), 2.42 (s, 3H), 1.03 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.79, 167.07, 165.56, 161.98, 160.82, 130.88, 129.41, 115.85, 113.65, 61.07, 55.24, 22.53, 13.66; HRMS: calcd. for $C_{15}H_{18}N_3O_3$ $[M+H]^+$: 288.1343; found 288.1348.

Ethyl 2-amino-4-methyl-6-(4-nitrophenyl)pyrimidine-5-carboxylate (**2g**): White solid, mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.42 (s, 1H), 8.27 (d, 1H, J = 8.0 Hz), 7.84 (d, 1H, J = 7.6 Hz), 7.58 (t, 1H, J = 8.0 Hz), 5.75 (s, 2H), 4.11 (q, 2H, J = 7.2 Hz), 2.49 (s, 3H), 1.03 (t, 3H, J = 7.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.45, 167.65, 163.86, 161.94, 140.25, 129.23, 124.11, 123.16, 116.07, 61.43, 22.98, 13.64; HRMS: calcd. for $C_{14}H_{15}N_4O_4$ $[M+H]^+$: 303.1088; found 303.1093.

Ethyl 2-amino-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate (**2h**): White solid, mp 131–132 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.28 (d, 1H, J = 8.0 Hz), 7.85 (d, 1H, J = 7.6 Hz), 7.59 (t, 1H, J = 8.0 Hz), 5.73 (s, 2H), 4.12 (q, 2H, J = 6.8 Hz), 2.50 (s, 3H), 1.04 (t, 3H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.45, 167.64, 163.85, 161.92, 148.06, 140.25, 133.86, 129.23, 124.11, 123.16, 116.05, 61.42, 22.98, 13.64; HRMS: calcd. for $C_{14}H_{15}N_4O_4$ $[M+H]^+$: 303.1088; found 303.1095.

Methyl 2-amino-4-(4-fluorophenyl)-6-isopropylpyrimidine-5-carboxylate (**2i**): White solid, mp 146–148 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55 (s, 2H), 7.11 (t, 2H, J = 6.6 Hz), 5.56 (d, 2H, J = 12.4 Hz), 3.62 (s, 3H), 3.13 (s, 1H), 1.25 (t, 6H, J = 3.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.27, 169.32, 164.78, 164.46, 162.42, 134.65, 129.78 (d, J = 8.0 Hz), 115.51, 115.29, 52.14, 32.82, 21.50; HRMS: calcd. for $C_{15}H_{17}FN_3O_2$ $[M+H]^+$: 290.1299; found 290.1302.

6-Methyl-N^2-phenylpyrimidine-2,4-diamine (**2j**): White solid, mp 122–124 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (s, 1H), 7.52 (d, 2H, J = 7.6 Hz), 7.20 (t, 2H, J = 7.2 Hz), 6.90 (t, 1H, J = 7.4 Hz), 5.70 (s, 1H), 4.77 (s, 2H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.97, 163.81, 159.45, 139.89, 128.64, 121.97, 119.32, 95.48, 23.25; HRMS: calcd. for $C_{11}H_{13}N_4$ $[M+H]^+$: 201.1135; found 201.1139.

6-Methyl-N^2-*o*-tolylpyrimidine-2,4-diamine (**2k**): White solid, mp 188–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.95 (d, 1H, J = 8.0 Hz), 7.11 (q, 2H, J = 8.0 Hz), 6.90 (t, 1H, J = 7.2 Hz), 6.60 (s, 1H), 5.71 (s, 1H), 4.60 (s, 2H), 2.21 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.73, 163.89, 160.33, 137.96, 130.28, 128.36, 126.34, 122.95, 121.83, 95.47, 23.76, 18.10; HRMS: calcd. for $C_{12}H_{15}N_4$ $[M+H]^+$: 215.1291; found 215.1295.

6-Methyl-N^2-*m*-tolylpyrimidine-2,4-diamine (**2l**): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.26 (m, 3H), 7.09 (t, 1H, J = 7.6 Hz), 6.72 (d, 1H, J = 7.2 Hz), 5.70 (s, 1H), 4.75 (s, 2H), 2.24 (s,