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Study on the cyclization of 6-arylethynylpyrimidine-5-carbaldehydes with *tert*-butylamine: microwave versus thermal preparation of pyrido[4,3-*d*]pyrimidines

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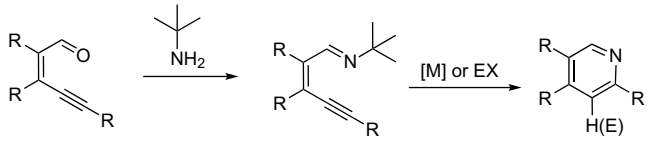
ABSTRACT

Thermal and microwave initiated cyclization of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes with *tert*-butylamine has been studied. A novel high-yielding preparation of 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines has been developed. The intermediate compounds were isolated and possible mechanism of the reactions is discussed.

1. Introduction

Functionally substituted alkynes are versatile intermediates in the synthesis of heterocyclic or carbocyclic compounds.[1] A literature survey revealed that intramolecular cyclization of alkynes, which contain a nucleophile in close proximity to the carbon–carbon triple bond is extremely effective for the synthesis of a wide variety of heterocycles.[2] Several years ago, Larock's group reported about interesting transition metal-mediated[3] or electrophile-induced[4] cyclization of *N*-*tert*-butyl-*o*-(1-alkynyl)benzaldimines and their analogs. These methods are very effective for the synthesis of a wide variety of isoquinolines, pyridines, and naphthyridines (Scheme 1).



Scheme 1. Literature results overview.

In our research, which was aimed at the use of 6-arylethynylpyrimidines for the synthesis of fused pyrimidine derivatives,[5] we have successfully applied Larock's method for the synthesis of the pyrido[4,3-*d*]pyrimidine heterosystem by the intramolecular cyclization of 4-amino-5-*N*-*tert*-butyliminomethyl-2-methylthio-6-phenylethynylpyrimidine catalyzed by $AgNO_3$.[6] However, on the way to explore the scope of the formation of the pyrido[4,3-*d*]pyrimidine system and to synthesize more derivatives with potential biological activity,[7] we have found recently that some 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes, bearing *N*-alkylamino- or *N*,*N*-dialkylamino groups in position 4 of the pyrimidine ring, underwent unexpected thermal cyclization with *tert*-butylamine to produce 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines in good yields in the absence of any catalysts. The intermediate compounds were isolated and possible mechanisms of the reactions were discussed.[8] In this paper we wish to report results of our more extensive investigations.

2. Results and discussion

The starting compounds **2a**–**t** were synthesized by the palladium-catalyzed Sonagashira coupling of the corresponding 2,4-disubstituted 6-chloropyrimidine-5-carbaldehydes[9] **1a**–**t** with 1-arylacetylenes according to procedure described earlier (Scheme 2, Table 1).[5c,d]

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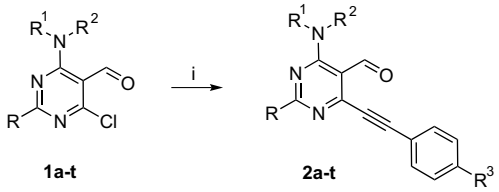


Scheme 2. Reagents: (i) 1-arylacetylene (1.2 equiv), $PdCl_2(PPh_3)_2$ (2 mol %), CuI (1 mol %), Et_3N, DMF, Ar, 40 °C, 2–4 h.

Table 1
Data of the synthesis of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **2a–t**

Entry	Starting comp.	R	NR^1R^2	Product	R^3	Yield, %
1	**1a**	SCH_3	NH_2	**2a**	H	42
2	**1b**	SCH_3	NH_2	**2b**	C_2H_5	45
3	**1c**	SCH_3	$NHCH_3$	**2c**	H	85
4	**1d**	SCH_3	NHC_2H_5	**2d**	H	59
5	**1e**	SCH_3	$N(CH_2)_4O$	**2e**	H	80
6	**1f**	SCH_3	$N(CH_2)_5$	**2f**	H	85
7	**1g**	SCH_3	NHC_6H_5	**2g**	H	82
8	**1h**	SCH_3	NHC_6H_5	**2h**	C_2H_5	75
9	**1i**	SCH_3	$NHCH_2C_6H_5$	**2i**	H	82
10	**1j**	SCH_3	$N(CH_3)_2$	**2j**	H	66
11	**1k**	SCH_3	$N(CH_2)_4$	**2k**	H	90
12	**1l**	SCH_3	$N(CH_2)_4$	**2l**	C_2H_5	89
13	**1m**	SCH_3	$N(CH_2)_4$	**2m**	F	82
14	**1n**	SCH_3	$N(CH_2)_4O$	**2n**	C_2H_5	88
15	**1o**	SCH_3	$N(CH_2)_4O$	**2o**	F	85
16	**1p**	SCH_3	$N(CH_2)_5$	**2p**	C_2H_5	56
17	**1q**	H	$NHCH_2C_6H_5$	**2q**	H	74
18	**1r**	H	$NHCH_2C_6H_5$	**2r**	C_2H_5	63
19	**1s**	H	$N(CH_2)_4$	**2s**	H	45
20	**1t**	H	$N(CH_2)_4O$	**2t**	H	65

In order to study the generality of the preparation of the pyrido[4,3-*d*]pyrimidine framework via a one-pot synthetic method from 2,4-disubstituted 6-arylethynylpyridopyrimidines and *tert*-butylamine, several starting compounds bearing substituents possessing different steric and electronical properties in position 4 of the pyrimidine ring were chosen and their reactions with *tert*-butylamine under different conditions were studied. The reaction of title compounds with *tert*-butylamine revealed a variety of behaviors depending on reaction conditions. The results are summarized in Figure 1 and Table 2.

Thus, compounds **2a**,**b** bearing a primary amino group in position 4 of the pyrimidine ring, treated with *tert*-butylamine in sealed tube at 80–90 °C temperature, gave the corresponding 4-amino-6-arylethynyl-5-*N*-*tert*-butyliminomethyl-2-methylthiopyrimidines **3a**,**b** (conditions 1, entries 1 and 2). These were the only two examples of the selective formation of logically expected[3,4] *tert*-butylimines **3**. When the reaction of the other 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes (**1c**–**h**) with an excess of *tert*-butylamine in sealed tubes at 80–90 °C was performed, we have found that not only the reaction of *tert*-butylamine with the carbonyl

Table 2
Optimization of the synthesis of 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines

Entry	Starting comp.	Conditions 1		Conditions 2		Conditions 3	
		tert-$BuNH_2$, sealed tube, 80–90 °C		*tert*-$BuNH_2$, sealed tube, 120–130 °C		*tert*-$BuNH_2$, DMF, microwave oven, 500 W	
		Product	Yield, %	Product	Yield, %	Product	Yield, %
1	**2a**	**3a**	93[a]	**5a**	25[b]	**5a**	95[c]
2	**2b**	**3b**	93[a]	**5b**	18[b]	**5b**	90[c]
3	**2c**	**4c**	60[a]	**5c**	80[b]	**5c**	91[c]
4	**2d**	**4d**	58[a]	**5d**	80[a]	**5d**	92[c]
5	**2e**	**4e**	62[a]	**5e**	95[a]	**5e**	98[d]
6	**2f**	**4f**	58[a]	**5f**	85[a]	**5f**	97[d]
7	**2g**	**4g**	24[a]	**4g**	75[a]	**5g**	97[e]
8	**2h**	**4h**	20[a]	**4h**	72[a]	**5h**	96[e]

[a] Reaction time: 24 h.
[b] Reaction time: 48 h.
[c] Reaction time: 20 min.
[d] Reaction time: 10 min.
[e] Reaction time: 1 h.

moiety, but also a 1,2-addition of the second *tert*-butylamine molecule to the C≡C bond took place, leading to a formation of yellow colored products **4c**–**h** (conditions 1, entries 3–8). The stereochemistry of addition of nucleophiles to the C≡C bond of 6-arylethynylpyrimidines has been studied and reported in our previous paper.[10] When the same reactions proceeded under higher (120–130 °C) temperatures, compounds **1a**–**f** converted to the corresponding 7-arylpyrido[4,3-*d*]pyrimidines **5a**–**f** (conditions 2, entries 1–6). It is noteworthy that formation of 4-amino-2-methylthiopyrido[4,3-*d*]pyrimidines **5a**,**b** was slower and the yields of the obtained products were low (conditions 2, entries 1 and 2). On the other hand, heating of the corresponding 4-anilino-6-arylethynyl-2-methylthiopyrimido-5-carbaldehydes **1g**,**h** with an excess of *tert*-butylamine in sealed tubes at 120–130 °C did not lead to the formation of 4-anilino-7-aryl-2-methylthiopyrido[4,3-*d*]pyrimidines (**5g**,**h**), but formation of the intermediates **4g**,**h** was observed (conditions 2, entries 7 and 8). To our pleasant surprise, when solutions of compounds **1a**–**h** and *tert*-butylamine in dimethylformamide were irradiated in a microwave oven, after 10–60 min a high-yielding formation of 2,4-disubstituted 7-arylpyrido[4,3-*d*]-pyrimidines (**5a**–**h**) was observed (conditions 3, entries 1–8). Thus, we have optimized an efficient, concise, and high-yielding method of synthesis of 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines from 2,4-disubstituted 6-arylethynylpyridopyrimidines and *tert*-butylamine. According to the present methodology, we have prepared various 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines **5a**–**t** via the thermal reaction of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **1a**–**t** with *tert*-butylamine. The results are summarized in Scheme 3 and Table 3.

In our previous report[8] we have shown that the cyclization of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **2** with *tert*-butylamine proceeded via *N*-(*tert*-butyl)-*N*-{4-[(*Z*)-2-aryl-2-(*tert*-butylamino)vinyl]pyrimidin-5-yl}methyleneamines **4**.

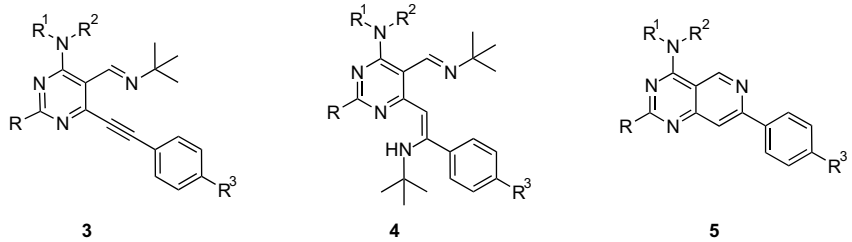
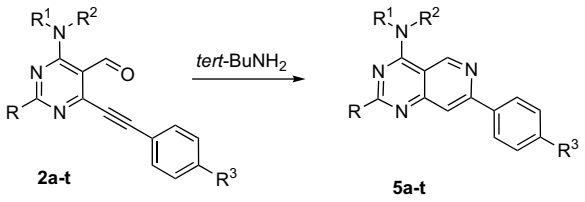


Figure 1. Products of the reactions of 2,4-disubstituted-6-arylethynylpyrimidine-5-carbaldehydes (**2**) with *tert*-butylamine.



Scheme 3.

Table 3
Data of the synthesis of 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines **5a**–**t**

Entry	Starting comp.	R	NR^1R^2	R^3	Product	Method A[a]	Method B[b]
						Yield, %	Yield, %
1	**2a**	SCH_3	NH_2	H	**5a**	25	95
2	**2b**	SCH_3	NH_2	C_2H_5	**5b**	18	90
3	**2c**	SCH_3	$NHCH_3$	H	**5c**	80	91
4	**2d**	SCH_3	NHC_2H_5	H	**5d**	80	92
5	**2e**	SCH_3	$N(CH_2)_4O$	H	**5e**	95	98
6	**2f**	SCH_3	$N(CH_2)_5$	H	**5f**	85	97
7	**2g**	SCH_3	NHC_6H_5	H	**5g**	0[c]	97
8	**2h**	SCH_3	NHC_6H_5	C_2H_5	**5h**	0[c]	96
9	**2i**	SCH_3	$NHCH_2C_6H_5$	H	**5i**	81	98
10	**2j**	SCH_3	$N(CH_3)_2$	H	**5j**	92	100
11	**2k**	SCH_3	$N(CH_2)_4$	H	**5k**	89	100
12	**2l**	SCH_3	$N(CH_2)_4$	C_2H_5	**5l**	91	94
13	**2m**	SCH_3	$N(CH_2)_4$	F	**5m**	92	95
14	**2n**	SCH_3	$N(CH_2)_4O$	C_2H_5	**5n**	90	95
15	**2o**	SCH_3	$N(CH_2)_4O$	F	**5o**	92	97
16	**2p**	SCH_3	$N(CH_2)_5$	C_2H_5	**5p**	87	93
17	**2q**	H	$NHCH_2C_6H_5$	H	**5q**	80	95
18	**2r**	H	$NHCH_2C_6H_5$	C_2H_5	**5r**	91	96
19	**2s**	H	$N(CH_2)_4$	H	**5s**	95	100
20	**2t**	H	$N(CH_2)_4O$	H	**5t**	89	99

[a] Method A: *tert*-butylamine, sealed tube, 120–130 °C, 24–48 h.
[b] Method B: *tert*-butylamine (10 equiv), DMF, microwave oven, 500 W, 10–60 min.
[c] Intermediates **4g**,**h** were formed, instead.

The possible mechanism is presented in Scheme 4. We assume that intermediate adducts **4** underwent a 1,6-electrocyclic reaction to form a six-membered ring. The aromatization of cyclic adduct leads to elimination of *tert*-butylamine and 2-methylpropene molecules.

4-Amino-6-arylethynyl-5-*N*-*tert*-butyliminomethyl-2-methylthiopyrimidines **3a**,**b** during heating in DMF either at 120–130 °C or in the microwave oven at 500–700 W did not undergo intramolecular catalyst-free cyclization into compounds **5a**,**b**. Cyclization of **3a**,**b** was successful only in the presence of an equivalent of *tert*-butylamine in DMF. So we believe that in latter case the formation of the intermediate *N*-(*tert*-butyl)-*N*-{4-[(*Z*)-2-aryl-2-(*tert*-butylamino)vinyl]pyrimidin-5-yl}methyleneamines **4a**,**b** proceeded followed by 1,6-electrocyclic reaction and aromatization to 4-amino-7-aryl-2-methylthiopyrido[4,3-*d*]pyrimidines **5a**,**b** (Scheme 4).

Table 4
Rates of the intramolecular cyclizations of *N*-(*tert*-butyl)-*N*-{4-[(*Z*)-2-aryl-2-(*tert*-butylamino)vinyl]pyrimidin-5-yl}methyleneamines **4** under various conditions[a]

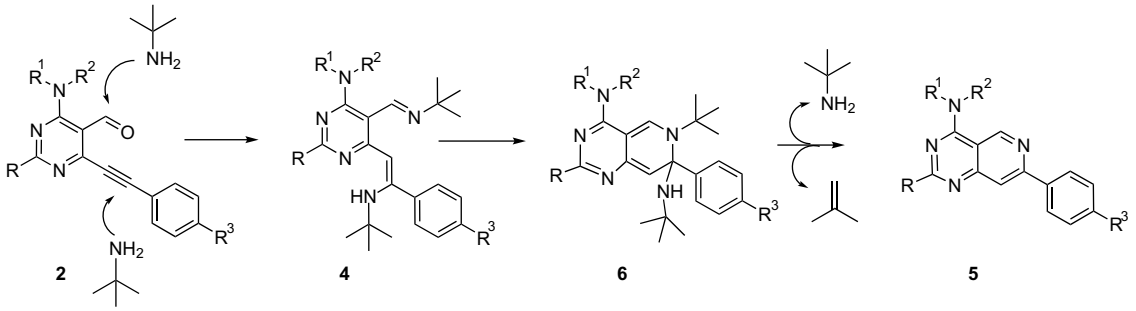
Entry	Comp.	*tert*-$BuNH_2$, 120 °C	DMF, 120 °C	2-PrOH, reflux	Xylene, reflux	DMF, MW, 500 W
1	**4d**	10 h	30 min	6 h	3 h	20 min
2	**4e**	3 h	10 min	3 h	1.5 h	5 min
3	**4g**	n/a	n/a	n/a	n/a	40 min

[a] Reactions were analyzed by TLC.

It is noteworthy that the reaction rates depend on the nature of the substituent in position 4 of the pyrimidine ring. Thus, the shortest reaction times were for the 4-*N*,*N*-dialkylamino derivatives, and the longest—for the 4-anilino derivatives. We have studied the influence of solvent on cyclization rates of intermediates **4d**,**e**,**g**. The results are summarized in Table 4. The most suitable solvent for the cyclization of the intermediates **4** under either convectional or microwave-induced heating was dimethylformamide, followed by *p*-xylene. On the other hand, 2-propanol and *tert*-butylamine seemed to be less effective. It should be noted that the cyclization of the intermediate adduct **4g** bearing an anilino substituent in position 4 of the pyrimidine ring did not undergo cyclization into 4-anilino-2-methylthio-7-phenylpyrido[4,3-*d*]pyrimidine **5g** under conventional heating conditions. The satisfactory result was obtained only when compound **4g** was dissolved in dimethylformamide and heated using microwave irradiation (last column in Table 4).

We assumed that different cyclization rates could depend mainly on the different conformations of the intermediates **4**. So intermediates **4c** (NR^1R^2=$NHCH_3$), **4g** (NR^1R^2=NHC_6H_5), and **4j** (NR^1R^2=$N(CH_3)_2$) were chosen and explored computationally. Compounds **4c** and **4j** were selected to model the compounds **4d** and **4e**, respectively, to reduce the size of calculations and for the sake of simplicity. Because of their flexibility, compounds **4** exhibit especial richness of conformations. Several important rotamers are shown in Figure 2. We did not attempt to explore all conformational space exhaustively. Instead, only what we deemed to be important rotamers were optimized, based on the rotation (flipping) of the *tert*-butylimino and vinyl substituents with respect to the plane of the pyrimidine ring. For example, we did not look for conformers, which involve flipping of R and NR^1R^2 substituents in Figure 2. However, the latter substituent was normally selected in a conformation, which maximized the number of formed hydrogen bonds (where applicable).

Table 5 contains the data of calculated relative energies of rotamers of compounds **4c**, **4g**, and **4j**. Analysis of the geometries of the rotamers shows that the energy levels appear to be influenced by the number and strength of the intramolecular hydrogen bonds formed. The lowest energy rotamer **4_2** for **4c** and **4g** has two intramolecular hydrogen bonds while lowest conformer of **4j**–**4_1j** has only one hydrogen bond and the *tert*-butylimino moiety is



Scheme 4.

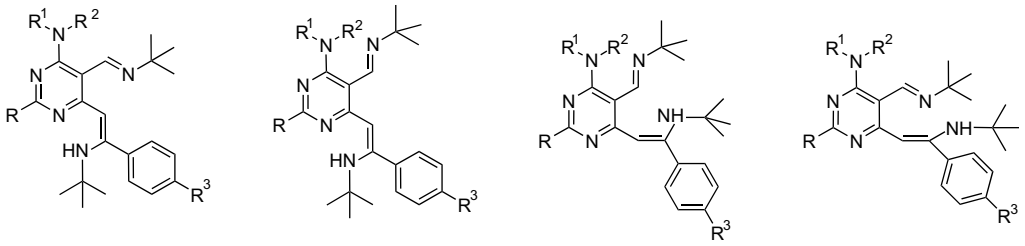


Figure 2. Possible conformers of compounds **4**.

Table 5
Energies of important rotamers of **4c**, **4g**, and **4j**[a]

Entry	Comp.	NR^1R^2	**4_1**	**4_2**	**4_3**	**4_4**
1	**4c**	$NHCH_3$	7.7 (8.6)	0.0 (0.0)	6.0 (6.2)	15.6 (16.8)
2	**4g**	NHC_6H_5	8.6 (9.4)	0.0 (0.0)	5.7 (5.8)	16.4 (17.3)
3	**4j**	$N(CH_3)_2$	0.0 (0.0)	1.8 (1.7)	8.3 (8.5)	6.0 (6.2)

[a] The lowest energy conformer is attributed zero energy. The numbers refer to relative energies in kcal/mol at DFT-PCM//DFT level, with DFT//DFT result shown in parentheses.

turned away from bulky *N*,*N*-dimethylamino group. Comparison of **4_1** and **4_2** rotamers for **4c** and **4g** in Table 5 seems to suggest that the hydrogen bond between NHR and the imino nitrogen is stronger by about 1 kcal/mol for **4g** compared to **4c**. This is consistent with observation that the phenyl amine hydrogen is more acidic compared to the aliphatic. It is of interest to note that only conformation **4_4** directly leads to cyclization since for the new bond to be formed both *tert*-butylimino and vinyl moieties have to face each other. For **4c** and **4g**, this rotamer has a relatively high energy. The rotamer **4_4j** has a similar geometry to analogous rotamers of **4_4c** and **4_4g**. However, the former rotamer's energy is relatively closer to the lowest energy rotamer compared to **4_4c** and **4_4g** (6.2 vs 16.8 and 17.3 kcal/mol) because of lower number of hydrogen bonds formed in the lowest energy conformation, as discussed above.

More detailed DFT calculations of these reactions will be published in due course.

3. Conclusions

In summary, we have developed a novel, concise, and high-yielding synthetic method of pyrido[4,3-*d*]pyrimidine framework via thermal or microwave-induced cyclization of 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes with *tert*-butylamine. The possible mechanism of the cyclization is proposed and the evidence has been established by isolation of intermediate compounds. We believe that the present methodology extends promise for the convenient synthetic protocol for the preparation of pyrido[4,3-*d*]pyrimidine derivatives of biological interest.

4. Experimental

4.1. General

Melting points were determined in open capillaries and are uncorrected. IR spectra were run in Nujol mulls or in KBr discs on a Perkin–Elmer FT spectrophotometer Spectrum BX II. ^{1}H NMR spectra were recorded with a Varian Unity INOVA spectrometer (300 MHz) using tetramethylsilane as internal standard. Elemental analysis (C, N, H) results were found to be in good agreement (±0.4%) with the calculated values. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminum plates (Merck). Visualization was accomplished by UV light.

The structures of the molecules were initially optimized using restricted closed shell Hartree–Fock (RHF) wave function, with subsequently re-optimizing using Density Functional Theory (DFT) with Becke's[11] three-parameter (B3) exchange functional correction and the gradient corrected correlation functional due to Lee, Yang, and Parr[12] (LYP). The optimization was generally performed within C_1 symmetry, except for few instances where symmetry of the molecule allowed to use higher symmetry. The 6-31G(d,p) basis function was used throughout the calculations: the 6-31G basis set[13] augmented with a d polarization functions on all heavy atoms, and p polarization functions on all hydrogen atoms. To describe levels of theory used to obtain results, we use notation A//B, which denotes level of theory A applied using a geometry optimized at level of theory B, for instance DFT//HF.

The solvent effects in *tert*-butylamine were estimated using the Polarizable Continuum Model[14] (PCM) representing solvent as a continuum surrounding the solute. We used the integral equation formalism[14c] approach (IEF-PCM) as implemented in the GAMESS[15] package (IEF=–3 keyword). For the PCM calculations, dielectric constant ε=4.31[16] and *tert*-butylamine solvent radius r=3.4 Å, estimated from atomic van der Waals radii, were used.

The calculations were performed using GAMESS quantum chemistry package[15] running under Linux operating system.

4.2. Compounds 2a–t

Compounds **2a–t** were prepared according to the method published earlier.[5c,d] Data for compounds **2a**[6] and **2e–g**,**k**[5c,d] have been published in the previous papers.

4.2.1. 4-Amino-2-methylthio-6-(4-ethylphenyl)ethynylpyrimidine-5-carbaldehyde ***2b***

Yield 45%, mp 163–164 °C (from octane). IR (KBr): ν_{max}=3384, 3274 (NH_2), 2213 (C≡C), 1660 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, CD_2Cl_2): δ=1.29 (3H, t, J=7.5 Hz, CH_3), 2.59 (3H, s, SCH_3), 2.75 (2H, q, J=7.5 Hz, CH_2), 5.86 (1H, br s, NH), 7.32 (2H, d, J=8.4 Hz, ArH), 7.61 (2H, d, J=8.4 Hz, ArH), 8.56 (1H, br s, NH), 10.50 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, CD_2Cl_2): δ=14.3, 15.2, 29.2, 83.6, 98.4, 108.8, 117.9, 128.5, 132.7, 147.7, 155.1, 160.9, 177.1, 191.6 ppm. Anal. Calcd for $C_{16}H_{15}N_3OS$: C 71.36, H 5.42, N 11.89; found: C 71.27, H 5.45, N 11.91.

4.2.2. 4-N-Methylamino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde ***2c***

Yield 85%, mp 121–123 °C (from octane). IR (KBr): ν_{max}=3303 (NH), 2213 (C≡C), 1653 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.61 (3H, s, SCH_3), 3.15 (3H, d, J=4.8 Hz, NCH_3), 7.42–7.46 (3H, m, ArH), 7.63–7.67 (2H, m, ArH), 9.00 (1H, br s, NH), 10.46 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.6, 41.3, 84.8, 97.7, 111.3, 121.3, 128.8, 130.4, 132.6, 156.1, 159.9, 174.1, 188.2 ppm. Anal. Calcd

for $C_{15}H_{13}N_3OS$: C 63.58, H 4.62, N 14.83; found: C 63.70, H 4.56, N 14.95.

4.2.3. 4-N-Ethylamino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde **2d**

Yield 59%, mp 105–107 °C (from 2-PrOH). IR (KBr): ν_{max}=3424 (NH), 2216 (C≡C), 1654 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.33 (3H, t, J=3.0 Hz, CH_3), 2.59 (3H, s, SCH_3), 3.61–3.70 (2H, m, CH_2), 7.42–7.45 (5H, m, ArH), 7.63–7.66 (2H, m, ArH), 9.03 (1H, br s, NH), 10.45 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.6, 14.4, 41.2, 84.9, 97.2, 111.5, 121.2, 128.9, 130.0, 132.8, 156.2, 159.9, 174.1, 188.8 ppm. Anal. Calcd for $C_{16}H_{15}N_3OS$: C 64.62, H 5.08, N 14.13; found: C 64.71, H 4.98, N 14.08.

4.2.4. 4-Anilino-2-methylthio-6-(4-ethylphenyl)ethynylpyrimidine-5-carbaldehyde **2h**

Yield 75%, mp 150–152 °C (from 2-PrOH). IR (KBr): ν_{max}=3281 (NH), 2214 (C≡C), 1638 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.25 (3H, t, J=7.5 Hz, CH_3), 2.57 (3H, s, SCH_3), 2.71 (2H, q, J=7.5 Hz, CH_2), 7.17 (1H, t, J=7.5 Hz, ArH), 7.21 (2H, t, J=7.5 Hz, ArH), 7.37 (2H, t, J=7.5 Hz, ArH), 7.55 (2H, d, J=7.8 Hz, ArH), 7.70 (2H, d, J=7.8 Hz, ArH), 10.49 (1H, s, CHO), 11.05 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.6, 15.1, 28.9, 83.3, 98.9, 108.3, 117.7, 122.2, 124.8, 128.2, 128.8, 132.6, 137.3, 147.2, 155.4, 157.1, 177.7, 191.9 ppm. Anal. Calcd for $C_{22}H_{19}N_3OS$: C 70.75, H 5.13, N 11.25; found: C 70.49, H 5.21, N 11.29.

4.2.5. 4-N-Benzylamino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde **2i**

Yield 82%, mp 138–139 °C (from 2-PrOH). IR (KBr): ν_{max}=3284 (NH), 2211 (C≡C), 1652 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.56 (3H, s, SCH_3), 4.84 (2H, d, J=5.7 Hz, CH_2), 7.35–7.46 (8H, m, ArH), 7.64–7.67 (2H, m, ArH), 9.41 (1H, br s, NH), 10.48 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 44.4, 83.7, 97.7, 108.5, 120.7, 127.6, 128.6, 128.7, 130.3, 132.5, 137.6, 154.8, 159.0, 177.2, 191.6 ppm. Anal. Calcd for $C_{21}H_{17}N_3OS$: C 70.17, H 4.77, N 11.69; found: C 70.42, H 5.00, N 11.53.

4.2.6. 4-N,N-Dimethylamino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde **2j**

Yield 86%, mp 181–183 °C (from 2-PrOH). IR (KBr): ν_{max}=2217 (C≡C), 1666 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.58 (3H, s, SCH_3), 3.19 (6H, s, $N(CH_3)_2$), 7.42–7.45 (3H, m, ArH), 7.64–7.67 (2H, m, ArH), 10.51 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 41.0, 84.5, 97.4, 111.0, 120.9, 128.5, 130.1, 132.4, 155.8, 159.7, 173.8, 187.9 ppm. Anal. Calcd for $C_{16}H_{15}N_3OS$: C 64.62, H 5.08, N 14.13; found: C 64.72, H 5.17, N 14.20.

4.2.7. 2-Methylthio-6-(4-ethylphenyl)ethynyl-4-pyrrolidin-1-ylpyrimidine-5-carbaldehyde **2l**

Yield 89%, mp 187–189 °C (from 2-PrOH). IR (KBr): ν_{max}=2216 (C≡C), 1669 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.27 (3H, t, J=7.5 Hz, CH_3), 2.00 (4H, br s, $(CH_2)_2$), 2.56 (3H, s, SCH_3), 2.72 (2H, q, J=7.5 Hz, CH_2), 3.55 (4H, br s, $N(CH_2)_2$), 7.24 (2H, d, J=8.4 Hz, ArH), 7.58 (2H, d, J=8.4 Hz, ArH), 10.53 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 15.1, 25.3, 28.9, 50.9, 84.2, 97.7, 111.4, 118.2, 128.1, 132.4, 146.7, 155.0, 156.7, 173.7, 188.3 ppm. Anal. Calcd for $C_{20}H_{21}N_3OS$: C 68.35, H 6.02, N 11.96; found: C 68.62, H 5.98, N 12.15.

4.2.8. 6-(4-Fluorophenyl)ethynyl-2-methylthio-4-pyrrolidin-1-ylpyrimidine-5-carbaldehyde **2m**

Yield 82%, mp 210–212 °C (from 2-PrOH). IR (KBr): ν_{max}=2217 (C≡C), 1665 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.00 (4H, br s, $(CH_2)_2$), 2.56 (3H, s, SCH_3), 3.55 (4H, br s, $N(CH_2)_2$), 7.08–7.13 (2H, m, ArH), 7.61–7.66 (2H, m, ArH), 10.50 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.3, 25.3, 50.6, 84.4, 95.9, 111.4, 115.8, 116.1, 117.1, 134.4, 134.5, 154.7, 156.7, 161.8, 165.1, 173.8, 188.0 ppm. Anal. Calcd for $C_{18}H_{16}FN_3OS$: C 63.32, H 4.72, N 12.31; found: C 63.60, H 5.00, N 12.12.

4.2.9. 6-(4-Ethylphenyl)ethynyl-2-methylthio-4-morpholin-4-ylpyrimidine-5-carbaldehyde **2n**

Yield 88%, mp 139–140 °C (from 2-PrOH). IR (KBr): ν_{max}=2213 (C≡C), 1664 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, t, J=7.2 Hz, CH_3), 2.57 (3H, s, SCH_3), 2.72 (2H, q, J=7.2 Hz, CH_2), 3.73 (4H, t, J=4.5 Hz, $N(CH_2)_2$), 3.87 (4H, t, J=4.5 Hz, $O(CH_2)_2$), 7.26 (2H, d, J=8.1 Hz, ArH), 7.58 (2H, d, J=8.1 Hz, ArH), 10.48 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 15.1, 28.9, 49.1, 66.8, 84.1, 98.8, 111.0, 117.9, 128.2, 128.3, 132.5, 147.0, 157.2, 159.2, 174.9, 187.9 ppm. Anal. Calcd for $C_{20}H_{21}N_3O_2S$: C 65.37, H 5.76, N 11.44; found: C 65.46, H 5.79, N 11.41.

4.2.10. 6-(4-Fluorophenyl)ethynyl-2-methylthio-4-morpholin-4-ylpyrimidine-5-carbaldehyde **2o**

Yield 85%, mp 212–213 °C (from 2-PrOH). IR (KBr): ν_{max}=2216 (C≡C), 1667 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.57 (3H, s, SCH_3), 3.72 (4H, t, J=5.2 Hz, $N(CH_2)_2$), 3.87 (4H, t, J=5.2 Hz, $O(CH_2)_2$), 7.07–7.13 (2H, m, ArH), 7.62–7.67 (2H, m, ArH), 10.52 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.0, 49.6, 66.8, 84.5, 95.7, 111.2, 115.9, 116.1, 117.3, 134.6, 134.7, 154.5, 156.5, 161.9, 165.1, 173.8, 188.3 ppm. Anal. Calcd for $C_{18}H_{16}FN_3O_2S$: C 60.49, H 4.51, N 11.76; found: C 60.62, H 4.33, N 11.88.

4.2.11. 6-(4-Ethylphenyl)ethynyl-2-methylthio-4-piperidin-1-ylpyrimidine-5-carbaldehyde **2p**

Yield 56%, mp 102–103 °C (from 2-PrOH). IR (KBr): ν_{max}=2211 (C≡C), 1671 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.28 (3H, t, J=7.5 Hz, CH_3), 1.73 (6H, br s, $(CH_2)_3$), 2.56 (3H, s, SCH_3), 2.70 (2H, q, J=7.5 Hz, CH_2), 3.64 (4H, br s, $N(CH_2)_2$), 7.24 (2H, d, J=8.4 Hz, ArH), 7.57 (2H, d, J=8.4 Hz, ArH), 10.44 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 15.2, 24.1, 26.0, 28.9, 49.8, 84.8, 98.2, 111.0, 118.1, 128.1, 132.4, 146.8, 156.9, 158.9, 174.2, 187.9 ppm. Anal. Calcd for $C_{21}H_{23}N_3OS$: C 69.01, H 6.34, N 11.50; found: C 69.10, H 5.99, N 11.29.

4.2.12. 4-N-Benzylamino-6-phenylethynylpyrimidine-5-carbaldehyde **2q**

Yield 74%, mp 119–121 °C (from 2-PrOH). IR (KBr): ν_{max}=3281 (NH), 2213 (C≡C), 1671 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=4.85 (2H, d, J=5.4 Hz, CH_2), 7.38–7.49 (8H, m, ArH), 7.65–7.69 (2H, m, ArH), 8.74 (1H, br s, NH), 9.31 (1H, s, CH), 10.61 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=44.4, 84.3, 98.5, 120.6, 127.6, 128.6, 128.8, 130.4, 132.4, 137.3, 155.2, 159.8, 161.5, 192.7 ppm. Anal. Calcd for $C_{20}H_{15}N_3O$: C 76.66, H 4.82, N 13.41; found: C 76.82, H 5.00, N 13.51.

4.2.13. 4-N-Benzylamino-6-(4-ethylphenyl)ethynylpyrimidine-5-carbaldehyde **2r**

Yield 63%, mp 115–117 °C (from 2-PrOH). IR (KBr): ν_{max}=3280 (NH), 2213 (C≡C), 1668 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.28 (3H, t, J=7.5 Hz, CH_2CH_3), 2.72 (2H, q, J=7.5 Hz, CH_2CH_3), 4.83 (2H, d, J=5.4 Hz, CH_2), 7.26 (2H, d, J=6.9 Hz, ArH), 7.37 (5H, s, ArH), 7.59 (2H, d, J=6.9 Hz, ArH), 8.77 (1H, br s, NH), 9.31 (1H, s, CH), 10.59 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=15.5, 29.3, 44.7, 84.9, 99.5, 111.7, 118.1, 127.8, 127.9, 128.6, 129.1, 132.8, 137.7, 147.5, 156.3, 160.2, 161.9, 193.2 ppm. Anal. Calcd for $C_{22}H_{19}N_3O$: C 77.40, H 5.61, N 12.31; found: C 77.62, H 5.44, N 12.55.

4.2.14. 6-Phenylethynyl-4-pyrrolidin-1-ylpyrimidine-5-carbaldehyde **2s**

Yield 45%, mp 84–86 °C (from 2-PrOH). IR (KBr): ν_{max}=2212 (C≡C), 1669 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.05 (4H,

br s, CH_2CH_2), 3.50 (4H, br s, $N(CH_2)_2$), 7.45–7.46 (3H, m, ArH), 7.65–7.68 (2H, m, ArH), 8.61 (1H, s, CH), 10.66 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=25.3, 49.8, 84.5, 97.1, 111.5, 121.1, 128.4, 129.9, 132.5, 154.8, 156.6, 163.7, 188.2 ppm. Anal. Calcd for $C_{17}H_{15}N_3O$: C 77.40, H 5.45, N 15.15; found: C 77.57, H 5.39, N 15.35.

4.2.15. 4-Morpholin-4-yl-6-phenylethynylpyrimidine-5-carbaldehyde **2t**

Yield 65%, mp 96–98 °C (from 2-PrOH). IR (KBr): ν_{max}=2213 (C≡C), 1680 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.71 (4H, t, J=4.2 Hz, $N(CH_2)_2$), 3.84 (4H, t, J=4.2 Hz, $O(CH_2)_2$), 7.43–7.47 (3H, m, ArH), 7.64–7.67 (2H, m, ArH), 8.62 (1H, s, CH), 10.59 (1H, s, CHO) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=49.2, 66.8, 84.4, 98.2, 111.1, 120.8, 128.6, 130.2, 132.4, 157.2, 159.2, 164.9, 187.9 ppm. Anal. Calcd for $C_{17}H_{15}N_3O_2$: C 69.61, H 5.15, N 14.33; found: C 69.50, H 5.25, N 14.39.

4.3. 4-Amino-5-(*tert*-butyliminomethyl)-6-(arylethynyl)-2-methylthiopirimidines 3a,b and *N*-{4-[(*Z*)-2-(*tert*-butylamino)-2-arylvinyl]-2-(methylthio)pyrimidin-5-ylmethylene}2-methylpropan-2-amines 4c–h

Compounds **3a**,**b** and **4c**–**h** were prepared according to the method published earlier.[6,8] Data for compounds **3a**[6] and **4e**,**f**[8] have been published in the previous papers.

4.3.1. 4-Amino-5-(tert-butyliminomethyl)-6-[(4-ethylphenyl)-ethynyl]-2-methylthiopyrimidine **3b**

Yield 93%, mp 119–120 °C (from 2-PrOH–H_2O). IR (KBr): ν_{max}=3451, 3429 (NH_2), 2211 (C≡C) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (3H, t, J=7.7 Hz, CH_3), 1.36 (9H, s, *t*-Bu), 2.53 (3H, s, SCH_3), 2.75 (2H, q, J=7.7 Hz, CH_2), 5.83 (1H, br s, NH), 7.41 (2H, d, J=8.6 Hz, ArH), 7.63 (2H, d, J=8.6 Hz, ArH), 8.89 (1H, s, CH), 9.93 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.9, 14.3, 28.6, 29.7, 57.4, 83.8, 98.4, 108.9, 117.9, 128.5, 132.7, 147.7, 155.1, 160.9, 161.6, 174.1 ppm. Anal. Calcd for $C_{10}H_{24}N_4S$: C 68.15, H 6.86, N 15.89; found: C 68.31, H 6.88, N 15.83.

4.3.2. N-{4-(Z)-2-[(tert-Butylamino)-2-phenylvinyl]-6-N-methylamino-2-methylthiopyrimidin-5-ylmethylene}-2-methylpropan-2-amine **4c**

Yield 60%, mp 112–113 °C (from 2-PrOH), R_f=0.77 (toluene–ethylacetate, 1:1). IR (KBr): ν_{max}=3449, 3444 (NH) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.08 (9H, s, *t*-Bu), 1.15 (9H, s, *t*-Bu), 2.55 (3H, s, SCH_3), 3.07 (3H, d, J=6.0 Hz, NCH_3), 6.48 (1H, s, CH), 7.41 (5H, s, ArH), 7.98 (1H, s, CH), 9.78 (1H, br s, NH), 9.88 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.9, 27.6, 27.9, 28.4, 52.9, 56.7, 106.2, 116.4, 128.2, 128.4, 128.9, 137.0, 144.9, 153.2, 164.0, 169.0, 176.4 ppm. Anal. Calcd for $C_{23}H_{33}N_5S$: C 67.11, H 8.08, N 17.01; found: C 67.40, H 8.09, N 17.19.

4.3.3. N-{4-(Z)-2-[(tert-Butylamino)-2-phenylvinyl]-6-N-ethylamino-2-methylthiopyrimidin-5-ylmethylene}-2-methylpropan-2-amine **4d**

Yield 58%, mp 107–109 °C (from 2-PrOH), R_f=0.79 (toluene–ethylacetate, 1:1). IR (KBr): ν_{max}=3445, 3440 (NH) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.09 (9H, s, *t*-Bu), 1.22 (9H, s, *t*-Bu), 1.21 (3H, t, J=6.0 Hz, CH_3), 2.52 (3H, s, SCH_3), 3.52 (2H, q, J=6 Hz, CH_2), 5.22 (1H, s, CH), 7.45 (5H, s, ArH), 8.59 (1H, s, CH), 10.25 (1H, s, NH), 10.96 (1H, t, J=6.0 Hz, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.9, 14.4, 27.7, 27.9, 28.6, 52.9, 56.9, 106.5, 116.3, 128.2, 128.4, 128.6, 137.2, 144.1, 153.2, 164.0, 169.0, 176.5 ppm. Anal. Calcd for $C_{24}H_{35}N_5S$: C 67.72, H 8.29, N 16.45; found: C 67.50, H 8.19, N 16.55.

4.3.4. N-{6-Anilino-4-(Z)-2-[(tert-butylamino)-2-phenylvinyl]-2-methylthiopyrimidin-5-ylmethylene}-2-methylpropan-2-amine **4g**

Yield 75%, mp 137–139 °C (from 2-PrOH).

IR (KBr): ν_{max}=3442, 3438 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (9H, s, *t*-Bu), 1.30 (9H, s, *t*-Bu), 2.64 (3H, s, SCH_3), 5.21 (1H, s, CH), 7.07 (1H, t, J=7.8 Hz, ArH), 7.29–7.52 (7H, m, ArH), 7.78–7.81 (2H, m, ArH), 8.67 (1H, s, CH), 10.55 (1H, br s, NH), 13.61 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 30.3, 32.3, 54.1, 57.7, 92.5, 98.8, 121.4, 122.8, 127.9, 128.7, 128.9, 129.3, 140.4, 140.8, 152.9, 157.9, 160.5, 163.4, 169.9 ppm. Anal. Calcd for $C_{28}H_{35}N_5S$: C 71.00, H 7.45, N 14.79; found: C 71.21, H 7.19, N 15.00.

4.3.5. N-{6-Anilino-4-(Z)-2-[(tert-butylamino)-2-(4-ethylphenyl)-vinyl]-2-methylthiopyrimidin-5-ylmethylene}-2-methylpropan-2-amine **4h**

Yield 72%, mp 133–134 °C (from 2-PrOH). IR (KBr): ν_{max}=3439, 3428 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (9H, s, *t*-Bu), 1.32 (3H, t, J=7.5 Hz, CH_2CH_3), 1.34 (9H, s, *t*-Bu), 2.64 (3H, s, SCH_3), 2.74 (2H, q, J=7.5 Hz, CH_2CH_3), 5.23 (1H, s, CH), 7.04–7.42 (8H, m, ArH), 7.78–7.82 (2H, m, ArH), 8.68 (1H, s, CH), 10.54 (1H, br s, NH), 13.62 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 15.4, 28.6, 30.1, 32.0, 53.8, 57.4, 92.1, 98.4, 121.1, 122.1, 127.1, 128.6, 128.9, 137.8, 140.1, 144.6, 152.7, 157.6, 160.5, 163.2, 169.6 ppm. Anal. Calcd for $C_{30}H_{39}N_5S$: C 71.82, H 7.83, N 13.96; found: C 72.01, H 7.96, N 14.00.

4.4. Typical procedure for the preparation of 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines 5a–t

Data for compounds **5a**[6] and **5e**,**f**,**j**,**n**[8] have been published in the previous papers.

Method A. A mixture of the corresponding 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **2a**–**t** (0.2 mmol) and *tert*-butylamine (3 mL) in a reaction tube was flushed with argon and the tube was carefully sealed. The mixture was heated at 120 °C for 24 h (for compounds **5c**–**t**) or 48 h (for compounds **2a**,**b**). The solvent was evaporated under reduced pressure, and the residue was recrystallized to give compounds **5a**–**t**.

Method B. A solution of the corresponding 2,4-disubstituted 6-arylethynylpyrimidine-5-carbaldehydes **2a**–**t** (0.2 mmol) and *tert*-butylamine (0.15 g, 2 mmol) in DMF (3 mL) was irradiated in a microwave oven at 500 W for 10 min (for compounds **2e**,**f**,**j**–**p**,**s**,**t**), 20 min (for compounds **2a**–**d**,**i**,**q**,**r**) or 1 h (for compounds **2g**,**h**). After heating, the solution was cooled to room temperature, then cold water (10 mL) was added. The precipitate was filtered, dried, and recrystallized to give **5a**–**t**.

4.4.1. 4-Amino-7-(4-ethylphenyl)-2-methylthiopyrido[4,3-d]pyrimidine **5b**

Yield 18% (method A), 90% (method B), mp 147–149 °C (from octane). IR (KBr): ν_{max}=3392, 3372 (NH_2) cm^{-1}. ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ=1.27 (3H, t, J=7.8 Hz, CH_3), 2.51 (3H, s, SCH_3), 2.74 (2H, q, J=7.8 Hz, CH_2), 7.05 (2H, br s, NH_2), 7.25 (1H, s, CH), 7.38 (2H, d, J=8.7 Hz, ArH), 7.61 (2H, d, J=8.7 Hz, ArH), 8.74 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.8, 14.2, 27.9, 109.3, 115.3, 127.1, 128.8, 129.5, 138.4, 149.6, 157.2, 157.5, 160.8, 171.8 ppm. Anal. Calcd for $C_{16}H_{16}N_4S$: C 64.84, H 5.44, N 18.90; found: C 64.79, H 5.51, N 18.84.

4.4.2. 4-N-Methylamino-2-methylthio-7-phenylpyrido[4,3-d]pyrimidine **5c**

Yield 80% (method A), 91% (method B), mp 205–207 °C (from 2-PrOH). IR (KBr): ν_{max}=3262 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.68 (3H, s, SCH_3), 3.23 (3H, d, J=3.6 Hz, $NHCH_3$), 6.24 (1H, br s, NH), 7.51–7.53 (3H, m, ArH), 7.89 (1H, s, CH), 8.09–8.12 (2H, m, ArH), 9.11 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.4, 42.1, 109.5, 115.6, 127.4, 129.1, 129.8, 138.6, 149.9, 157.5, 157.7, 161.1, 172.0 ppm. Anal. Calcd for $C_{15}H_{14}N_4S$: C 63.80, H 5.00, N 19.84; found: C 64.00, H 5.12, N 19.97.

4.4.3. 4-N-Ethylamino-2-methylthio-7-phenylpyrido[4,3-d]pyrimidine ***5d***

Yield 80% (method A), 92% (method B), mp 190–192 °C (from octane). IR (KBr): ν_{max}=3441 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.41 (3H, t, J=6.0 Hz, CH_3), 2.67 (3H, s, SCH_3), 3.75–3.81 (2H, m, CH_2), 6.19 (1H, br s, NH), 7.51–7.53 (3H, m, ArH), 7.89 (1H, s, CH), 8.10 (2H, d, J=6.0 Hz, ArH), 9.18 (1H, br s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.1, 14.3, 36.3, 115.7, 126.8, 127.1, 128.8, 129.5, 138.4, 145.7, 154.8, 158.2, 158.6, 173.7 ppm. Anal. Calcd for $C_{16}H_{16}N_4S$: C 64.84, H 5.44, N 18.90; found: C 64.71, H 5.78, N 18.99.

4.4.4. 4-Anilino-2-methylthio-7-phenylpyrido[4,3-d]pyrimidine ***5g***

Yield 0% (method A), 97% (method B), mp 104–105 °C (from 2-PrOH). IR (KBr): ν_{max}=3442 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.52 (3H, s, SCH_3), 7.13 (1H, t, J=7.8 Hz, ArH), 7.33–7.48 (5H, m, ArH), 7.79–7.82 (2H, m, ArH), 7.94 (1H, s, CH), 8.11–8.14 (2H, m, ArH), 9.75 (1H, s, CH), 10.16 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.3, 111.8, 115.7, 122.0, 125.1, 127.2, 128.9, 129.0, 127.7, 137.4, 138.3, 145.4, 147.5, 155.2, 156.3, 159.0, 173.6 ppm. Anal. Calcd for $C_{20}H_{16}N_4S$: C 69.74, H 4.68, N 16.17; found: C 69.71, H 5.00, N 16.41.

4.4.5. 4-Anilino-7-(4-ethylphenyl)-2-methylthiopyrido[4,3-d]pyrimidine ***5h***

Yield 0% (method A), 96% (method B), mp 117–119 °C (from 2-PrOH). IR (KBr): ν_{max}=3440 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (3H, t, J=7.5 Hz, CH_2CH_3), 2.51 (3H, s, SCH_3), 2.71 (2H, q, J=7.5 Hz, CH_2CH_3), 7.14 (1H, t, J=7.6 Hz, ArH), 7.33–7.48 (4H, m, ArH), 7.82 (2H, d, J=7.5 Hz, ArH), 7.95 (1H, s, CH), 8.12 (2H, d, J=7.5 Hz, ArH), 9.77 (1H, s, CH), 10.15 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.7, 14.3, 26.0, 111.9, 115.5, 122.1, 125.5, 127.2, 128.6, 129.2, 127.8, 137.4, 138.3, 145.5, 147.8, 155.2, 156.3, 159.0, 173.6 ppm. Anal. Calcd for $C_{22}H_{20}N_4S$: C 70.94, H 5.41, N 15.04; found: C 70.79, H 5.33, N 14.94.

4.4.6. 4-N-Benzylamino-2-methylthio-7-phenylpyrido[4,3-d]pyrimidine ***5i***

Yield 81% (method A), 98% (method B), mp 199–200 °C (from 2-PrOH). IR (KBr): ν_{max}=3440 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.58 (3H, s, SCH_3), 4.97 (2H, d, J=5.4 Hz, CH_2), 6.39 (1H, br s, NH) 7.41–7.56 (8H, m, ArH) 8.05 (1H, s, CH), 8.14–8.17 (2H, m, ArH), 9.23 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.5, 44.6, 114.3, 127.0, 127.2, 127.6, 128.3, 128.6, 129.4, 137.6, 137.9, 147.7, 151.7, 157.8, 158.7, 159.7 ppm. Anal. Calcd for $C_{21}H_{18}N_4S$: C 70.36, H 5.06, N 15.63; found: C 70.08, H 5.13, N 15.88.

4.4.7. 2-Methylthio-7-phenyl-4-pyrrolidin-1-ylpyrido[4,3-d]pyrimidine ***5k***

Yield 89% (method A), 100% (method B), mp 155–157 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.11 (4H, br s, $(CH_2)_2$), 2.64 (3H, s, SCH_3), 3.99 (4H, br s, $N(CH_2)_2$), 7.46–7.55 (3H, m, ArH), 7.88 (1H, s, CH), 8.12 (2H, d, J=7.5 Hz, ArH), 9.46 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.1, 35.3, 50.9, 109.9, 115.3, 127.0, 128.8, 129.4, 138.4, 149.3, 156.8, 157.3, 157.6, 172.0 ppm. Anal. Calcd for $C_{18}H_{18}N_4S$: C 67.05, H 5.63, N 17.38; found: C 66.97, H 5.72, N 17.25.

4.4.8. 7-(4-Ethylphenyl)-2-methylthio-4-pyrrolidin-1-ylpyrido[4,3-d]pyrimidine ***5l***

Yield 91% (method A), 94% (method B), mp 190–191 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (3H, t, J=7.5 Hz, CH_3), 2.12 (4H, br s, $(CH_2)_2$), 2.64 (3H, s, SCH_3), 2.75 (2H, q, J=7.5 Hz, CH_2), 4.00 (4H, br s, $N(CH_2)_2$), 7.36 (2H, d, J=8.1 Hz, ArH), 7.87 (1H, s, CH), 8.06 (2H, d, J=8.1 Hz, ArH), 9.46 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.1, 15.4, 28.7, 35.4, 50.9, 109.8, 110.6, 114.8, 127.0, 128.4, 135.9, 145.9, 149.3, 156.8, 157.4, 157.7, 171.9 ppm. Anal. Calcd for $C_{20}H_{22}N_4S$: C 68.54, H 6.33, N 15.99; found: C 68.77, H 6.44, N 16.25.

4.4.9. 7-(4-Fluorophenyl)-2-methylthio-4-pyrrolidin-1-ylpyrido[4,3-d]pyrimidine ***5m***

Yield 92% (method A), 95% (method B), mp 195–197 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.12 (4H, br s, $(CH_2)_2$), 2.63 (3H, s, SCH_3), 3.98 (4H, br s, $N(CH_2)_2$), 7.17–7.23 (2H, m, ArH), 7.81 (1H, s, CH), 8.08–8.13 (2H, m, ArH), 9.42 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.1, 25.3, 51.0, 114.9, 115.6, 115.9, 128.8, 128.9, 134.6, 149.3, 156.3, 156.7, 157.5, 162.1, 165.4, 172.1 ppm. Anal. Calcd for $C_{18}H_{17}FN_4S$: C 63.51, H 5.03, N 16.46; found: C 63.70, H 5.14, N 16.25.

4.4.10. 7-(4-Fluorophenyl)-2-methylthio-4-morfolin-4-ylpyrido[4,3-d]pyrimidine ***5o***

Yield 92% (method A), 97% (method B), mp 196–197 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.64 (3H, s, SCH_3), 3.93 (4H, t, J=3.9 Hz, $N(CH_2)_2$), 4.02 (4H, t, J=3.9 Hz, $O(CH_2)_2$), 7.16–7.21 (2H, m, ArH), 7.82 (1H, s, CH), 8.09–8.13 (2H, m, ArH), 9.41 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.5, 49.9, 66.8, 107.9, 115.4, 127.1, 128.9, 129.8, 138.4, 149.0, 157.1, 157.9, 162.9, 172.4 ppm. Anal. Calcd for $C_{18}H_{17}FN_4OS$: C 60.66, H 4.81, N 15.72; found: C 60.70, H 5.04, N 16.00.

4.4.11. 7-(4-Ethylphenyl)-2-methylthio-4-piperidin-1-ylpyrido[4,3-d]pyrimidine ***5p***

Yield 87% (method A), 93% (method B), mp 126–127 °C (from hexane). ^1H NMR (300 MHz, $CDCl_3$): δ=1.33 (3H, t, J=7.5 Hz, CH_3), 1.66 (6H, br s, $(CH_2)_3$), 2.64 (3H, s, SCH_3), 2.76 (2H, q, J=7.5 Hz, CH_2), 3.98 (4H, br s, $N(CH_2)_2$), 7.38 (2H, d, J=8.0 Hz, ArH), 7.87 (1H, s, CH), 8.07 (2H, d, J=8.0 Hz, ArH), 9.46 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.0, 14.2, 24.6, 25.5, 26.4, 50.5, 115.3, 127.1, 128.8, 129.5, 138.4, 149.3, 157.2, 157.6, 161.7, 172.4 ppm. Anal. Calcd for $C_{21}H_{24}N_4S$: C 69.20, H 6.64, N 15.37; found: C 68.98, H 6.74, N 15.45.

4.4.12. 4-N-Benzylamino-7-phenylpyrido[4,3-d]pyrimidine ***5q***

Yield 80% (method A), 95% (method B), mp 249–250 °C (from 2-PrOH). IR (KBr): ν_{max}=3442 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=4.97 (2H, d, J=5.4 Hz, CH_2), 6.34 (1H, br s, NH), 7.40–7.56 (8H, m, ArH), 8.09 (1H, s, CH), 8.14–8.16 (2H, m, ArH), 8.83 (1H, s, CH), 9.26 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=44.6, 114.3, 127.0, 127.2, 127.6, 128.3, 128.6, 129.4, 137.6, 137.9, 147.7, 151.7, 157.8, 158.7, 159.7 ppm. Anal. Calcd for $C_{20}H_{16}N_4$: C 76.90, H 5.16, N 17.94; found: C 77.01, H 5.11, N 18.03.

4.4.13. 4-N-Benzylamino-7-(4-ethylphenyl)pyrido[4,3-d]pyrimidine ***5r***

Yield 91% (method A), 96% (method B), mp 220–222 °C (from 2-PrOH). IR (KBr): ν_{max}=3440 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (3H, t, J=7.5 Hz, CH_2CH_3), 2.76 (2H, q, J=7.5 Hz, CH_2CH_3), 4.95–5.00 (2H, m, CH_2), 6.35 (1H, br s, NH), 7.29–7.48 (7H, m, ArH), 8.01 (1H, s, CH), 8.06–8.09 (2H, d, J=7.8 Hz, ArH), 8.81 (1H, s, CH), 9.24 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.9, 25.3, 44.7, 114.5, 127.1, 127.3, 127.6, 128.2, 128.7, 129.5, 137.6, 137.9, 147.8, 151.8, 157.9, 158.5, 159.6 ppm. Anal. Calcd for $C_{22}H_{20}N_4$: C 77.62, H 5.92, N 16.46; found: C 78.00, H 5.81, N 16.44.

4.4.14. 7-Phenyl-4-pyrrolidin-1-ylpyrido[4,3-d]pyrimidine ***5s***

Yield 95% (method A), 100% (method B), mp 170–172 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.15 (4H, br s, CH_2CH_2), 4.01 (4H, br s, $N(CH_2)_2$), 7.49–7.59 (3H, m, ArH), 8.05 (1H, s, CH), 8.15–8.18 (2H, m, ArH), 8.70 (1H, s, CH), 9.60 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=35.3, 50.9, 109.9, 115.3, 127.2, 128.8, 129.2, 138.5, 149.3, 156.9, 157.3, 157.6, 162.8 ppm. Anal. Calcd for $C_{17}H_{16}N_4$: C 73.89, H 5.84, N 20.27; found: C 73.65, H 5.69, N 20.21.

4.4.15. 7-Phenyl-4-morpholin-4-ylpyrido[4,3-d]pyrimidine ***5t***

Yield 89% (method A), 99% (method B), mp 160–161 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=3.91 (4H, t, J=3.9 Hz,

$N(CH_2)_2$), 4.01 (4H, t, J=3.9 Hz, $O(CH_2)_2$), 7.46–7.56 (3H, m, ArH), 8.07 (1H, s, CH), 8.15–8.19 (2H, m, ArH), 8.71 (1H, s, CH), 9.62 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=49.8, 66.6, 108.9, 115.4, 127.2, 128.9, 129.6, 138.2, 149.5, 157.1, 157.7, 161.9, 165.2 ppm. Anal. Calcd for $C_{17}H_{16}N_4O$: C 69.85, H 5.52, N 19.17; found: C 70.01, H 5.60, N 19.29.

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