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Research Article

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Synthesis of Some Pyrido[4,3- d] pyrimidine Derivatives from Malononitrile

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Abstract

A series of pyrido[4,3-d]pyrimidine derivatives (**5a-f**) were synthesized using malononitrile (**1**) as a starting material. Initially **1** was bubbled by HBr in toluene for 2 hrs, which forms 4,6-Diamino-2-bromo-3-cyanopyridine (**2**). The compound **2** by direct hydrolysis of the nitrile group to the corresponding carboxamide by treatment of H_2O_2 in aqueous alkaline conditions gives4,6-Diamino-2-bromonicotinamide (**3**). By refluxing **3** under nitrogen with setoforthoesters, triethylorthoformate and triethyorthoacetate gives 7-Amino-5-bromopyrido[4,3-d]pyrimidin-4(3H)-one(**4x**) and 7-Amino-5-bromo-2-methylpyrido[4,3-d]pyrimidin-4(3H)-one(**4y**) respectively. Finally, by using **4x-y** series,pyrido[4,3-d]pyrimidine derivatives (**5a-f**) were synthesized.

Key words: Malononitrile, Pyrido[4,3-d]pyrimidine, Orthoesters and Synthesis.

1. Introduction

Synthesis of pyrido[4,3-d]pyrimidines fall into two categories. Synthesis may involve fusion of the pyridine rings onto the preformed pyrimidine ring or they may involve fusion of the pyrimidine ring onto an already existent pyridine. Cyclic*o*-amino nitriles (Schaefer *et al.,* 1978) and *o*-amino carboxamides (Mascal *et al.,* 2006) are versatile starting materials for the synthesis of fused ring systems. Cyclizationof4-aminonicotinamidewith ortho esters (Taylor *et al.,* 1967) and esters (Mascal *et al.,* 2006; Lornad*et al.,* 1985) in basic conditions leads to pyrido [4,3-d]pyrimidin-4(3*H*)-ones (Bredereck *et al.,* 1968).

The synthesis of pyrido [4,3-d] pyrimidines from pyrimidine derivatives has not been very well explored, presumably due to the poor availability of suitable pyrimidine derivatives as starting materials. Three general methods have been reported. The first one is based on the intra molecular cyclization of alkynyl or alkenyl pyrimidine derivatives (which are obtained by palladium-catalyzed cross-coupling reactions), yielding pyrano[4,3-d]pyrimidin-5-ones (Bennett *et al.,* 1978; Sonogashira *et al.,* 1975). These are obtained either by an acid-catalyzed 6-*endo* di cyclization of alkynyl pyrimidines or by bromination of alkenyl pyrimidines (Iamail and Wibberley, 1968). Treatment of the pyrano[4,3-d]pyrimidin-5-ones with ammonia, hydroxyl amine or hydrazines affords the desired pyrido [4,3-d] pyrimidines (Griffin *et al.,* 1998; El-Sayed *et al.,* 2003).

Secondly, pyrido[4,3-d]pyrimidin-5(6*H*)-ones are formed directly from alkynyl pyrimidines on heating with ethanolic ammonia. Imine derivatives, formed by the treatment of a pyridine-carboxaldehyde with an excess of *t*-butylamine, can also undergo an intra molecular cyclization in the presence of Ag(I) salt, yielding pyrido[4,3-d]pyrimidin-5(6*H*)-ones (Susvilo *et al.,* 2005).

Final approach involves a Mannich reaction. The cyclization of dihydropyrimidin-2-thiones with primary amines and formaldehyde gives rise to pyrido [4,3-d] pyrimidine derivatives. Alternatively, treatment of 5-cyano-6-cyanomethyl pyrimidines with sulfuric acid leads to pyrido [4,3-d] pyrimidines (Elnagdi *et al.,* 1982).

As a part of an ongoing medicinal chemistry research program, the synthetic schemes described

for the preparation of pyrido [4,3-d] pyrimidine analogues allow only to introduce structural variety in one or two particular positions of the scaffold. To our knowledge, there are no systematic studies done on how to elaborate in a systematic way the chemistry of this compound class. Therefore, the main goal of present research is to develop synthetic schemes that can be easily adapted for use in parallel chemistry. In that respect, we will try to introduce abroad structural variety into the pyrido [4,3-d] pyrimidine scaffold in which three or more substitution sites can be varied in one synthetic cycle.

2. Material and Methods

2.1Chemicals and Instrumentation

General solvents were dried over standard drying agents and freshly distilled prior to use. Thereagents were purchased from Aldrich and Acros and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Organic solutions were dried (Na_2SO_4) and concentrated in vacuum below 408. Column chromatographic (CC): silica gel (SiO_2, 60–120 mesh; Acme's). Optical rotations: HoribaSEPA-300 high-sensitive polarimeter; at 258. IR Spectra: Perkin-Elmer-IR-683 spectrophotometer with NaCl optics; n˜ in cm^{-1}. 1H- (300 MHz) and 13C-NMR (75 MHz) Spectra: Bruker-Avance-300 instrument; in $CDCl_3$; d in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: Agilent Technologies 1100 series (Agilent Chemistation Software); in m/z.

2.2 Method for development of analogues and their chemistry

It was envisioned that **2** could act as a versatile starting material for the synthesis of pyrido [4,3-d] pyrimidine libraries. The bromine on the pyridine ring offers the possibility of performing nucleophilic aromatic substitutions, as well as palladium-catalyzed cross-coupling reactions to construct C-O,C-N,C-S and C-Cbonds (Ley Thomas, 2003).

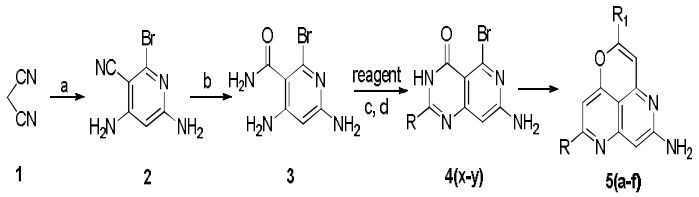
Moreover, bromine can be reduced off by catalytic hydrogenation to get access to 5-unsubstituted compounds. In this respect, compound **2** was prepared from malono nitrile **(1)** by bubbling HBr gas into toluene. Nicotinamide **3** was synthesized from **2** by direct hydrolysis of the nitrile group to the corresponding carboxamide by treatment with hydrogen peroxide in aqueous alkaline conditions.

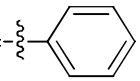
Nicotinamides are valuable starting materials for the construction of the pyrido [4,3-d] pyrimidin-4(3*H*)-one scaffold. Within this context, **3** was reacted with aset of ortho esters to form the pyrimidine ring. In this way, H and methyl groups could be introduced at position 2 of the scaffold. The bromine atom at position 5 of compounds **4x** and **4y** can act as a versatile material for a wide variety of palladium-catalyzedcross-coupling reactions to form new C-C bonds (such as for example Suzuki, Heckand Sonogashira reactions). For the synthesis of compound **5a**, a copper-free version of the Sonogashira reaction was performed (Sorensen Pombo-Villar, 2005). This might be important for industrial applications, as copper is very tedious to recycle. We made a number of new tricyclic analogues **5b-f** with commercially available acetylene derivatives. When tri methyl silylacetyle new as used as the coupling partner, *insitu* de protection of the silyl group was observed (Mi-Yeon Jang *et al.,* 2006; Mi-Yeon Jang *et al.,* 2006).

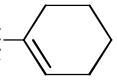
3. Results and Discussion

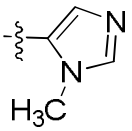
Procedure for preparation of 4,6-Diamino-2-bromo-3-cyanopyridine **(2)** HBr (*insitu* prepared from H_2SO_4 and NaBr) was bubbled for 2h through a solution of malono nitrile **(1)** (13g,0.197mol) in toluene (400mL) at $0^{\circ}C$. Alight yellow precipitate was formed and there action mixture was then heated at$100^{o}C$ for 2h, with a lot of gas evolution. After cooling to room temperature, the yellow solid was filtered off and washed with toluene and air dried. The solid was mixed with water and the pH of the suspension was adjusted to 9-10 by the addition of a 33% aqueous NH_3 solution. After stirring at room temperature for 1h, the mixture was filtered. Re

crystallization from ethanol afforded a yellow solid. After drying at 60^{O}C in a vacuum oven, the title compound was obtained as an orange solid **[Fig 1-(1) to (2)]** (10.1g,48%). ^{1}HNMR (300MHz, DMSO-*d*,25^{O}C): δ=6.66(brs,2H,NH), 6.54(brs,2H,NH_2), 5.59 (s,1H,H-5) ppm. ^{13}CNMR (75MHz,DMSO-*d6*,25^{O}C):δ=160.91,157.73,143.98,117.20,86.55,85.49ppm. HRMS: calculated for $C_6H_6BrN_4$ $[M+H]^+$ 212.9776/214.9755, found 212.9772/214.9738.



5a: R=H, R_1=- 

5b: R=CH_3, R_1=- 

5c: R=CH_3, R_1=- 

5d: R=CH_3, R_1= -CH_2OH

5e: R=CH_3, R_1= -$CH_2N(CH_3)_2$

5f: R=CH_3, R_1=H

Fig 1. Schematic pathway of pyrido [4,3-d] pyrimidine derivatives

a)HBr (g), 0^{O}C,2h,toluenethen100^{O}C,2h;

b) H_2O_2,NaOH,DMSO,50^{O}C,24h;

c) Tri ethyl ortho formate [$HC(OEt)_3$], N_2 140^{O}C,24h, then5NNaOH, 30mins and neutralized with 6N HCl;

d)Triethyl ortho acetate [$CH_3HC(OEt)_3$],140^{O}C,24h; then5NNaOH, 30mins and neutralized with 6N HCl

4x:Reagent=c, R=H; 4y:Reagent=d, R= CH_3

4,6-Diamino-2-bromonicotinamide **(3)** to a solution of **2** (4g,18.8mmol) in DMSO (46mL) was added H_2O_2 (15.6mL of a 35wt % solution, 56.3mmol) and 6N NaOH (2.82mL, 56.3mmol). The reaction mixture evolves oxygen and starts very soon to warm up. The temperature of the reaction mixture was kept at 40–50°C by external cooling. After approximately 1h, no more heat evolved and the temperature was maintained at 50°C by external heating for another 3h. Then, an additional amount of H_2O_2 (5mL of a 35wt %solution) and 6N NaOH (0.9mL) was added and the mixture was stirred overnight. The mixture was neutralized with a 5% sulfuric acid solution. After removal of the volatiles under reduced pressure, the residue was purified by flash chromatography on silica gel with a mobile phase consisting of CH_2Cl_2/MeOH (in a ratio of 70:1), followed by a mixture of CH_2Cl_2/acetone (in a ratio of 1:1), yielding the title compound as a pale yellow solid (3.88g,89%) [**Fig 1-(2) to (3)]**. mp223-226° C. ^{1}HNMR (300MHz, DMSO-*d6*, 25^{O}C):δ=7.58 (brs, 1H, CONH), 7.39 (brs,1H,CONH), 5.91 (brs, 2H, NH_2), 5.76 (brs, 2H, NH_2), 5.59 (s,1H,5-H) ppm.^{13}CNMR (75MHz, DMSO-*d6*, 25^{O}C):δ=168.4, 159.2, 154.6, 137.6, 110.5, 88.9ppm. IR(KBr):$\tilde{\upsilon}$=3457, 3350, 3178, 2924, 2364, 1631,1594,1530, 1480, 1458, 1383, 1290, 1245,1133, 1002cm^{-1}. MS: calculated for $C_6H_8BrN_4O[M+H]^+$230.99/232.99, found 231. 0/233.0 7-Amino-5-bromopyrido[4,3-d]pyrimidin-4(3*H*)-one**(4x)**. This compound was prepared from **3** (2g,13.1mmol) in triethyl orthoformate (60mL) was refluxed under a nitrogen atmosphere for 24h. The solvents were evaporated *in vacuum* and the residue was re dissolved in a hot 5N NaOH solution (20mL) for 30mins and thereafter neutralized with a 6N HCl (6.5mL) solution. On cooling,7-aminopyrido [4,3-d] pyrimidin-4(3*H*)-one precipitated out. The yellow solid was filtered off and was dried in a vacuum oven, yielding the pure title compound (in a yield of 88%) [**Fig 1-(3) to (4x)]**. mp>290^{O}C. ^{1}H NMR (300MHz, DMSO-*d*, 25^{O}C):δ=11.86(brs,1H,NH), 7.94 (s,1H,2-H),7.06 (brs, 2H, NH_2), 6.33 (s,1H,8-H)ppm.^{13}C NMR (75MHz, DMSO-*d6*, 25^{O}C):δ=161.6, 158.2, 157.3, 149.2, 140.8, 107.4, 99.4ppm. IR(KBr):$\tilde{\upsilon}$=3436, 3317, 3171, 3067, 2925, 2854, 1683, 1623, 1585, 1522, 1466, 1382, 1299,

1240, 1214, 1133, 1091cm^{-1}. MS: calculated for $C_7H_6BrN_4O[M+H]^+$ 240.9/242.9, found 240.9/242.9.

7-Amino-5-bromo-2-methylpyrido [4,3-d] pyrimidin-4(3*H*)-one **(4y)**. This compound was prepared from **3** (3g,13mmol) in triethyl orthoacetate (60mL) was refluxed under N_2 for 24h. After removing the solvent, the residue was dissolved in hot 5N NaOH (20mL) for 30mins and then neutralized with 6N HCl (6–7mL). On cooling, 7-amino-2-methylpyrido[4,3-d]pyrimidin-4(3*H*)-one precipitates out. The yellow solid was filtered off and dried in a vacuum oven, affording the pure title compound (2.4g, 72%) **[Fig 1-(3) to (4y)]**. mp>290^{o}C. ^{1}HNMR (300MHz, DMSO-*d*,25^{o}C):δ=11.81(brs,1H,NH), 6.98 (brs, 2H,NH_2), 6.24(s,1H,8-H), 2.21(s,3H,2-CH_3) ppm. ^{13}C NMR (75MHz,DMSO-*d6*, 25^{o}C):δ=161.6, 159.1, 158.5, 157.6, 140.8, 105.8, 98.8, 21.4 ppm. IR(KBr):ῡ=3306, 3188, 2924,1686,1580, 1467, 1287, 1208, 1133cm^{-1}. MS: calculated for $C_8H_8BrN_4O[M+H]^+$ 254.99/256.99, found 255.0/257.16.

5-Phenyl-4-oxa-1,3,7-triazaphenalen-8-ylamine **(5a)**. To a solution of bis (triphenylphosphine) palladium (II) acetate (6mg, 0.01mmol), **4x** (0.1g, 0.41mmol) and triethylamine (0.415mL) in DMF (8mL) was added a solution of phenylacetylene (0.091mL, 0.83mmol) in DMF (0.3mL) over a period of 30mins. The reaction mixture was refluxed under nitrogen for 1h and then cooled to room temperature. The volatiles were removed under reduced pressure. The crude residue was diluted with dichloromethane and washed with water. The combined organic layers were dried over $MgSO_4$ and evaporated *in vacuum*.

The crude residue was purified by chromatography on silicagel (CH_2Cl_2/MeOH30:1), yielding the pure title compound as a yellowish green solid (52mg,48%) [**Fig 1-(4x) to (5a)]**. mp276^{o}C. ^{1}H NMR (300MHz, DMSO-*d6*, 25^{o}C):δ=8.50(s, 1H, 2-H), 8.03-7.99 (m, 2H, ArH), 7.59-7.54 (m,3H,ArH), 7.31 (s,1H,6-H), 6.98 (brs,2H,NH_2), 6.27(s,1H,9-H) ppm. ^{13}C NMR (75MHz, DMSO-*d6*, 25^{o}C):δ=165.7, 164.3, 160.0, 157.6, 155.9, 153.4, 131.2, 131.8, 129.2, 128.7, 125.7, 106.2, 93.4ppm. IR(KBr):ῡ=3318, 3167, 1645, 1590, 1565, 1133cm^{-1}. MS: calculated for $C_{15}H_{10}N_4O[M+H]^+$ 263.0932, found 263.0930.

5-Cyclohex-1-enyl-2-methyl-4-oxa-1,3,7-triazaphenalen-8-ylamine **(5b)**. To a solution of bis-(triphenylphosphin) palladium (II) acetate (4mg,0.01mmol), CuI (1mg,0.001mmol), **4y** (70mg,0.27mmol) and triethylamine (0.274mL) in DMF (5mL) was added a solution of phenyl acetylene (0.091mL, 0.83mmol) in DMF (0.3mL) over a period of 30mins. The reaction mixture was heated at 70^{o}C under nitrogen for 24h and then cooled to room temperature. The volatiles were removed under reduced pressure. The crude residue was purified by chromatography on silica gel (CH_2Cl_2/MeOH30:1), yielding the pure title compound as a light brown solid (13mg,17%) **[Fig 1-(4y) to (5b)]**. mp228^{o}C. ^{1}H NMR (300MHz, $CDCl_3$, 25^{o}C) δ=7.00 (t,^{3}J=4.6Hz, 1H, cyclohexenyl2-H), 6.48(s,1H,9-H), 6.32(s,1H,6-H), 4.90 (brs,2H,NH_2), 2.63(s,3H,2-CH_3), 2.30-2.27(m, 4H, cyclohexenyl3-H, cyclohexenyl6-H), 1.80-1.70 (m,4H,cyclohexenyl4-H,cyclohexenyl5-H)ppm. ^{13}C NMR (75MHz, $CDCl_3$, 25^{o}C): δ=170.9, 163.1, 159.6, 157.7, 154.2, 150.8,133.3, 128.7,104.2,103.0, 94.53, 27.1, 25.9, 24.2, 22.3, 21.7ppm. IR(KBr):ῡ=3378, 3186, 2925, 2854, 1663, 1648, 1630, 1586, 1567, 1448, 1422, 1349, 1321, 1260, 1223, 1199, 1139, 1080, 1040cm^{-1}. HRMS: calculated for $C_{16}H_{17}N_4O[M+H]^+$ 281.1402, found281.1393.

2-Methyl-5-(3-methyl-3*H*-imidazol-4-yl)-4-oxa-1,3,7-triazaphenalen-8-ylamine **(5c)**. This compound was prepared in a yield of 65%, according to the procedure for the synthesis of compound 5b,

using 5-ethynyl-1-methyl-1*H*-imidazole **[Fig 1 (4y) to (5c)]**. mp>290^{O}C. ^{1}H NMR (300MHz, DMSO-*d6*,25^{O}C):*δ*=7.89 (s, 1H, imidazolyl-H), 7.63 (s, 1H, imidazolyl-H), 6.89 (s,3H,NH,9-H), 6.17 (s,1H,6-H), 3.89 (s, 3H, NCH3), 2.44 (s, 3H, 2-CH3)ppm. ^{13}C NMR (75MHz, DMSO-*d6*, 25^{O}C):*δ*=169.0, 165.2, 164.1, 156.2, 152.7, 150.4, 142.6, 132.4, 105.9, 101.0, 92.8, 33.8, 26.3ppm. IR(KBr):ῦ=3300, 3138, 2925, 2854, 1735, 1645, 1568, 1458, 1349, 1248, 1219, 1129cm^{-1}. HRMS: calculated for $C_{14}H_{13}N_6O[M+H]^+$ found 281.1181.

(8-Amino-2-methyl-4-oxa-1,3,7-triazaphenalen-5-yl)-methanol **(5d)**. This compound was prepared in a yield of 88%, according to the procedure for the synthesis of compound 5b, using proper gylalcohol [**Fig 1-(4y) to (5d)]**. mp>290^{O}C. ^{1}H NMR (300MHz, DMSO-*d*, 25^{O}C):*δ*=6.88 (s,2H,HN), 6.54 (s,1H,9-H), 6.15 (s,1H,6-H), 5.74 (t,^{3}*J*=6.2Hz,1H,OH), 4.34 (d,^{3}*J*=6.2Hz,2H,5-CH), 2.41(s,3H,2-CH3)ppm. ^{13}C NMR (75MHz, DMSO-*d6*, 25^{O}C):*δ*=169.0, 165.6, 164.1, 163.0, 156.4, 152.7, 105.8, 101.1, 92.7, 59.7, 26.4ppm. IR(KBr):ῦ=3413, 3341, 3207, 2924, 2853, 1654, 1624, 1607, 1587, 1573, 1431, 1354, 1274, 1217, 1177, 1131, 1035cm^{-1}. HRMS: calculated for $C_{11}H_{11}N_4O_2[M+H]^+$231.0882, found231.0880.

5-Dimethyl amino methyl-2-methyl-4-oxa-1,3,7-triazaphenalen-8-ylamine **(5e)**. This compound was prepared in a yield of 50%, according to the procedure for the synthesis of compound 5b using 3-dimethylaminopropyne [**Fig 1-(4y) to (5e)]**. mp>290^{O}C. ^{1}H NMR(300MHz, DMSO-*d6*, 25^{O}C):*δ*=6.90(brs, 2H, NH), 6.62(s, 1H, 9-H), 6.17 (s,1H,6-H), 3.57(s,2H,5-CH),2.42(s,3H,2-CH), 2.39(s,6H,-N(CH3)2)ppm. ^{13}C NMR (75MHz, DMSO-*d6*, 25^{O}C):*δ*=169.5, 166.0, 164.3, 163.0, 156.4, 152.6, 111.1, 101.7, 93.4, 58.8, 44.2, 26.5ppm. IR(KBr):ῦ=3413, 2924, 1663, 1618, 1602, 1458, 1384, 1330, 1262, 1119cm^{-1}. HRMS: calculated for $C_{13}H_{16}N_5O[M+H]^+$ 258.1355, found258.1357.

2-Methyl-4-oxa-1,3,7-triazaphenalen-8-ylamine **(5f).** This compound was prepared in a yield of 17%, according to the procedure for the synthesis of compound 5b, using trimethyl silyl acetylene **[Fig 1-(4y) to (5f)]**. mp>290^{O}C. ^{1}H NMR (300MHz, CDOD, 25^{O}C):*δ*=7.90(s, 1H, 9- H), 7.75(d, ^{3}*J*=5.8Hz, 1H, 5-H), 6.67(d,^{3}*J*=5.8Hz, 1H, H-6), 6.33 (s, 2H, NH), 2.50 (s,3H,2-CH)ppm. ^{13}CNMR (75MHz, DMSO-*d6*, 25^{O}C):*δ*=168.9, 162.7, 161.5, 160.1, 152.0, 150.9, 111.0, 102.4, 92.9, 26.2ppm. IR(KBr):ῦ=3327, 3150, 2924, 2854, 1648, 1582, 1452, 1333, 1270, 1221, 1200, 1111, 1045cm^{-1}. HRMS: calculated for $C_{10}H_9N_4O[M+H]^+$201.0776, found 201.0769.

4. Conclusion

In conclusion, we have demonstrated a new series of pyrido[4,3-d]pyrimidine analog ues preparation and this type of chemistry is useful for parallel synthesis of new highly diverse libraries based on the pyrido [4,3-d]pyrimidine scaffold.

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Conflicts of interest

Author has none to declare.

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