A READY ENTRY TO SUBSTITUTED DERIVATIVES OF PYRIDO[3'',2'':4',5']THIENO[2',3':5,6]PYRIDO[2,3-*d*]-PYRIMIDINES, A NEW TETRAHETEROCYCLIC RING SYSTEM

Carlos Peinador, Mª. Carmen Veiga, Vicente Ojea, and José Mª. Quintela*

Departamento de Química Fundamental e Industrial, Facultad de Ciencias, Universidad de La Coruña, Campus de A Zapateira, E-15071, La Coruña, Spain

Abstract- Several 4-substituted pyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido-[2,3-*d*]pyrimidines **(4)** and **(5)** were prepared by reaction of an appropriate substituted thieno[2,3-*b*:4,5-*b*']dipyridine **(2)** and (dichloromethylene)dimethylammonium chloride.

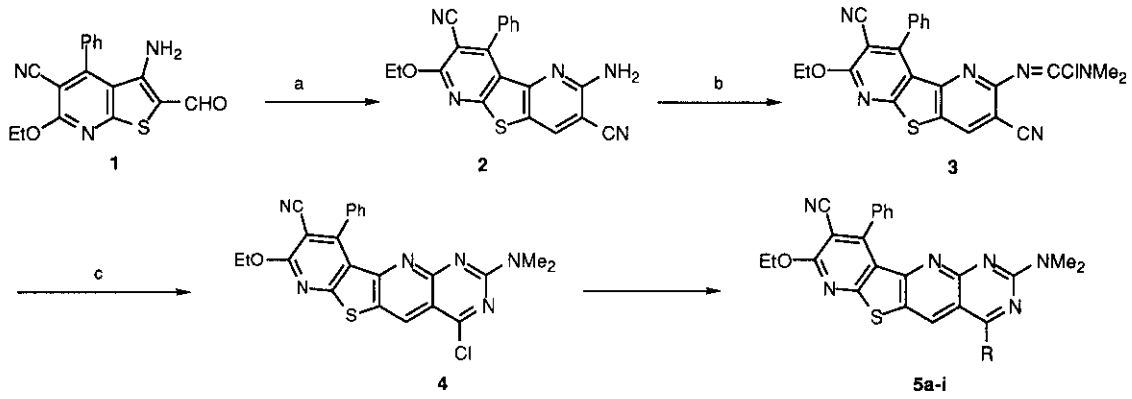
The pyrimidine ring is a frequent partner in polycyclic heterocyclic systems of biological significance.[1] Compounds containing a fused pyrimidine ring make up a broad class that has attracted attention in the past few years owing to its wide range of biological activity. Many potential drugs have been modelled on these compounds, particularly in cancer and virus research.[2] On the other hand, pyridothienopyrimidines, instances of the triheterocyclic ring system, have also attracted attention because of their promising biological activities. These derivatives have analgesic,[3] antipyretic,[4] antianaphilactic[5] and antiinflammatory[6] effects. Also, some are clinically effective antialergic,[7] potentially antineoplastic agents[8] or have a significant hypocholesterolemic[9] activity. This asset prompted us to prepare new polyheterocyclic systems containing the pyridothienopyrimidine moiety with potential biological activity in our search for new compounds of pharmacological interest.[10]

Syntheses for fused bi- and polycyclic compounds by annelation of a pyrimidine ring to an existing ring are high in number and were recently reviewed.[11] The structure of the required starting compounds is mainly determined by the nature of the substituents on the pyrimidine ring; as a rule, systems with an amino group next to another functional group are the most widely used.[11] For this purpose the electrophilic character and structural diversity of methyleneiminium salts have placed them in a prominent position in synthetic chemistry. Succesive replacement of methylene hydrogens with chlorine leads to the dichloromethylene salt first characterized and imaginatively exploited by Viehe *et al.*[12] The chemistry of phosgene iminium salts, which can function as a Vilsmeier or Mannich reagents has proved to be very useful in synthetic chemistry, especially in various one-step heterocyclization reactions by insertion of one carbon atom bearing a

dialkylamino group.[13-17] This paper reports a new method for the preparation of 4-substituted pyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido[2,3-*d*]pyrimidines by reaction of an appropriately substituted thienodipyridine derivative **(2)** and *N,N*-dimethylphosgene iminium salt. The synthetic concept of contructing fused pyrimidines from phosgene iminium salts and *o*-aminonitrile structure has already been applied to the synthesis of chloroquinazolines,[18] but this is, to the best of our knowledge, the first example of the preparation of fused pyrimidines with phosgene iminium salt in which the existing ring is a substituted *ortho*-aminonitrile heterocyclic compound. The substituted derivatives of this previously unknown tetraheterocyclic system are expected to exhibit interesting biological properties.

The readily available 3-aminothieno[2,3-*b*]pyridine carbaldehyde **(1)**[19] was employed as the starting material (Scheme 1). Knoevenagel condensation of **1** with malononitrile afforded the thieno[2,3-*b*:4,5-*b*']dipyridine derivative **(2)** in a 98% yield. Structural elucidation of compound **(2)**

Scheme 1



1 **2** **3** **4** **5a-i**

Reagents. a. $CH_2(CN)_2$, piperidine, THF, room temperature, 15 h
b. $Cl_2CN^+(CH_3)_2Cl^-$, $Cl(CH_2)_2Cl$, reflux, 45 min
c: HCl, $Cl(CH_2)_2Cl$, room temperature

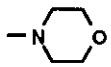
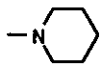
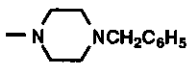
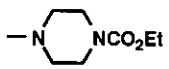
5	R	5	R
a	morpholino	**f**	OPh
b	piperidino	**g**	SPh
c	4-benzylpiperazino	**h**	OEt
d	4-ethoxycarbonylpiperazino	**i**	N_3
e	NHBn		

was accomplished from analitycal and spectral data. The mass spectra showed the expected molecular ion peak and the ir spectra exhibited two absortion bands at ν = 2210 and 2220 cm^{-1} due to the two cyano groups. Formation of the desired *ortho*-aminonitrile compound **(2)** was also confirmed by the ^1H nmr and decoupled ^{13}C nmr spectra. On treatment with (dichloromethylene)-dimethylammonium chloride in refluxing 1,2-dichloroethane, **2** gave the amide halide intermediate **(3)**, which underwent cyclization to the corresponding fused tetraheterocyclic compound **(4)** by reaction with dry hydrogen chloride. The structure of compounds **(3** and **4)** were consistent with their elemental analyses and spectral data. The mass spectra showed the expected molecular ion peak and the ir spectra of **3** exhibited an absortion band at ν = 1630 cm^{-1} due to the imino group,

while the ^{13}C nmr spectra showed two signals at δ = 114.6 and δ = 116.9 due to the two carbon atoms in the cyano groups. By contrast, compound **(4)** showed one absorption band at δ = 114.5 due to the carbon atom in the one cyano group.

Table 1

9-Cyano-8-ethoxy-2-dimethylamino-10-phenyl-4-substituted pyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido[2,3-*d*]pyrimidines **(5a-l)**

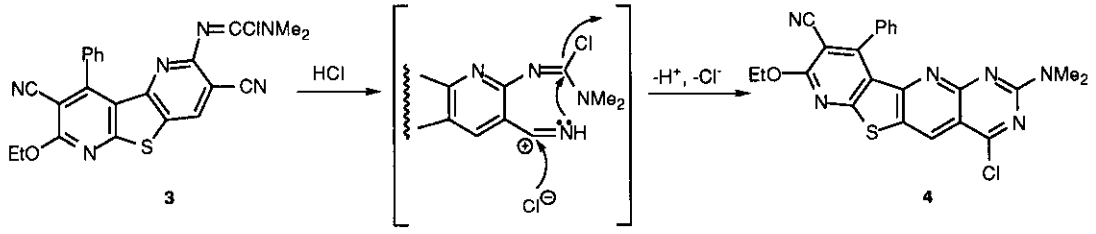
Product	R	mp °C	Yield (%)	Molecular Formula	Analysis (%) Calcd/Found C	H	N
5a		>290	78	$C_{27}H_{25}N_7O_2S$	63.39 63.47	4.93 4.78	19.17 19 05
5b		252-254	85	$C_{28}H_{27}N_7OS$	65 99 66.12	5.34 5.21	19 24 19.39
5c		215-217	86	$C_{34}H_{32}N_8OS$	67.98 68.11	5 37 5.42	18.65 18 71
5d		>290	75	$C_{30}H_{30}N_8O_3S$	61 84 61.92	5.19 4.98	19 23 19.27
5e	**NHBn**	>290	86	$C_{30}H_{25}N_7OS$	67.78 67 95	4.74 4.57	18.44 18.25
5f	**OPh**	274-276	90	$C_{29}H_{22}N_6O_2S$	67.17 67.29	4.28 4.12	16.21 16 27
5g	**SPh**	276-278	86	$C_{29}H_{22}N_6OS_2$	65.15 65.35	4.15 4.01	15.72 15.60
5h	**OEt**	278-280	90	$C_{25}H_{22}N_6O_2S$	63.81 63.65	4.71 4.86	17.86 17.68
5i	**N_3**	290-292[a]	65	$C_{23}H_{17}N_9OS$	59.09 59.20	3.67 3.78	26.96 27.01

a Decomposition.

Dichloromethyleneiminium salts are known to undergo condensation with CH-acidic compounds such as ketones, carboxylic acid and chlorides, nitriles and amides to give amide halides.[17] Amide

chlorides have been similarly obtained from enamines,[20] fulvenes,[21] barbituric acid derivatives[22] and pyridopyrimidines[23] by reaction with phosgene iminium salts. On the other hand, phosgeneniminium salts do no react with the nitrile group unless it is sufficiently activated or the salts are previously transformed into chloroiminiun chlorides by means of dry hydrogen chloride. Since the intermediate adduct **(3)** was isolated the reaction can be assumed to proceed as follows :[15]

Scheme 2



3 4

The chloride bearing group in the polycyclic compound **(4)** reacts readily with nucleophilic agents to give the corresponding substituted products **(5a-i)** in good yields. The structures of these compounds were determined from microanalytical and spectral data (Tables 1 and 2).

Table 2

9-Cyano-8-ethoxy-2-dimethylamino-10-phenyl-4-substituted pyrido[3",2".4',5']thieno[2',3':5,6]pyrido[2,3-*d*]pyrimidines **(5a-i)**

Product	Ir (KBr) ν (cm^{-1})	Ms (70 eV) m/z (%)	^{1}H Nmr (CCl_3D/TMS) δ, J (Hz)[a]	^{13}C Nmr (CCl_3D/TMS)[b] δ
5a	2220 (CN), 1540, 1410, 1345	511 (M^+, 100), 509 (12), 496 (23), 482 (11)	3.19 (s, 6H, $N(CH_3)_2$), 3.64 (t, 4H, J = 4 5, $2CH_2$), 3.85 (t, 4H, J = 4.5, $2CH_2$), 7.57 (s, 5H, C_6H_5), 8.28 (s, 1H, H-5)	50.5 (NCH_2), 66.6 (OCH_2), 104.2 (C-4a), 119.0 (C-10a), 122.4 (C-5a), 128.0, 129.3, 129.8, 133.3, 154.9, 155.6, 160.1, 160.4, 164.0, 165.5, 167.3
5b	2220 (CN), 1540, 1410, 1345	509 (M^+, 67), 494 (22), 466 (18), 213 (15)	1.76 (br s, 6H, $(CH_2)_3$), 3.19 (s, 6H, $N(CH_3)_2$), 3.61 (br s, 4H, CH_2NCH_2), 7 60 (s, 5H, C_6H_5), 8.28 (s, 1H, H-5)	24.7 (CH_2), 25.8 (CH_2), 51.1 (NCH_2), 104.6 (C-4a), 119.1 (C-10a), 122.0 (C-5a), 128.2, 129.3, 129.7, 133.4, 154.4, 155.4, 160.2, 160.6, 163.8, 165.5, 167.2
5c	2220 (CN), 1565, 1540, 1400, 1345	600 (M^+, 3), 518 (2), 481 (3)	2.63 (br s, 4H, CH_2NCH_2), 3.18 (s, 6H, $N(CH_3)_2$), 3 58 (s, 2H, $CH_2C_6H_5$), 3 68 (br s, 4H, CH_2NCH_2), 7.29-7.35 (m, 5H, C_6H_5), 7.58 (s, 5H, C_6H_5), 8.28 (s, 1H, H-5)	50.0 (CH_2), 52.7 (CH_2), 63.0 (CH_2), 104.4 (C-4a), 119.1 (C-10a), 122.1 (C-5a), 127.2, 127.9, 128.3, 129.1, 129.4, 129.7, 133.2, 137.6, 154.7, 155.6, 160.1, 160.6, 164.0, 165.3, 167.2

5d	2220 (CN), 1700 (CO), 1540, 1410	582 (M^+, 26), 509 (7), 454 (10)	1.28 (t, 3H, J = 7.1, CH_3), 3.17 (s, 6H, $N(CH_3)_2$), 3.64 (br s, 8H, CH_2NCH_2), 4.18 (q, 2H, J = 7.1, OCH_2), 7.57 (s, 5H, C_6H_5), 8 26 (s, 1H, H-5)	14 6 (CH_3), 43.2 (NCH_2), 49.7 (NCH_2), 61.6 (OCH_2), 104.2 (C-4a), 118.9 (C-10a), 122.4 (C-5a), 127.9, 129.3, 129.7, 133 2, 154.8, 155.4, 155.5, 160.0, 160.3, 163.9, 165.4, 167.3
5e	3280 (NH), 2220 (CN), 1570, 1540, 1400	531 (M^+, 33), 516 (17), 326 (12)	3.17 (s, 6H, $N(CH_3)_2$), 4.75 (d, 2H, J = 5.3, CH_2-C_6H_5), 5,80[c] (t, 1H, J = 5.3, NH), 7.29-7.61 (m, 10H, $2C_6H_5$), 8.15 (s, 1H, H-5)	[d]
5f	2220 (CN), 1620, 1540, 1400	518 (M^+, 4)	2 96 (s, 3H, NCH_3), 3.12 (s, 3H, NCH_3), 7 25-7 62 (m, 10H, $2C_6H_5$), 8.76 (s, 1H, H-5)	103.6 (C-4a), 119.0 (C-10a), 121.8 (C-5a), 124 0, 125.6, 127 9, 129 3, 129.4, 129.6, 133.3, 152.3, 155.9, 156.0, 159.7, 160.2, 164.0, 166 2, 167.5
5g	2220 (CN), 1570, 1540, 1500, 1400	534 (M^+, 50), 489 (19), 353 (20)	2.80 (s, 3H, NCH_3), 3 06 (s, 3H, NCH_3), 7.43-7.62 (m, 10H, $2C_6H_5$), 8.58 (s, 1H, H-5)	110.1 (C-4a), 118.8 (C-10a), 123.9 (C-5a), 127.2, 127.9, 129.0, 129.4, 129 5, 129.7, 133.1, 136.0, 155.9, 156.2, 157.0, 159.5, 164.2, 167.7, 171.4
5h	2220 (CN), 1600, 1550, 1390, 1345	470 (M^+, 40), 441 (15), 413 (7), 399 (6), 207 (19)	1.48 (t, 3H, J = 7.1, CH_3), 3.21 (s, 6H, $N(CH_3)_2$), 4 55 (q, 2H, J = 7.1, OCH_2), 7 60 (s, 5H, C_6H_5), 8.56 (s, 1H, H-5)	14.2 (CH_3), 63.1 (OCH_2), 104.2 (C-4a), 119.1 (C-10a), 123.7 (C-5a), 128.0, 129.3, 129.7, 133.4, 155 5, 155 7, 159.4, 160.7, 163.9, 166.3, 167.4
5i	2220 (CN), 2120 (N_3), 1620, 1540	467 (M^+, 3)	3.24[e] (s, 3.6H, $N(CH_3)_2$), 3.62 (s, 2.4H, $N(CH_3)_2$), 7.60 (s, 5H, C_6H_5), 8.43 (s, 0.6H, H-5), 9.07 (s, 0.4H, H-5)	

[a] The ^{1}H nmr spectra of compounds **(5a-i)** exhibit typical absortions signals for OCH_2CH_3 [1.51-1.54 (t, 3H, J = 7.1, $OCH_2\mathbf{CH_3}$), 4.64-4 67 (q, 2H, J = 7.1, $OC\mathbf{H_2}CH_3$)].

[b] The ^{13}C nmr spectra of compounds **(5a-d)** and **(5f-h)** exhibit typical absortions signals for OCH_2CH_3 [14.2-14.4, ($OCH_2\mathbf{CH_3}$), 64.3-64.5 ($O\mathbf{CH_2}CH_3$)], $N(CH_3)_2$ [36 5-37.0], C-5 [126.8-128 1], C-9 [95 7-95 9], CN [114.6-114.9].

[c] Exchangeable with D_2O.

[d] **5e** is insoluble in most common nmr solvents.

[e] Signals ratios of the ^{1}H nmr spectra of **5i** indicate equilibrium mixture with the tetrazole isomeric form.

As shown above, the reaction of *ortho*-aminocyanothienodipyridine with (dichloromethylene)-dimethylammonium chloride provides a general entry to substituted derivatives of pyrido-[3'',2'':4',5']thieno[2',3':5,6]pyrido[2,3-*d*]pyrimidine.

EXPERIMENTAL SECTION

All reagents used were commercial grade chemicals from freshly opened containers. Melting points were determined on a Büchi 510 apparatus and are reported uncorrected. Ir spectra were recorded on potassium bromide disks on a Perkin-Elmer 383 spectrophotometer. ^{1}H and ^{13}C nmr spectra were obtained on a Bruker AC200F instrument at room temperature. Mass spectra were obtained at 70 eV by using a VG4 spectrometer. The Silica gel 60 $HF_{254+366}$ used for analytical thin layer chromatography and the Silica gel 60 (230-400 mesh) employed for medium-pressure chromatography (MPLC) were purchased from Merck. Microanalyses for C, H, and N were performed by the Elemental Analyses General Service of the University of La Coruña.

2-Amino-3,8-dicyano-7-ethoxy-9-phenylthieno[2,3-*b*:4,5-*b*']dipyridine (2):

A solution of **1** (2.25 g, 7.0 mmol), malononitrile (0.51 g, 7.7 mmol) and piperidine (1.40 ml) in THF (100 ml) was stirred at room temperature for 15 h. The solvent was removed under reduced pressure and the resulting solid was recrystallized from acetone to obtain **2** (2 56 g, 98%); mp 275-277 °C Ir (KBr) ν 3460 (NH), 3340 (NH), 2220 (CN), 2210 (CN), 1620, 1550 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 1.53 (t, 3H, J = 7.1 Hz, CH_3), 4.66 (q, 2H, J = 7.1 Hz, CH_2O), 4.79 (br s, 2H, NH_2), 7.44-7.54 (m, 5H, C_6H_5), 8 06 (s, 1H, H-4). ^{13}C Nmr ($CDCl_3$)· δ 14.4 (CH_3), 64.7 (OCH_2), 90 0 (C-3), 96.1 (C-8), 114.5 (CN), 116.4 (CN), 118.5 (C-9a), 120.1, 127.9, 129.0, 129.7, 133.3, 135.4 (C-4), 152.3, 155.3, 156.4, 163.8, 166.8. Ms (DEI): *m/z* (%) 371 (M^+, 100), 370 (26), 342 (89), 315 (17) *Anal.* Calcd for $C_{20}H_{13}N_5OS$: C, 64.68; H, 3.53; N, 18.86. Found: C, 64.49; H, 3.67; N, 18.71.

2-(Chlorodimethylaminomethyleneamino)-3,8-dicyano-7-ethoxy-9-phenylthieno[2,3-*b*:4,5-*b*']-dipyridine (3):

A solution of **2** (0.50 g, 1.3 mmol) and phosgene iminium salt (0.26 g, 1.6 mmol) in 1,2-dichloroethane (20 ml) was refluxed for 45 min. The solvent was removed under reduced pressure and the resulting solid was purified by MPLC using dichloromethane/hexane (3.1) as eluent to obtain **3** (0.43 g, 70%), mp 265-267 °C (decomp.). Ir (KBr). ν 2220 (CN), 1630, 1550, 1400, 1330 cm^{-1} ^{1}H Nmr ($CDCl_3$): δ 1.53 (t, 3H, J = 7.1 Hz, CH_3), 3 18 (s, 6H, $N(CH_3)_2$), 4.67 (q, 2H, J = 7.1 Hz, CH_2O), 7.47 (s, 5H, C_6H_5), 8.22 (s, 1H, H-4). ^{13}C Nmr ($CDCl_3$): δ 14.4 (CH_3), 40.1 ($N(CH_3)_2$), 64.6 (OCH_2), 96.3 (C-8), 101.1 (C-3), 114.6 (CN), 116.9 (CN), 119.2 (C-9a), 124.1, 127.9, 128.2, 129 3, 133.2, 135.3 (C-4), 141.9, 151.2, 155.5, 158.1, 163.7, 166.4. Ms (DEI): *m/z* (%) 460 (M^+, 10), 425 (14), 370 (12). *Anal.* Calcd for $C_{23}H_{17}N_6OClS$: C, 59.93; H, 3.72; N, 18.23. Found: C, 60.09; H, 3.59, N, 18 16.

4-Chloro-9-cyano-8-ethoxy-2-dimethylamino-10-phenylpyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido-[2,3-*d*]pyrimidine (4):

A stream of dry hydrogen chloride was passed through a mixture of **3** (0 20 g, 0.43 mmol) in 1,2-dichloroethane (10 ml) for 3 h. The reaction mixture was allowed to stand overnight at room temperature. The solvent was then removed under reduced pressure and the resulting solid was purified by MPLC using dichloromethane as eluent to obtain **4** (0.15 g, 75%); mp 288-290 °C (decomp.). Ir (KBr). ν 2210 (CN), 1590, 1560, 1400, 1390, 1320 cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 1.56 (t, 3H, J = 7.1 Hz, CH_3), 3.25 (s, 6H, $N(CH_3)_2$), 4.70 (q, 2H, J = 7 1 Hz, CH_2O), 7.59-7.61 (m, 5H, C_6H_5), 8.61 (s, 1H, H-4). ^{13}C Nmr ($CDCl_3$): δ 14.4 (CH_3), 37.2 ($N(CH_3)_2$), 64.8 (OCH_2), 96.2 (C-9), 110.3, 114.5 (CN), 118.5 (C-10a), 125.5, 128.0,

129.3, 129.8, 133.0, 156.3, 157 3, 158.4, 159 7, 161.8, 164 4, 168.1. Ms (DEI): *m/z* (%) 462 (M^++2, 18), 460 (M^+, 62), 216 (11). *Anal.* Calcd for $C_{23}H_{17}N_6OClS$: C, 59.93, H, 3.72; N, 18 23. Found: C, 60.13; H, 3.80, N, 18.36.

9-Cyano-8-ethoxy-2-dimethylamino-10-phenyl-4-substituted Pyrido[3'',2'':4',5']thieno[2',3':5,6]-pyrido[2,3-*d*]pyrimidines 5a-e; General Procedure:

A solution of **4** (0 44 mmol) and the appropriate amine (0 66 mmol) in EtOH/dichloromethane (3:2) (10 ml) was refluxed for 6 h. The solid obtained was then filtered off and recrystallized from EtOH/dichloromethane. (Tables 1 and 2).

9-Cyano-8-ethoxy-2-dimethylamino-10-phenyl-4-substituted Pyrido[3'',2'':4',5']thieno[2',3':5,6]-pyrido[2,3-*d*]pyrimidines 5f, 5g; General Procedure:

A solution of **4** (0.44 mmol), phenol or thiophenol (0.66 mmol) and a few drops of KOH (10% ethanolic) in THF (10 ml) was refluxed for 1 h. The solid formed was filtered off and recrystallized from EtOH/dichloromethane. (Tables 1 and 2).

9-Cyano-4,8-diethoxy-2-dimethylamino-10-phenylpyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido[2,3-*d*]pyrimidine (5h):

A mixture of **4** (0.10 g, 0.22 mmol) and an excess of sodium ethoxide in EtOH (20 ml) was refluxed for 1 h The solid was filtered off and recrystallized from EtOH/dichloromethane. (Tables 1 and 2).

4-Azido-9-cyano-8-ethoxy-2-dimethylamino-10-phenylpyrido[3'',2'':4',5']thieno[2',3':5,6]pyrido-[2,3-*d*]pyrimidine (5i):

To a mixtue of **4** (0.20 g, 0.44 mmol) in DMSO (5 ml) was added sodium azide (0 03 g, 0.53 mmol) in water (0.2 ml). The reaction mixture was stirred at room temperature for 24 h and water (30 ml) was then added. The solid formed was finally filtered off and recrystallized from EtOH/dichloromethane (Tables 1 and 2).

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