An Efficient One-Pot Synthetic Method for 2,4-Disubstituted 7-Arylpyrido [4,3-*d*]pyrimidines from 2,4-Disubstituted 6-(Arylethynyl)pyrimidine-5-carbaldehydes and *tert*-Butylamine

Inga Cikotiene,* Marius Morkunas, Simonas Rudys, Rita Buksnaitiene, Algirdas Brukstus

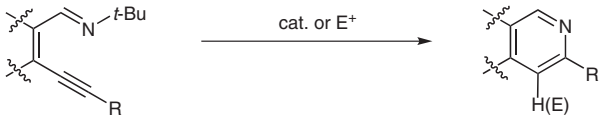
Department of Organic Chemistry, Faculty of Chemistry, Vilnius University, Naugarduko 24, 03225 Vilnius, Lithuania
Fax +370(5)2330987; E-mail: inga.cikotiene@chf.vu.lt

Received 15 July 2008

Abstract: Unexpected thermal cyclization of 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehydes with *tert*-butylamine proceeded to give 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 mechanism of the reactions is discussed.

Key words: cyclization, alkynes, aldehydes, pyrido[4,3-*d*]pyrimidines, 1,6-electrocyclic reaction

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



Scheme 1 Literature results overview

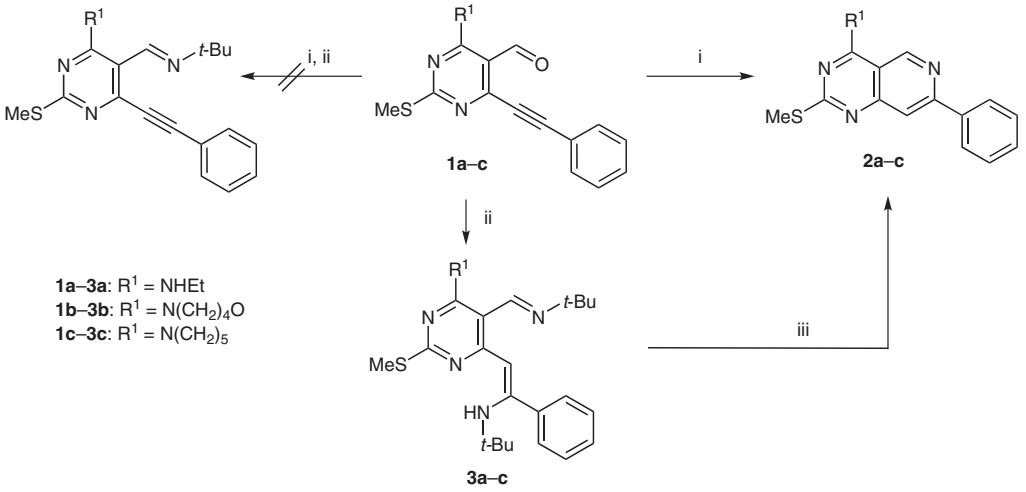
During continuation of our researches aimed on the use of 6-(arylethynyl)pyrimidines in the synthesis of fused pyrimidine derivatives[5] we have found that 6-(arylethynyl)pyrimidine-5-carbaldehydes during heating with *tert*-butylamine in sealed tubes at 110–120 °C underwent cyclization reactions to form 7-arylpyrido[4,3-*d*]pyrimidines in good yields. We were surprised that these reactions underwent easily without any transition-metal catalysts or electrophilic initiator, so herein we wish to report a novel, environmentally friendly synthetic method of pyrido[4,3-*d*]pyrimidine framework via unexpected thermal cyclization of 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehydes with *tert*-butylamine.

The starting compounds **1** were synthesized by the palladium-catalyzed Sonagashira coupling of the corresponding 2,4-disubstituted 6-chloropyrimidine-5-carbaldehydes with 1-arylacetylenes by the way we have reported earlier.[5c] We were intrigued, while performing a classical synthesis of *tert*-butylimines (compounds **1a–c**, *tert*-butylamine, sealed tube, 110–120 °C), to see that we triggered instead formation of the 4-substituted 2-(methylthio)-7-phenylpyrido[4,3-*d*]pyrimidines **2a–c** in good yields (Scheme 2).

These results prompted us to investigate the thermal cyclization of the title compounds with *tert*-butylamine. We assumed that thermal cyclization of the title compounds underwent via intermediate *tert*-butylimines as it was proposed in one literature source[3a] dealed with synthesis of γ-carbolines. However, when the reactions of compounds **1a–c** with *tert*-butylamine were carried out in sealed tubes at lower 80–90 °C temperature for 20 hours, we found that not only reaction of *tert*-butylamine with carbonyl group, but also 1,2-addition of second molecule of *tert*-butylamine to C≡C bond took place, so products **3a–c** were produced (Scheme 2). As we have been reported earlier, the C≡C bond of some 6-(arylethynyl)pyrimidines is electron defficient due to activating effect of the pyrimidine ring, therefore it is easily attacked by various nucleophiles in regio- and stereoselective manner.[6] After the comparison with the ^{1}H NMR and ^{13}C NMR data of obtained compounds with our previous results, we supposed that the addition reactions of *tert*-butylamine to C≡C bond of the starting compounds led to formation of *anti*-addition product or *Z*-isomer, stabilized by possible intramolecular H-bonding. To our pleasant surprise, compounds **3a–c** heated with *tert*-butylamine in sealed tubes at higher (110–120 °C) temperature after 10 hours convert to the corresponding 2-(methylthio)-7-phenylpyrido[4,3-*d*]pyrimidines **2a–c** in good yields. On the other hand, cyclization of compounds **3a–c**[9,10] to pyrido[4,3-*d*]pyrimidines **2a–c**[11] underwent smoothly in hot (110 °C) dimethylsulfoxide (Scheme 2).

Moreover, the chronology of the cyclization of intermediate compound **3c** to **2c** has been studied by ^{1}H NMR experiment. When compound **3c** was carefully dissolved in DMSO-d_6 at room temperature we observed its ^{1}H NMR spectrum. The ^{1}H NMR spectrum recorded after heating

SYNLETT 2008, No. 18, pp 2799–2802
Advanced online publication: 15.10.2008
DOI: 10.1055/s-0028-1083500; Art ID: G23408ST



Scheme 2 *Reagents and conditions*: i) *t*-BuNH$_2$, sealed tube, 110–120 °C, 24 h; ii) *t*-BuNH$_2$, sealed tube, 80–90 °C, 20 h; iii) solvent, 120 °C.

of the sample contained signals of 2-(methylthio)-7-phenyl-4-piperidin-1-ylpyrido[4,3-*d*]pyrimidine **2c**, *tert*-butylamine, and traces of 2-methylpropene.

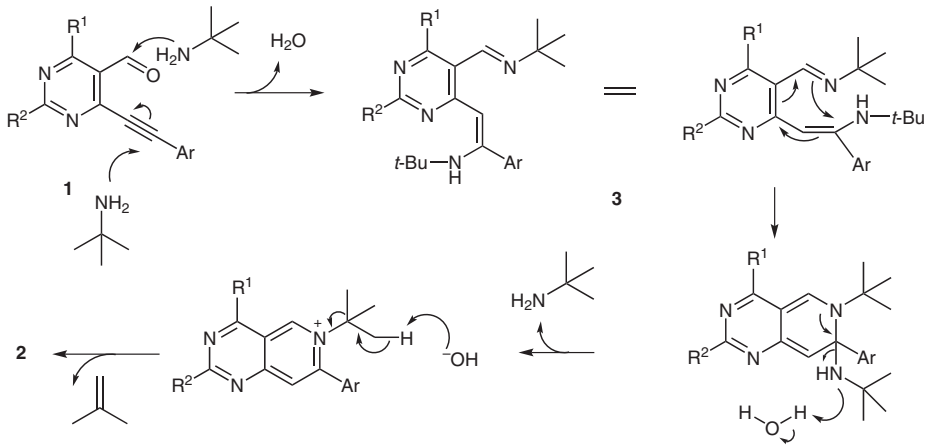
From these results it seems that the thermal cyclization of 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehydes **1** with *tert*-butylamine could proceed via *N*-(*tert*-butyl)-*N*-{4-[(*Z*)-2-aryl-2-(*tert*-butylamino)vinyl]pyrimidin-5-yl}methyleneamines **3**. The possible mechanism is presented in Scheme 3. We assume, that intermediate adducts **3** underwent 1,6-electrocyclic reaction to form six-membered ring. The aromatization of cyclic adduct lead to elimination of *tert*-butylamine and 2-methylpropene molecules.

Thus, according to the present methodology, we have prepared various 2,4-disubstituted 7-arylpyrido[4,3-*d*]pyrimidines **2a**–**u**[8,12] via thermal reaction of 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehydes **1a**–**u** with *tert*-butylamine. The results are summarized in Table 1. It is noteworthy that *tert*-butylamine is the only reagent which can be used in this transformation. Another amines such as propylamine, diethylamine, ammonia, and hydrazine did not cause cyclization of the starting compounds to pyrido[4,3-*d*]pyrimidine derivatives.

In summary, we have developed a novel, environmentally friendly synthetic method of pyrido[4,3-*d*]pyrimidine framework via unexpected thermal cyclization of 2,4-disubstituted 6-(arylethynyl)pyrimidine-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.[7] Extension of these reactions is currently under way in our laboratory, and the results will be published in the nearest future.

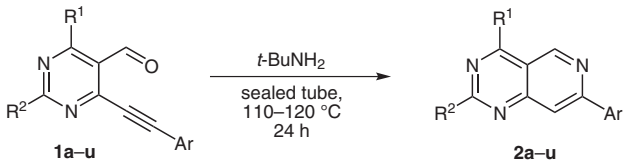
Acknowledgment

We express our gratitude to *M. Kreneviciene* and *A. Karosiene* for the recording of NMR and IR spectra and to *M. Gavrilova* for the elemental analyses data. The work was supported by Lithuanian Science and Study Foundation, Reg. No. T-08032, Grant No. T-18/08.



Scheme 3 Possible mechanism of the thermal cyclization of 2,4-disubstituted 6-(arylethynyl)-2-(methylthio)pyrimidine-5-carbaldehydes with *tert*-butylamine

Table 1 Synthesis of 2,4-Disubstituted 7-Arylpyrido[4,3-*d*]pyrimidines by the Presented Method



Entry	Starting material	R^1	R^2	Ar	Product	Yield (%)
1	**1a**	NHEt	SMe	Ph	**2a**	80
2	**1b**	$N(CH_2)_4O$	SMe	Ph	**2b**	95
3	**1c**	$N(CH_2)_5$	SMe	Ph	**2c**	85
4	**1d**	NHMe	SMe	Ph	**2d**	80
5	**1e**	NHBn	SMe	Ph	**2e**	81
6	**1f**	NMe_2	SMe	Ph	**2f**	92
7	**1g**	$N(CH_2)_4$	SMe	Ph	**2g**	89
8	**1h**	$N(CH_2)_4$	SMe	4-EtC_6H_4	**2h**	91
9	**1k**	$N(CH_2)_4$	SMe	4-FC_6H_4	**2k**	92
10	**1l**	$N(CH_2)_4O$	SMe	4-EtC_6H_4	**2l**	90
11	**1m**	$N(CH_2)_4O$	SMe	4-FC_6H_4	**2m**	92
12	**1n**	$N(CH_2)_5$	SMe	4-EtC_6H_4	**2n**	87
13	**1o**	NHBn	H	Ph	**2o**	80
14	**1p**	NHBn	H	4-EtC_6H_4	**2p**	91
15	**1r**	$N(CH_2)_4$	H	Ph	**2r**	95
16	**1s**	$N(CH_2)_4O$	H	Ph	**2s**	92
17	**1t**	$N(CH_2)_4$	NH_2	Ph	**2t**	80
18	**1u**	$N(CH_2)_4O$	NH_2	Ph	**2u**	89

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(8) **Typical Procedure for the Preparation of 2,4-Disubstituted 7-Arylpyrido[4,3-*d*]pyrimidines 2a–u**
The mixture of the corresponding 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehyde **1a**–**u** (0.2 mmol) and *t*-$BuNH_2$ (3 mL) in tube was flushed with argon, and the tube was carefully sealed. The mixture was heated at 110–120 °C for 24 h. The solvent was evaporated under reduced pressure, residue recrystallized to give compounds **2a**–**u**.
2-(Methylthio)-4-morpholin-1-yl-7-phenylpyrido[4,3-*d*]-pyrimidine (2b)
Yield 95%, mp 145–147 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.66 (3 H, s, SCH_3), 3.93 [4 H, t, *J* = 3.9 Hz, $N(CH_2)_2$], 4.01 [4 H, t, *J* = 3.9 Hz, $O(CH_2)_2$], 7.49–7.55 (3 H, m, ArH), 7.95 (1 H, s, CH), 8.13–8.16 (2 H, m, ArH), 9.27 (1 H, s, CH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 14.3, 49.8, 66.6, 108.9, 115.4, 127.1, 128.9, 129.6, 138.2, 149.0, 157.1,

157.9, 161.9, 172.2. Anal. Calcd for $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.56. Found: C, 63.96; H, 5.44; N, 16.70.

2-(Methylthio)-7-phenyl-4-piperidin-1-ylpyrido[4,3-*d*]-pyrimidine (2c)

Yield 85%, mp 126–128 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.84 [4 H, br s, $(CH_2)_3$], 2.65 (3 H, s, SCH_3), 3.94 [4 H, br s, $N(CH_2)_2$], 7.49–7.54 (3 H, m, ArH), 7.90 (1 H, s, CH), 8.13 (2 H, d, *J* = 6.9 Hz, ArH), 9.24 (1 H, s, CH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.74 [4 H, br s, $(CH_2)_3$], 2.56 (3 H, s, SCH_3), 3.92 [4 H, br s, $N(CH_2)_2$], 7.49–7.54 (3 H, m, ArH), 7.94 (1 H, s, CH), 8.22–8.25 (2 H, m, ArH), 9.25 (1 H, s, CH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 14.2, 24.6, 26.0, 50.5, 115.3, 127.1, 128.8, 129.5, 138.4, 149.3, 157.2, 157.6, 161.7, 172.0. Anal. Calcd for $C_{19}H_{20}N_4S$: C, 67.83; H, 5.99; N, 16.65. Found: C, 67.90; H, 6.07; N, 16.59.

4-*N*,*N*-Dimethylamino-2-(methylthio)-7-phenylpyrido-[4,3-*d*]pyrimidine (2f)

Yield 92%, mp 155–156 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.65 (3 H, s, SCH_3), 3.51 [6 H, s, $N(CH_3)_2$], 7.49–7.53 (3 H, m, ArH), 7.90 (1 H, s, CH), 8.13 (2 H, d, *J* = 7.2 Hz, ArH), 9.41 (1 H, s, CH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 14.2, 41.8, 109.3, 115.3, 127.1, 128.8, 129.5, 138.4, 149.6, 157.2, 157.4, 160.8, 171.7. Anal. Calcd for $C_{16}H_{16}N_4S$: C, 64.84; H, 5.44; N, 18.90. Found: C, 64.79; H, 5.32; N, 18.99.

7-(4-Ethylphenyl)-2-(methylthio)-4-morpholin-1-yl-pyrido-[4,3-*d*]pyrimidine (2l)

Yield 90%, mp 127–128 °C (from hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (3 H, t, *J* = 7.5 Hz, CH_3), 2.63 (3 H, s, SCH_3), 2.76 (2 H, q, *J* = 7.5 Hz, CH_2), 3.92 [4 H, t, *J* = 2.1 Hz, $N(CH_2)_2$], 3.96 [4 H, t, *J* = 2.1 Hz, $O(CH_2)_2$], 7.38 (2 H, d, *J* = 8.1 Hz, ArH), 7.72 (1 H, s, CH), 7.79 (2 H, d, *J* = 8.1 Hz, ArH), 9.04 (1 H, s, CH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 14.3, 15.4, 28.7, 49.8, 66.7, 108.8, 114.5, 127.1, 128.4, 135.6, 146.2, 148.9, 157.1, 158.0, 161.9, 172.1. Anal. Calcd for $C_{20}H_{22}N_4OS$: C, 65.55; H, 6.05; N, 15.29. Found: C, 65.76; H, 5.93; N, 15.44.

(9) **Typical Procedure for the Preparation of *N*-{4-[(*Z*)-2-(*tert*-butylamino)-2-phenylvinyl]-2-(methylthio)-pyrimidin-5-ylmethylene}-2-methylpropan-2-amines 3a–c**

The mixture of the corresponding 2,4-disubstituted 6-(arylethynyl)pyrimidine-5-carbaldehyde **1a–c** (0.2 mmol) and *t*-$BuNH_2$ (3 mL) in tube was flushed with argon, and the tube was carefully sealed. The mixture was heated at 80–90 °C for 20 h. The solvent was evaporated under reduced pressure, compounds **3a–c** were isolated by column flash chromatography.

***N*-{4-(*Z*)-2-[(*tert*-butylamino)-2-phenylvinyl]-2-(methylthio)-6-morpholin-1-ylpyrimidin-5-ylmethylene}-2-methylpropan-2-amine (3b)**

Yield 62%, mp 140–142 °C (from MeOH–H_2O); R_f = 0.78 (toluene–EtOAc, 1:1). IR (KBr): 3442 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (9 H, s, *t*-Bu), 1.22 (9 H, s, *t*-Bu), 2.57 (3 H, s, SCH_3), 3.46 [4 H, t, *J* = 4.2 Hz, $N(CH_2)_2$], 3.79 [4 H, t, *J* = 4.2 Hz, $O(CH_2)_2$], 6.17 (1 H, s, CH), 7.34–7.36 (3 H, m, ArH), 7.46–7.49 (2 H, m, ArH), 8.15 (1 H, s, CH), 10.08 (1 H, br s, NH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 13.9, 29.5, 32.1, 49.8, 53.9, 57.7, 66.8, 96.3, 105.5, 127.3, 128.2, 128.8, 140.9, 153.4, 160.6, 162.2, 164.2, 168.0. Anal. Calcd for $C_{26}H_{37}N_5OS$: C, 66.77; H, 7.97; N, 14.95. Found: C, 66.49; H, 8.08; N, 15.10.

(10) ***N*-{4-(*Z*)-2-[(*tert*-butylamino)-2-phenylvinyl]-2-(methylthio)-6-piperidin-1-ylpyrimidin-5-ylmethylene}-2-methylpropan-2-amine (3c)**

Yield 58%, mp 109–110 °C (from 2-PrOH); R_f = 0.81 (toluene–EtOAc, 1:1). IR (KBr): 3443 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17 (9 H, s, *t*-Bu), 1.23 (9 H, s, *t*-Bu), 1.65 [6 H, br s, $(CH_2)_3$], 2.57 (3 H, s, SCH_3), 3.41 [4 H, br s, $N(CH_2)_2$], 6.31 (1 H, s, CH), 7.32–7.34 (3 H, m, ArH), 7.48–7.51 (2 H, m, ArH), 8.07 (1 H, s, CH), 9.98 (1 H, br s, NH). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 1.09 (9 H, s, *t*-Bu), 1.14 (9 H, s, *t*-Bu), 1.61 [6 H, br s, $(CH_2)_3$], 2.52 (3 H, s, SCH_3), 3.37 [4 H, br s, $N(CH_2)_2$], 6.50 (1 H, s, CH), 7.40 (5 H, s, ArH), 7.99 (1 H, s, CH), 9.88 (1 H, br s, NH). ^{13}C NMR (75 Hz, $CDCl_3$): δ = 13.9, 24.6, 26.1, 29.6, 32.1, 50.5, 53.9, 57.5, 97.3, 105.5, 127.3, 128.0, 128.9, 141.3, 153.9, 160.1, 161.9, 164.8, 167.7. Anal. Calcd for $C_{27}H_{39}N_5S$: C, 69.63; H, 8.44; N, 15.04. Found: C, 69.42; H, 8.59; N, 15.19.

(11) **Typical Procedure for the Cyclization of *N*-{4-[(*Z*)-2-(*tert*-butylamino)-2-phenylvinyl]pyrimidin-5-yl-methylene}-2-methylpropan-2-amines 3a–c into 4-Substituted 2-(Methylthio)-7-phenylpyrido[4,3-*d*]-pyrimidines 2a–c**

The solution of compounds **3a–c** (2 mmol) in DMSO (2 mL) was heated at 110–120 °C for 15 min. After cooling, reaction mixture was diluted with H_2O (10 mL), precipitate collected by filtration and recrystallyzed to give compounds **2a–c**.

(12) Compounds **2a**,**d–e**,**g–k**,**m–u** and **3a** were also fully characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopic and microanalytical data.