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Synthesis and Heterocyclization of 5-Amino-4-cyano-1, 3-oxazoles

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A convenient one-pot method for synthesis of some new oxazolo[5,4-d]pyrimidines *via* base catalyzed heterocyclization of 2-substituted 5-amino-4-cyano-1,3-oxazoles with various isothiocyanates is described.

Key Words: Oxazolopyrimidine, Heterocyclization, Isothiocyanate, Amino malononitrile tosylate, 1,4-Diazabicyclo[2,2,2]octane.

INTRODUCTION

Oxazoles continue to hold a center stage in organic synthesis, although the structure of the first oxazole was reported over a century ago. This is evidenced by the continued growth in the number of research publications and reviews[1]. 1,3-Oxazole derivatives are heterocyclic ring system present in a number of natural products, should this be medicine and materials or synthetic products endowed with interesting pharmacological or physical properties[2]. They also elicit a variety of biological responses[3], including anti-cancer and anti-HIV/AIDS activity[4]. Annulated 1,3-oxazoles such as oxazolopyrimi-dines have also been reported to exhibit a host of biological activities such as inhibitors of receptor tyrosine kinases (RTK)[5] and A_{2A} adenosine receptor antagonists[6]. In pursuing our efforts towards the synthesis of bioactive heterocycles[7] in this communication we wish to present a convenient and versatile method for the synthesis of some new 7-amino-2,6-disubstituted-oxazolo[5,4-d]pyrimidine-5(4H)-thiones through cyclocondensation of 1,3-oxazoles with various aryl and alkylisothiocyanates.

EXPERIMENTAL

Reactions were monitored by TLC using precoated silica gel aluminum plates. Detection was done by UV (254 nm) followed by dipping in either sulfuric acid in EtOH (10 %) or 0.5 % phosphomolybdic acid in 95 % EtOH solutions and subsequent charring at 200 ºC or dipping in a 1 % aqueous potassium permanganate solution and air drying. Anhydrous $MgSO_4$ was used to dry organic solutions during work up and the removal of solvents was carried out under vacuum with a rotary evaporator. Melting points were determined on a Buchi 510 and are uncorrected. IR spectra were obtained on a Bruker Alpha-P FTIR Diamond ATR spectrophotometer ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker 400 spectrometer, using tetrmethylsilane as internal standard. All the assignments for proton and carbon were made *via* 2D COSY, HSQC and HMBC experiments. High-resolution mass spectra were obtained by a thermo scientific exactive high resolution MS (ESI probe).

Synthesis of 2-substituted-5-amino-4-cyano-1,3-oxazoles (1-4): According to Freeman and Kim[8b], to a stirred solution of aminomalononitrile tosylate, (2.71 g, 8.60 mmol) in 1-methyl-2-pyrrolidinone (28 mL), were added 1.0-1.4 equiv (depending on the case) of the corresponding acid chloride in one portion. The reaction mixture was stirred at room temperature until the reaction was complete. Then, the mixture was diluted with a mixture of EtOAc and Et_2O (1:1) and washed with water, 10 % aqueous $NaHCO_3$ and water. The organic layer was dried, the solvent was evaporated *in vacuo* and the crude product was purified by flash silica gel chromatography (PE/EtOAc). The 1,3-oxazoles were recrystallized from Et_2O/EtOAc.

5-Amino-4-cyano-2-methyl-1,3-oxazole (1): Amino-malononitrile tosylate (1.17 g, 4.6 mmol), 1-methyl-2-pyrro-lidinone (10 mL) and acetyl chloride 1 equiv, were reacted at room temperature for 8 days. Work up (EtOAc: Et_2O, 1:1) and flash silica gel chromatography (1:1, hexanes: EtOAc) afforded compound (**1**). Yield (57 %) as a yellow solid: m.p. 150-153 ºC; IR ν_{max} 3305, 3259, 2922, 2850, 2212, 1428, 1659, 1093 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 7.51 (br s, NH_2, 2 H), 2.21 (s, CH_3, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.59 (C5), 150.14 (C2), 116.05 (CN), 82.57 (C4), 13.42 (CH_3); HR MS: *m/z* calcd. for $C_5H_4N_3O$ ($M-H^+$) 122.0360, found 122.0349.

5-Amino-4-cyano-2-(4-nitrophenyl)-1, 3-oxazole (2). Amino malononitrile tosylate (2.71 g, 8.60 mmol), 1-methyl-2-pyrrolidinone (28 mL) and *p*-nitrophenyl benzoyl chloride 1.1 equiv, were reacted at room temperature for 7 days. Work up and flash chromatography (PE:EtOAc, 1:1) rendered compound (**2**), Yield (90 %) as yellow crystals: m.p. 274-277 ºC; IR ν_{max} 3285, 3227, 2221, 1668, 1597, 1514, 1319, 1057, 852 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.26 (br s, NH_2, 2H), 8.33 (d, H2', H6', 2 H), 7.95 (d, H3', H5', 2 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.8 (C5), 147.47 (2C,C2, C4'), 131.27 (C1'), 125.74 (2C, C2', C6'), 124.50 (2C, C3', C5'), 114.87 (CN), 85.54 (C4); HR MS: *m/z* calcd. for $C_{10}H_5N_4O_3$ (M-H^+) 229.0362, found 229.0360.

5-Amino-4-cyano-2-phenyl-1,3-oxazole (3): Amino-malononitrile tosylate (1.17 g, 4.6 mmol), 1-methyl-2-pyrrolidinone (10 mL) and benzoyl chloride 1.4 equiv, were reacted at room temperature for 8 days. Work up and flash chromatography (6:4, CH_2Cl_2: EtOAc) afforded compound (**3**), (67 %, yield) and compound(4) (7 %, yield). 5-Amino-4-cyano-2-phenyl-1,3-oxazole (**3**): Yellow solid; m.p. 240-244 ºC; IR ν_{max} 3314, 3273, 2207, 1650, 1600, 1052.2 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.95 (br s, NH_2, 2H), 7.75 (dd, H2', H6', 2 H), 7.49 (m, H3', H4', H5', 3 H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.42 (C5), 149.50 (C2), 130.11 (C4'), 129.24 (2C, C3', C5'), 126.08 (C1'), 125.49 (2C, C2', C6'), 115.49 (CN), 85.34 (C4); HR MS: *m/z* calcd. for $C_{10}H_6N_3O$ (M-H^+) 184.0516, found 184.0509.

5-Amino-4-cyano-2-(phenylamino)-1,3-oxazole (4): Withe crystals; m.p. 240-243 ºC; IR ν_{max} 3220, 3062, 1687, 2240, 1599, 1490, 1063, 769 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 12.40 (br s, NH, 1 H), 8.1 (m, H2', H6', 2 H), 7.95 (m, H2', H6', 2H), 7.70 (m, H4", 1H), 7.60 (m, H3', H4', H5', H3", H5", 5H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 164.8 (C5), 155.1 (C1'), 151.6 (C2), 133.6 (C1'), 132.1 (C4'), 129.9 (2C, C3", C5"), 129.2 (2C, C3', C5'), 128.8 (2C, C2', C6'), 126.5 (2C, C2", C6"), 113.8 (CN), 100.4 (C4), 125.6 (C4"); HR MS: *m/z* calcd. for $C_{17}H_{10}N_3O_2$ (M-H^+) 288.0779, found 288.0778.

Synthesis of 2-substituted-5-amino-4-cyano-1,3-oxazoles (5-7): According to Freeman and Chen[4], to a stirred solution of amino malononitrile tosylate (2.66 g, 10.5 mmol) in pyridine (50 mL) was added the corresponding carboxylic acid (10 mmol) and 1,3-dicyclohexylcarbodiimide (DCC) (2.16 g, 10.5 mmol) and the reaction mixture was stirred at room temperature until the reaction was complete. The white precipitate (dicyclohexylurea) was removed by filtration and the filtrate was concentrated *in vacuo* to give a residue, which was purified by flash silica gel chromatography (1:1, PE/EtOAc) to give product. 1, 3-Oxazoles were crystallized from Et_2O/EtOAc.

5-Amino-4-cyano-2-(2-iodophenyl)-1,3-oxazole (5): Amino malononitrile tosylate (2.66 g, 10.5 mmol), pyridine (50 mL), 2-iodobenzoic acid (2.53 g, 10 mmol) and DCC (2.16 g, 10.5 mmol) were reacted at room temperature for 4 days. Work up and flash chromatography (1:1, EtOAc/Et_2O) gave compound (**5**) (56 % yield). Yellow crystals; m.p. 170-172 ºC; IR ν_{max} 3389, 3321, 3277, 2214, 1658, 1002, 762 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.03 (dd, H3, 1 H), 7.95 (br s, NH_2, 2 H), 7.50 (ddd, H4', 1H), 7.20 (ddd, H5', 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.4 (C5), 148.75 (C2), 140.9 (C1'), 131.5 (C3'), 130.5 (C4'), 130.3 (C6'), 128.4 (C5'), 115.3 (CN), 94.5 (C2'), 84.04 (C4); HR MS: *m/z* calcd. for $C_{10}H_5N_3O$ I(M-H^+) 309.9483, found 309.9479.

5-Amino-2-benzhydryl-4-cyano-1,3-oxazole (6): Amino malononitrile tosylate (2.13 g, 8.6 mmol), pyridine (41 mL), diphenylacetic acid (1.79 g, 8.34 mmol) and DCC (1.77 g, 8.6 mmol) were reacted at room temperature for 5 days. Work up and flash chromatography (1:1, EtOAc/PE) gave compound (**6**) (71 % yield). White crystals; m.p. 163-166; IR ν_{max} 3341, 3310, 3139, 2923, 2852, 2220,1660, 1591, 1158, 696, 744 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 7.70 (br s, NH_2, 2H), 7.2-7.4 (m, 10 $H_{arom.}$), 5.59 (s, CH, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.34 (C5), 152.65 (C2), 139.49 (2 C, 2C1'), 128.55 (4 C, 2C3', 2C5'), 128.44 (4 C, 2C2', 2C6'), 127.13 (2 C, 2C4'), 115.44 (CN), 82.52 (C4), 49.23 (CH); HR MS: *m/z* calcd. for $C_{17}H_{12}N_3O$ (M-H^+) 274.0986, found 274.0981 and *m/z* calcd. for $C_{17}H_{14}N_3O$ (MH^+) 276.1131, found 276.1131.

***N*-(9-(2-(5-amino-4-cyano-oxazol-2-yl)phenyl)-6-(diethylamino)-3*H*-xanthen-3-ylidene)-*N*-ethylethanaminium chloride (7):** Amino malononitrile tosylate (1.40 g, 5.5 mmol), pyridine (25 mL), Rhodamin B (2.5 g, 5 mmol) and DCC (1.13 g, 5.5 mmol) were reacted at room temperature for 7 days. Work up and flash chromatography (1:3, EtOAc/PE) gave compound (**7**) (47 % yield). Purple crystals; m.p. 298-300 ºC; IR ν_{max} 3392, 3324, 2927, 2850, 2219, 1625, 1046 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.22 (q, H3', 1 H), 7.65 (m, H4', H5', H6', 3 H), 7.15 (t, H8, 1 H), 7.05 (d, H7, 1H), 7.03 (s, H5, 1 H), 7.01 (br s, NH_2, 2 H), 6.72 (d, H2, 1H), 6.70 (d, H1, 1H), 6.67 (d, H4, 1H); ^{13}C NMR (DMSO-d_6 and $CDCl_3$, 100 MHz) δ 167.8 (C5"), 159.35 (C10a), 157.71 (C6), 155.24 (C4a), 142.04 (C3), 139.84 (C9), 133.56 (C1'), 132.96 (C1), 131.71 (C5'), 131.52 (C9a), 131.15 (C4'), 130.07 (C8), 129.41 (C3'), 128.51 (C4"), 125.71 (C6'), 113.59 (CN), 113.46 (C2), 95.95 (2 C, C4, C5), 45.74 (CH2), 13.83 (CH_3); HR MS: *m/z* calcd. for $C_{31}H_{32}N_5O_2$ MH^+ 506.2551, found 506.2548 and *m/z* calcd. for $C_{31}H_{30}N_5O_2$ M-H^+ 504.2400, found 504.2400.

Synthesis of oxazolo[5, 4-d]pyrimidine-5(4*H*)-thiones (8-14): To a solution of 1,4-diazabicyclo[2,2,2]octane (DABCO) (1.5 equiv) in dry DMF (5 mL) under Argon, the corresponding aryl- and alkylisothiocyanates (1.5 equiv) and the oxazole were added. The mixture was reacted at 120 ºC until the reaction was complete. Then, water and a solution of HCl (1 M) were added until PH 9. Then, the precipitate was filtered off and purified.

7-Amino-2-benzhydryl-6-(4-methoxyphenyl)-oxazolo [5,4-d]pyrimidine-5(4*H*)-thione (8): DABCO (266 mg, 2.3 mmol) in DMF dry (3 mL) was reacted with *p*-methoxy-phenylisothiocyanate (270 µL, 1.9 mmol) and oxazole (**6**) (551 mg, 2 mmol). The mixture was reacted at 120 ºC for overnight. Then, participate was filtered and was purified by flash chromatography (3:1, PE: EtOAc) to give compound (**8**) (71 % yield): White crystals; m.p. 273-276 ºC; IR ν_{max} 3392, 3330, 2954, 2852, 1692, 1509, 1257, 693, 738 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.90 (br s, NH_2, 2 H), 7.46 (m, 2 H4', 2H), 7.31 (m, 2H3', 2H5', 4H), 7.23 (m, 2H2', 2H6', 4H), 7.15 (m, H3", H5", 2H), 6.73 (d, H2", H6", 2H), 5.06 (s, CH, 1H), 3.68 (s, CH_3, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 170.27 (C5), 158.9 (C2), 154.5 (C3a), 150.5 (2 C, C7, C4"), 114 (C7a), 140.4 and 140.2 (2 C, 2C1'), 131 (2 C, C2", C6"), 129 (4C,

2C3', 2C5'), 128.4 (4 C, 2 C2', 2 C6'), 128.5 (C1''), 127 (2C, 2C4'), 110.86 (2C, C3'', C5''), 55 (CH_3), 50 (CH); HR MS: *m/z* calcd. for $C_{25}H_{21}N_4O_2S$ MH^+ 441.1380, found 441.1379 and *m/z* calcd. for $C_{25}H_{19}N_4O_2S$ M-H^+ 439.1223, found 439.1226.

7-Amino-6-(4-methoxyphenyl)-2-(4-nitrophenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione (9): DABCO (318 mg, 2.75 mmol) in DMF dry (5 mL) was reacted with *p*-methoxyphenylisothiocyanate (468 µL, 2.75 mmol) and oxazole (**2**) (575 mg, 2.5 mmol). The mixture was reacted at 120 ºC for overnight. Then, participate was filtered and recrystallized in EtOH, provided compound (**9**) (69 % yield): Yellow crystals; m.p. > 300 ºC; IR ν_{max} 3391, 3328, 2932, 2834, 1622, 1599, 1292, 1040, 854 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 10.0 (br s, NH_2, 2H), 8.42 (m, H3', H5', 2H), 8.23-8.34 (m, H2', H6', 2H), 7.7 (m, H3'', H5'', 2 H), 6.93 (m, H2'', H6'', 2H), 3.7 (s, CH3, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 162.8 (C5), 158.5 (C2), 156.5 (C3a), 147.46 (C4''), 147.42 (C7), 132.2 (C4'), 131.3 (C1'), 127.23 (2C, C2', C6'), 126 (2C, C2', C6'), 125.6 (C1''), 124.4 (2 C, C3', C5'), 115.04 (2C, C3', C5'), 115.04 (C7a), 55.4 (CH_3); HR MS: *m/z* calcd. for $C_{18}H_{14}O_4N_5S$ MH^+ 396.0761 found 396.0758 and *m/z* calcd. for $C_{18}H_{12}N_5O_4S$ M-H^+ 394.0616, found 394.0609.

7-Amino-2-(2-iodophenyl)-6-(4-methoxyphenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione (10): DABCO (213 mg, 2 mmol) in DMF dry (5 mL) was reacted with *p*-methoxyphenylisothiocyanate (270 µL, 1.9 mmol) and oxazole (**5**) (622 mg, 2 mmol). The mixture was reacted at 120 ºC under Argon for overnight. Then participate was filtered and purified by flash chromatography (1:1, PE/EtOAc), provided compound (**10**). (60 % yield): Brown crystals; m.p. 247-251 ºC; IR ν_{max} 3390, 3301, 2930, 2833, 1616, 1580, 1242, 763 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 9.81 (br s, NH_2, 2H), 8.10 (ddd, H3', 1H), 7.86 (ddd, H4', 1H), 7.57-7.70 (m, H5', H6', 2H), 7.29-7.39 (m, H3'', H5'', 2H), 6.90-6.95 (dd, H2'', H6'', 2H), 3.75 (s, CH_3, 3H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.6 (C5), 158.9 (C3a), 155.98 (C4''), 155.26 (C7), 140.62 (C1'), 140.58 (C3'), 132.26 (2C, C2'', C6''), 132.14 (C4'), 131.78 (C5'), 128.4 (C6'), 128.48 (C1''), 113.65 (2C, C3'', C5''), 113.74 (C7a), 95.6 (C2'), 55.2 (CH_3); HR MS: *m/z* calcd. for $C_{18}H_{12}N_4O_2IS$ M-H^+ 474.9731, found 474.9718.

7-Amino-6-(3-chlorophenyl)-2-(4-nitrophenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione (11): DABCO (213 mg, 2 mmol) in DMF dry (5 mL) was reacted with *m*-chlorophenylisothiocyanate (258 µL, 1.8 mmol) and oxazole (2) (460 mg, 2 mmol). The mixture was reacted at 120 ºC under argon for overnight. Then, participate was filtered and recrystallized with EtOH to give compound (**11**) (54 % yield): Yellow crystals; m.p. 242-244 ºC; IR ν_{max} 3374, 3325, 1620, 1548, 1338, 1308, 1105, 853, 898,776, 679 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 8.24-8.44 (m, H3', H5', 2 H), 8.02-8.1 (m, H5'', 1H), 7.74-7.82 (m, H2', H6', 2H), 7.34-7.39 (m, H4'', 1H), 7.10-7.12 (m, H2'', 1H), 6.67-6.71 (m, H6'', 1H), 6.03 (br s, NH_2, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 179.5 (C5), 162.8 (C2), 147.4 (C3a), 147.3 (C7), 140.8 (C4'), 135.3 (C1'), 133.9 (C1'), 132.6 (C3''), 131.5 (C5''), 131.2 (2 C, C2', C6'), 129.9 (C4''), 127.8 (2 C, C3', C5'), 122.9 (C6''), 121.8 (C2''); HR Ms: *m/z* calcd. for $C_{17}H_9N_5O_3ClS$ M-H^+ 398.0120, found 398.0114.

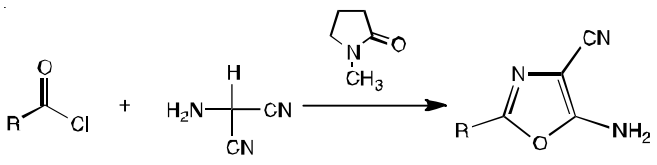
7-Amino-6-hexyl-2-(4-nitrophenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione(12): DABCO (290 mg, 2.5 mmol) in DMF dry (5 mL) was reacted with hexylisothiocyanate (330 µL, 2.4 mmol) and oxazole (2) (575 mg, 2.5 mmol). The mixture was reacted at 120 ºC under Argon for overnight. Then, participate was filtered and recrystallized in EtOH to give compound (12) (58 % yield): Red crystals; m.p. 220-223 ºC; IR ν_{max} 3379, 3297, 2925, 2854, 1622, 1551, 1336, 1275, 852 cm^{-1}; ^1H NMR($CDCl_3$, 400 MHz) δ 0.92 (m, 3H6'', 3H), 1.36 (m, 2H3'', 2H4'', 2H5'', 6H), 1.71 (m, 2H2'', 2H), 4 (br s, NH_2, 2H), 3.93 (m, 2 H1'', 2H), 8.13-8.41 (m, $4H_{arom.}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166 (C5), 159.6 (C3a), 155.27 (C2), 149.3 (C4'), 148.4 (C7),127.8 (C1'), 126.8 (2C, C2', C6'), 124.2 (2C, C3', C5'), 52.9 (C1''), 31.7 (C4''), 31.6 (C2''), 26.7 (C3''), 22.7 (C5''), 14.1 (C6''); HR MS: *m/z* calcd. for $C_{17}H_{20}O_3N_5S$ MH^+ 374.1281, found 374.1276 and *m/z* calcd. for $C_{17}H_{18}N_5O_3S$ M-H^+ 372.1136, found 372.1131.

7-Amino-6-cyclohexyl-2-(4-nitrophenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione (13): DABCO (290 mg, 2.5 mmol) in DMF dry (5 mL) was reacted with cyclohexylisothiocyanate (338 µL, 2.4 mmol) and oxazole (2) (575 mg, 2.5 mmol). The mixture was reacted at 120 ºC under argon for 2 days. Then, participate was filtered and recrystallized in EtOH to provided compound (**13**) (77 % yield): Brown crystals; m.p. 239-241 ºC; IR ν_{max} 3402, 3379, 2927, 2851, 1620, 1517, 1337, 1273, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.29-1.47 (m, 2H3'', 2H5'', 4H), 1.59-1.81 (m, 1H2'', 2H4'', 1H6'', 4H), 2.04-2.16 (m, 1H2'', 1H6'', 2H), 4.2 (br s, NH_2, 2H), 8.18-8.36 (m, 4 $H_{arom.}$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.2 (C5), 162.7 (C2), 159.7 (C3a), 148.3 (C7), 149.1 (C4'), 132.2 (C1'), 126.7 (2C, C2', C4'), 124.2 (2C, C3', C5'), 57.8 (C1''), 33.1 (2C, C2'', C6''), 25.6 (C4''), 24.9 (2C, C3'', C5''); HR MS: *m/z* calcd. for $C_{17}H_{18}N_5O_3S$ MH^+ 372.1125, found 372.1129 and *m/z* calcd. for $C_{17}H_{16}O_3N_5S$ M-H^+ 370.0968, found 370.0974.

7-Amino-6-[3,5-*bis*-(trifluoromethyl)phenyl]-2-(4-nitrophenyl)-oxazolo[5,4-d]pyrimidine-5(4*H*)-thione (14): DABCO (290 mg, 2.5 mmol) in DMF dry (5 mL) was reacted with 3,5-*bis*-(trifluoromethyl)phenylisothiocyanate (424 µL, 2.3 mmol) and oxazole (2) (575 mg, 2.5 mmol). The mixture was reacted at 120 ºC under argon for 2 days. Then, participate was filtered and purified by flash chromatography (1:1, PE/EtOAc) to provided compound (**14**) (57 % yield): m.p. >300 ºC; IR ν_{max} 3415, 3355, 3117, 1633, 1592, 1516, 1341, 1274, 1095, 1125, 937, 881, 854 cm^{-1}; ^1H NMR (DMSO-d_6 and $CDCl_3$, 400 MHz) δ 8.53 (d, H3', H5', 2H), 8.3 (d, H2', H6', 2H), 8.2 (s, H4'', 1H), 7.84 (s, H2'', H6'', 2H), 5.47 (br s, NH_2, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 166.1 (C5), 164.5 (C2), 158.7 (C3a), 153.3 (C4'), 140.6 (C7), 140.1 (C1'), 132.8 (C1''), 132.7 (2C, C2'', C6''), 129.9 (C3''), 129.8 (C5''), 126.8 (2C, C2', C6'), 124.3 (2C, C3', C5'), 120 (C4''), 120.3 (2C, CF_3), 120.17 (C7a); HR MS: *m/z* calcd. for $C_{19}H_8N_5O_3SF_6$ M-H^+ 500.0258, found 500.0250.

RESULTS AND DISCUSSION

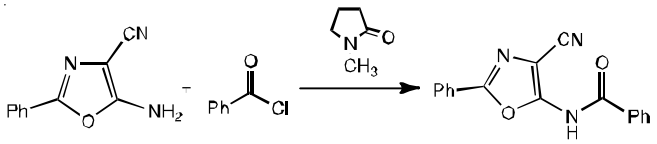
Two major routes for the synthesis of 1,3-oxazole derivatives has been previously reported[4,8]. Consequently, a solution of aminomalononitrile tosylate in 1-methyl-2-pyrrolidinone was reacted with various aryl or alkyl acid chlorides at room temperature (**Scheme-I**).



1) R = CH_3; 2) R = 4-NO_2-C_6H_4; 3) R = C_6H_5

Scheme-I: Synthesis of the 2-substituted-5-amino-4-cyano-1,3-oxazoles (1-3)

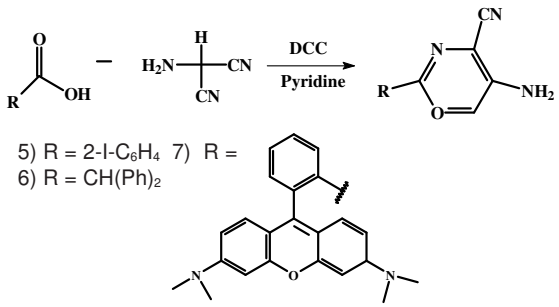
The standard procedure worked especially well in yielding the desired products (1-3) in moderate yield, although long reaction times (around 7 days) were required. In other circumstances, we were forced to employ an excess of the acid chloride since no reaction was observed when employing a 1.4 equiv. of the reagent, but under these conditions, by-products were formed which substantially lowered the yield of the target product (3). Concerning the undesirable by-products, we have isolated the 2-phenyl-5-(phenylamino)-oxazole-4-carbonitrile (4) (in 7 % yield) (**Scheme-II**).



Scheme-II: Synthesis of the N-acylated-5-amino-4-cyano-1,3-oxazole (by product 4)

For the other procedure used to synthesize 5, 6 and 7, we employed aminomalononitrile tosylate in pyridine with carboxylic acids at room temperature[4]. The carboxyl activating reagent, 1,3-dicyclohexylcarbodiimide, was used to synthesize compounds **5**, **6** and **7** (**Scheme-III**). All new compounds communicated in this work showed good analytical and spectroscopic data (see experimental). Furthermore, the ^{13}C NMR spectra (Fig. 1) have been assigned *via* HMBC and HSQC experiments and are in good agreement with those previously reported for other 1,3-oxazoles[9]. Cyclocondensation was carried out with these precursors by employing 1,4-diazabicyclo[2,2,2]octane (DABCO) under argon using aryl and alkylisothiocyanates (**Scheme-IV**). Under these conditions, the reaction with 1,3-oxazoles (2, 5 and 6) afforded the forecasted products (8-14) in moderate to good yields. In total, the investigated reaction took around 18 h to reach completion, under Argon and with excess of catalyst (DABCO).

The structures of these compounds have been confirmed by spectroscopic analysis (see experimental). For example, the IR spectrum of compound (**8**) was devoid of the stretching vibration bands at 3341, 3310 and 2220 cm^{-1} for NH_2 and CN



5) R = 2-I-C_6H_4 7) R =
6) R = $CH(Ph)_2$

Scheme-III: Synthesis of the 2-substituted-5-amino-4-cyano-1,3-oxazoles (5, 6 and7)

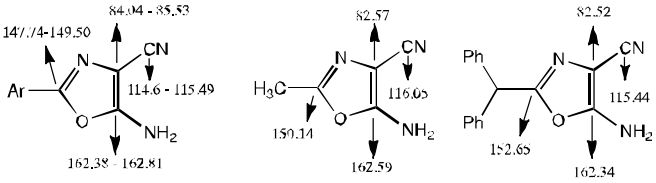


Fig. 1. ^{13}C NMR (DMSO-d_6, 400 MHz) data of the 2-alkyl(2-aryl)oxazolo derivatives

absorption of the precursor but instead showed new absorption bands at 3392, 3330 1692 and 1257 cm^{-1} for NH_2, C=N and C=S groups, respectively. The ^1H NMR spectra in DMSO-d_6 showed two broad singlets at 9.90 and 5.06 due to NH_2 and CH groups respectively, as well as a singlet 3.68 corresponding to methyl group and the characteristic signals at 7.14-7.48 for phenyl groups. High resolution mass spectra of the compound (**8**) showed the molecular ion peak at *m/z* 441.1379 and 439.1226 corresponding to the MH^+ and $M\text{-}H^+$, respectively.

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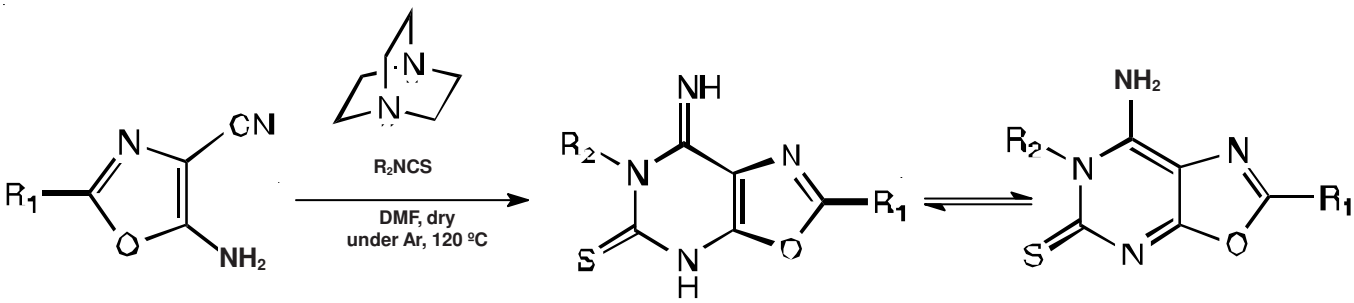

2 R_1 = 4-NO_2-C_6H_4
3 R_1 = 2-I-C_6H_4
4 R_1 = $(Ph)_2CH$

R_2 = 4-Meo-C_6H_4
3-Cl-C_6H_4
Cyclohexyl
3,5-*Bis*$(CF)_3$-C_6H_3
Hexyl

8 R_1 = $(Ph)_2CH$, R_2 = 4-MeO-C_6H_4 (71 %)
9 R_1 = 4-NO_2-C_6H_4, R_2 = 4-MeO-C_6H_4 (69 %)
10 R_1 = 2-I-C_6H_4, R_2 = 4-MeO-C_6H_4 (60 %)
11 R_1 = 4-NO_2-C_6H_4, R_2 = 3-Cl-C_6H_4 (54 %)
12 R_1 = 4-NO_2-C_6H_4, R_2 = Hexyl (58 %)
13 R_1 = 4-NO_2-C_6H_4, R_2 = Cyclohexyl (77 %)
14 R^1 = 4-NO_2-C_6H_4, R_2 = 3,5-*Bis*(CF)3-C_6H_3 (57%)

Scheme-IV: Synthesis of the oxazolo [5,4-d]pyrimidine analogues (8-14)

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