Simple and Efficient Three Component One-pot Synthesis of Pyrazolo[1,5,a]pyrimidines

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ABSTRACT

A series of novel 5-(2-bromophenyl)-N-cyclohexyl-2-(methylthio)-6-nitro-7-phenyl-4,7-dihydro-pyrazolo[1,5-a]pyrimidine-3-carboxamides were synthesized by a one-pot reaction of 5-amino-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide, 1-(2-bromophenyl)-2-nitroethanone and aryl aldehydes in the presence of boric acid in water at refluxing temperature. Structures of compounds were demonstrated by Fourier transform infrared, $^1$H NMR, $^{13}$C NMR and elemental analysis. The advantages of this method are mild reaction condition, good yields, and operational simplicity.

Keyword: Pyrazolopyrimidine; 5-amino-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide; 1-(2-bromophenyl)-2-nitroethanone; mild reaction condition

1. INTRODUCTION

Pyrazolo[1,5-a]pyrimidines are important pharmaceutical targets.[1] They and related fused heterocycles are of interest as potential bioactive molecules. Pyrazole and pyrimidine derivatives have attracted the attention of organic chemists because of their biological and chemotherapeutic importance. They are known to exhibit a wide range of biological activities and act as cSRC kinase inhibitors involved with ischemic brain pathology,[2] cyclin dependent kinase 1 (CDK1) inhibitors,[3] HIV reverse transcriptase inhibitors,[4] CCR1 antagonists,[5] protein kinase inhibitors,[6] antibacterial,[7] and herbicides and fungicides.[8] In last decade various synthetic methods have been reported for the synthesis of pyrazole[1,5-a]pyrimidine which involves 5-aminopyrazole and 1,3-bis-electrophilic compounds, such as $\beta$-dicarbonyl, alkoxyethylene-$\beta$-dicarbonyl, and $\beta$-enaminone compounds[9,10] and several starting from fused aminopyrazole,[11] but few from non-fused aminopyrazoles.[12]

As part of our interest in novel biologically active nitrogen-containing heterocyclic scaffolds and continuing our studies on the application of cyclocondensation procedures, we are here describing the reaction between 5-amino-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide Int-3, 1-(2-bromophenyl)-2-nitroethanone Int-b and various substituted aldehyde 3a-z in order to obtain the fused pyrazolo[1,5-a]pirimidines (Figure-3) AM-3a-z.
2. EXPERIMENTAL

Thin-layer chromatography was accomplished on 0.2 mm precoated plates of silica gel G60 F254 (Merck). Visualization was made with UV light (254 and 365 nm) or with an iodine vapor. IR spectra were recorded on a FTIR-8400 spectrophotometer using DRS prob. $^1$H (400 MHz), $^{13}$C (100 MHz) NMR spectra were recorded on a Bruker AVANCE II spectrometer in CDCl$_3$ and DMSO. Chemical shifts are expressed in δ ppm downfield from TMS as an internal standard. Mass spectra were determined using direct inlet probe on a GCMS-QP 2010 mass spectrometer (Shimadzu). Solvents were evaporated with a BUCHI rotary evaporator. Melting points were measured in open capillaries and are uncorrected.

**Synthesis of 1-(2-bromophenyl)-2-nitroethanol (Int-a).**

A mixture of 2-bromobenzaldehyde (0.1 mol), nitromethane (0.1 mol) and sodium acetate (0.2 mol) was stirred at RT for 24 h. The reaction was monitored by TLC. After completion of reaction, the solvent was removed under reduced pressure. The residue was poured in water and extracted with ethylacetate. The organic layer was dried and evaporated to afford Int-a in form of viscous oil. This oil was forwarded to next step without further purification.

**Synthesis of 1-(2-bromophenyl)-2-nitroethanone (Int-b).**

To the suspension of K$_2$Cr$_2$O$_7$ (24.8 mmol) in 15ml water, Int-a was added drop wise at 0 °C. This mixture was allowed to stir for 30 min and then solution of sulphuric acid (10 ml con H$_2$SO$_4$ and 6 ml water) was drop wise added at same temperature. Here the exothermicity was controlled by keeping addition rate very slow. After completion of addition reaction mixture was stirred for 15 min at the same temp. Color of the reaction mixture turns dark green then it was poured over crushed ice. Separated solid was immediately filtered before temperature rise and was dissolved in saturated NaHCO$_3$ solution. Filtration was again carried out to separate non-dissolved matter. Filtrate was acidified with con HCl. Precipitated solid was filtered and wash with distilled water. Crystallization was carried out from methanol to afford pure Int-b.

**Synthesis of 2-cyano-N-cyclohexylacetamide (Int-1).**

In a 250 mL round bottom flask equipped with magnetic stirrer and thermometer was placed ethyl 2-cyanoacetate (0.25 mol), cyclohexylamine (0.25 mol) and toluene (100 mL). The reaction mixture was heated up to 110-115 °C for 8 h. The progress of reaction was monitored by thin layer chromatography. The reaction mixture was cooled to room temperature and the solid product was filtered, washed with toluene to afford 90% yield.

**Synthesis of 2-cyano-N-cyclohexyl-3,3-bis(methylthio)acrylamide (Int-2).**

A 100 mL conical flask equipped with magnetic stirrer and septum was charged with a solution of 2-cyano-N-cyclohexylacetamide (1), (10 mmol) in DMF (10 mL). Dry K$_2$CO$_3$ (10 mmol) was added and the mixture was stirred at RT for 2 h. CS$_2$ (30 mmol) was added and the mixture was stirred for an additional 2 h at room temperature. Then, methyl iodide (20 mmol) was added at 0-5 °C and the mixture was stirred for 4 h at room temperature. The progress of the reaction was monitored by thin layer chromatography. After completion of the
reaction, it was poured into 50ml cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

Synthesis of 5-amino-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide (Int-3).

To the solution of 2-cyano-N-cyclohexyl-3,3-bis(methylthio)acrylamide (2) (0.1 mol) in isopropyl alcohol (100 mL), hydrazine hydrate (0.1 mol) was added. The reaction mixture was heated to reflux for 2 h. After completion of the reaction, it was poured into 50 mL cold water. The precipitated crude product was purified by filtration followed by crystallization from EtOH.

General synthesis of pyrazolopyrimidine (AM-3a-z).

In 50 ml RBF Int-b (2.5 mmol), Int-3 (2.5 mmol) and substituted aldehyde were suspended in 20 ml water under stirring on magnetic stirrer. H$_3$BO$_3$ (2.5 mmol) was added in to the reaction mixture and reaction mixture was refluxed for 10 to 12 h. The reaction was monitored by TLC. After the completion of reaction, water was decanted and solid residue was triturated with methanol to afford pure compound.

Figure 1. Reaction scheme for Int-b.

Figure 2. Reaction scheme for Int-3.
Figure 3. Reaction scheme for AM-3a-z.

1-(2-bromophenyl)-2-nitroethanone (Int-b):
IR (KBr): pale yellow solid; Melting range: 48-50 °C; Rf 0.24 (2:8 hexane-EtOAc); 1H NMR: δ ppm 5.9(s, 2H, -CH2-), 7.42-7.57(m, 3H, Ar-H), 7.77-7.79(m, 1H, Ar-H); MS (m/z): 199 (M+).

5-(2-bromophenyl)-N-cyclohexyl-2-(methylthio)-6-nitro-7-phenyl-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3a):
Yellow solid; Melting range: 196-198 °C; Rf 0.40 (4:6 hexane-EtOAc); IR (KBr): 3335, 2929, 2850, 1632, 1576, 1535, 1492, 1477, 1434, 1312, 1280, 1249, 1176, 1122, 1087, 1060, 975, 836, 774, 752 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.18-1.85(m, 10H, cyclohexane), 2.39(s, 3H, -SCH3), 3.7(m, 1H, cyclohexane), 6.68(s, 1H, -CH), 6.94(m, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 17.37, 24.49, 25.51, 33.88, 47.95, 60.69, 99.57, 123.72, 127.36, 127.84, 128.57, 128.90, 128.98, 130.16, 131.42, 132.30, 138.65, 139.44, 144.43, 162.32, 124.10, 132.72, 141.47; MS (m/z): 568 (M+); Anal. Calcd for C26H26BrN5O3S: C, 54.93; H, 4.61; N, 12.32; Found: C, 56.52; H, 5.21; N, 11.34.

5-(2-bromophenyl)-7-(4-chlorophenyl)-N-cyclohexyl-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3b):
Yellow solid; Melting range: 208-210 °C; Rf 0.40 (4:6 hexane-EtOAc); IR (KBr): 3341, 2930, 2850, 1632, 1576, 1535, 1492, 1477, 1434, 1312, 1280, 1249, 1176, 1122, 1087, 1060, 975, 836, 774, 752 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.18-1.85(m, 10H, cyclohexane) 2.41(s, 3H, -SCH3), 3.7(m, 1H, cyclohexane), 6.68(s, 1H, -CH), 6.92-6.94(m, 1H, -NH), 7.24-7.44(m, 8H, Ar-H), 8.93(s, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 17.26, 25.49, 32.86, 48.00, 60.03, 99.70, 123.67, 127.70, 128.65, 128.90, 129.22, 130.21, 131.53, 132.09, 132.62, 134.91, 136.86, 137.17, 139.65, 141.83, 144.83, 162.23; MS (m/z): 603 (M⁺); Anal. Calcd for C26H25BrClN5O3S: C, 51.79; H, 4.18; N, 11.62; Found: C, 53.47; H, 3.32; N, 14.48.

5-(2-bromophenyl)-N-cyclohexyl-7-(2,4-dichlorophenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3h):
Yellow solid; Melting range: 218-220 °C; Rf 0.38 (4:6 hexane-EtOAc); IR (KBr): 3333, 2929, 2850, 1625, 1578, 1535, 1489, 1438, 1397, 1315, 1288, 1253, 1226, 1175, 1104, 1057, 968, 860, 821 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.19-1.86(m, 10H, cyclohexane), 2.41(s, 3H, -SCH3), 3.7(m, 1H, cyclohexane), 6.68(s, 1H, -CH), 6.94(m, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 17.26, 25.49, 32.86, 48.00, 60.03, 99.70, 123.67, 127.70, 128.65, 128.90, 129.22, 130.21, 131.53, 132.09, 132.62, 134.91, 136.86, 137.17, 139.65, 141.83, 144.83, 162.23; MS (m/z): 603 (M⁺); Anal. Calcd for C26H25BrCl2N5O3S: C, 51.79; H, 4.18; N, 11.62; Found: C, 53.47; H, 3.32; N, 14.48.
3H, -SCH3), 3.88(s, 1H, -CH, cyclohexane), 6.68(s, 1H, Ar-H, -NH, -CH), 9.01(s, 1H, -NH): 13C NMR (100 MHz, DMSO) δ ppm: 17.13, 25.50, 32.85, 48.02, 58.91, 99.29, 122.56, 127.42, 127.65, 128.56, 129.95, 130.04, 130.44, 131.55, 132.14, 132.60, 133.61, 134.51, 135.30, 139.53, 142.28, 144.86, 162.24; MS (m/z): 637 (M+); Anal. Calcd for C_{26}H_{24}BrCl_{2}N_{3}O_{5}: C, 48.99; H, 3.80; N, 10.99; Found: C, 51.27; H, 4.59; N, 9.34.

5-(2-bromophenyl)-N-cyclohexyl-7-(2-hydroxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3k):
Yellow solid; Melting range: 218-220 °C; Rf 0.30 (4:6 hexane-EtOAc); IR (KBr): 3369, 3289, 3185, 2941, 2851, 1629, 1580, 1553, 1489, 1432, 1369, 1319, 1284, 1250, 1223, 1173, 1123, 1059, 1033, 975, 874, 819, 754 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.16-1.81(m, 10H, cyclohexane), 2.50(s, 3H, -SCH3), 3.75(m, 1H, -CH, cyclohexane), 6.80-7.46(m, 10H, Ar-H, -CH, -NH), 8.75(s, 1H, -OH), 8.96(s, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 13.59, 24.50, 25.47, 32.80, 48.09, 55.33, 99.35, 118.79, 120.92, 121.86, 124.58, 127.10, 127.43, 128.69, 130.16, 130.72, 131.43, 132.00, 132.38, 139.40, 142.73, 144.65, 154.89, 161.96; MS (m/z): 584 (M+); Anal. Calcd for C_{26}H_{26}BrN_{5}O_{4}: C, 53.43; H, 4.48; N, 11.98; Found: C, 53.97; H, 5.04; N, 11.31.

5-(2-bromophenyl)-N-cyclohexyl-7-(4-hydroxy-3-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3u):
Yellow solid; Melting range: 138-140 °C; Rf 0.36 (4:6 hexane-EtOAc); IR (KBr): 3363, 2932, 2849, 1624, 1573, 1519, 1486, 1433, 1313, 1282, 1247, 1177, 1126, 1033, 977, 777, 757 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.18-1.34(m, 10H, cyclohexane), 2.43(s, 3H, -SCH3), 3.77(s, 3H, -OCH3), 3.81(m, 1H, -CH, cyclohexane), 5.79(s, 1H, -OH), 6.65(s, 1H, -CH), 6.76-7.44(m, 8H, Ar-H, -NH), 8.89(s, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 17.46, 24.52, 25.49, 32.88, 47.95, 56.03, 60.55, 99.67, 110.32, 114.55, 119.56, 123.78, 127.37, 128.60, 129.94, 130.23, 131.40, 132.02, 132.40, 139.22, 141.20, 144.34, 146.18, 146.55, 162.36; MS (m/z): 614 (M+); Anal. Calcd for C_{27}H_{28}BrN_{5}O_{4}: C, 52.77; H, 4.59; N, 11.40; Found: C, 53.21; H, 3.98; N, 12.20.

5-(2-bromophenyl)-N-cyclohexyl-7-(3-cyclopropoxy-4-(difluoromethoxy)phenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3w):
Yellow solid; Melting range: 158-160 °C; Rf 0.38 (4:6 hexane-EtOAc); IR (KBr): 3335, 2929, 2853, 1623, 1578, 1574, 1494, 1433, 1313, 1280, 1219, 1173, 1125, 1052, 1007, 822, 769 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 0.27(m, 2H, cyclopropene), 0.56(m, 2H, cyclopropene), 1.18-1.86(m, 10H, cyclohexane), 2.42(s, 3H, -SCH3), 3.77-3.79(d, 1H, -CHF2), 3.81(m, 1H, -CH, cyclohexane), 3.86(s, 1H, -CH), 6.334-7.43(m, 10H, Ar-H, -NH), 8.92(s, 1H, -NH); 13C NMR (100 MHz, DMSO) δ ppm: 3.29, 10.07, 17.30, 25.48, 32.87, 47.99, 60.27, 73.95, 99.63, 113.50, 113.77, 116.08, 118.74, 122.65, 123.20, 127.40, 128.57, 129.98, 131.52, 132.00, 132.23, 136.65, 139.64, 141.65, 144.62, 150.57, 162.25; MS (m/z): 690 (M+); Anal. Calcd for C_{30}H_{30}BrF_{2}N_{3}O_{5}: C, 52.18; H, 4.38; N, 10.14; Found: C, 52.77; H, 4.68; N, 10.79.

5-(2-bromophenyl)-N-cyclohexyl-7-(4-methoxyphenyl)-2-(methylthio)-6-nitro-4,7-dihydropyrazolo[1,5-a]pyrimidine-3-carboxamide (AM-3x):
Yellow solid; Melting range: 224-226 °C; Rf 0.40 (4:6 hexane-EtOAc); IR (KBr): 3342, 2930, 2850, 1628, 1576, 1541, 1481, 1477, 1430, 1312, 1276, 1246, 1174, 1121, 1030, 973, 840, 759 cm⁻¹; 1H NMR(400 MHz, DMSO): δ ppm 1.17-1.78(m, 10H, cyclohexane), 2.38(s, 3H, -SCH3), 3.68(m, 1H, -CH, cyclohexane), 3.73(s, 3H, -OCH3), 6.63(s, 1H, -CH), 6.92-6.94(d,
2H, Ar-H, J = 8.4Hz), 7.37-7.39(d, 2H, Ar-H, J = 8.4Hz), 7.46-7.62(m, 4H, Ar-H), 10.85(s, 1H. -NH); MS (m/z): 598 (M⁺); Anal. Calcd for C_{27}H_{28}BrN_{5}O_{4}S: C, 54.18; H, 4.72; N, 11.70; Found: C, 55.04; H, 5.11; N, 12.58.

Table 1. Physical data of compound AM-3a-z.

| Entry | R                     | Time h | Yield % | Melting Range °C |
|-------|-----------------------|--------|---------|------------------|
| AM-3a | -H                    | 12     | 89      | 196-198          |
| AM-3b | -4-Cl                 | 12     | 78      | 208-210          |
| AM-3c | -4-Br                 | 12     | 86      | 238-240          |
| AM-3d | -4(N,N-dimethylamino) | 15     | 73      | 242-244          |
| AM-3e | -4-Me                 | 13     | 69      | 220-222          |
| AM-3f | -4-F                  | 12     | 85      | 228-230          |
| AM-3g | -2-Cl                 | 12     | 87      | 212-214          |
| AM-3h | -2,4-di Cl            | 12     | 74      | 218-220          |
| AM-3i | -3,4-di OMe           | 14     | 91      | 204-206          |
| AM-3j | -3-OMe                | 14     | 86      | 218-220          |
| AM-3k | -2-OH                 | 16     | 82      | 218-220          |
| AM-3l | -3-OH                 | 16     | 79      | 216-218          |
| AM-3m | -2,5-di OMe           | 15     | 82      | 176-178          |
| AM-3n | -3-Cl                 | 13     | 76      | 230-232          |
| AM-3o | -3-Br                 | 12     | 83      | 226-228          |
| AM-3p | -4-OH                 | 16     | 81      | 238-240          |
| AM-3q | -2-NO₂                | 18     | 89      | 200-202          |
| AM-3r | -3-NO₂                | 16     | 76      | 188-190          |
| AM-3s | Cinnamaldehyde        | 10     | 79      | 146-148          |
| AM-3t | Naphthaldehyde        | 11     | 74      | 178-180          |
| AM-3u | -3-OMe-4-OH           | 14     | 63      | 138-140          |
| AM-3v | -4-CN                 | 12     | 88      | 222-224          |
| AM-3w | -3-CHF₂               | 15     | 80      | 158-160          |
| AM-3x | -4-OMe                | 15     | 87      | 224-226          |
| AM-3y | -3-Me                 | 13     | 93      | 196-198          |
| AM-3z | -3-OH-4-OMe           | 16     | 77      | 142-144          |
Table 2. Optimization of yield with different solvent and catalyst for AM-3a.

| Solvent | Catalyst | Yield % |
|---------|----------|---------|
| Water   | H$_3$BO$_3$ | 89      |
|         | Con HCl  | 73      |
|         | Acetic acid | 61     |
| Methanol| H$_3$BO$_3$ | 88      |
|         | Con HCl  | 70      |
|         | Acetic acid | 65     |
| DMF     | H$_3$BO$_3$ | 84      |
|         | Con HCl  | 71      |
|         | Acetic acid | 52     |
| THF     | H$_3$BO$_3$ | 77      |
|         | Con HCl  | 65      |
|         | Acetic acid | 43     |
| IPA     | H$_3$BO$_3$ | 78      |
|         | Con HCl  | 68      |
|         | Acetic acid | 32     |

3. RESULT AND DISCUSSION

Various methodologies have been described for the synthesis of pyrazolo[1,5-a]pyrimidines. During the course of our ongoing interest on synthesis of various heterocyclic compounds using 1-(2-bromophenyl)-2-nitroethanone, we observed that 1-(2-bromophenyl)-2-nitroethanone are versatile intermediate for the synthesis of pyrazolopyrimidines.

Here compound AM-3a was synthesized by different reaction condition like changing solvents and catalyst. It is found from TLC and mass analysis that in organic solvent product is formed but beside this the formed intermediates remains unreacted and it is not converted to final product even after very long time of reaction. Water is found best media for this conversion because in water all intermediates are converted in to final product. Three reagents con. HCl, acetic acid and Boric acid were used to obtain final compounds. In acetic acid product formation is very less but using con. HCl or Boric acid gives good yield. Here optimization is given with solvents, catalyst and yield in Table 2.
4. CONCLUSION

In summary, we have described the water mediated synthesis of nitro substituted triazolopyrimidine derivatives in moderate to good yield. The reaction of various substituted aldehydes with 1-(2-bromophenyl)-2-nitroethanone and 5-amino-N-cyclohexyl-3-(methylthio)-1H-pyrazole-4-carboxamide afforded the triazolo pyrimidine derivatives in the presence boric acid and water as a solvent. We have confirmed the structure on the basis of spectroscopic technique.

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