Efficient One-Pot Synthesis of 6-Arylpyrrolo[3,2-*d*]pyrimidines from 6-Arylethynyl-5-nitropyrimidines

Inga Cikotiene,* Erika Pudziuvelyte, 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

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Abstract: A highly concise one-pot synthesis of 6-arylpyrrolo[3,2-*d*]pyrimidines via conjugative addition reaction of secondary amines to 6-arylethynyl-5-nitropyrimidines and subsequent reduction is described.

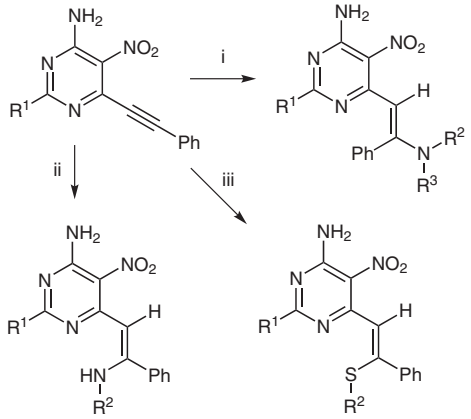
Key words: pyrrolo[3,2-*d*]pyrimidines, 6-arylethynyl-5-nitropyrimidines, enamines, cyclization

The pyrrolo[3,2-*d*]pyrimidine heterosystem is an important class of compounds, possessing notable biological activities, in particular purine nucleoside phosphorylase[1] and thymidylate synthase[2] inhibitory, neuropeptide Y5 receptor[3] and A_1, A_2-adenoside receptor[4] antagonistic properties. A literature survey revealed that 5-aminopyrimidines with suitable substituents are the most often used starting compound for this purpose.[5] Also there are only few examples of straightforward synthesis of pyrrolo[3,2-*d*]pyrimidines from 5-nitropyrimidines[6] and 4-alkynylpyrimidines.[7] The latter method includes classic formation of the pyrrole ring from the neighboring amino group and alkynyl moiety. Normally, the addition of heteroatomic nucleophiles to triple bonds requires high activation energy, so use of harsh reaction conditions, strong bases, or transition-metal catalysts are in practice.[8]

Previous work in our group showed that the triple bond of some 6-arylethynylpyrimidines is electron-deficient, therefore it is extremely reactive towards nucleophilic reagents, and for that reason the formation of addition products as well as various pyrimidine condensed derivatives are favorable.[9] Moreover, we showed that primary and secondary amines and thiols take part in a regio- and stereoselective addition reaction to the triple bond of 5-nitro-6-phenylethynylpyrimidines to form the corresponding *syn* addition (in the case of secondary amines) or *anti* addition (in the case of primary amines or thiols) products (Scheme 1).[10]

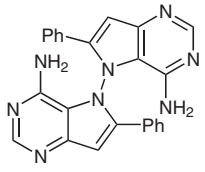
As the latter reaction of starting compounds with secondary amines were fast and high-yielding, we decide to study the possibility of straightforward one-pot synthesis of the pyrrolo[3,2-*d*]pyrimidine framework from 6-arylethynyl-5-nitropyrimidines via reductive cyclization of intermediate enamines.

Our initial studies were aimed at finding optimal conditions for the amine-mediated reductive cyclization of the 6-arylethynyl-5-nitropyrimidines. Our investigation began with 4-amino-5-nitro-6-phenylethynylpyrimidine (**1a**), the corresponding amine (1 equiv) in different solvents under the reductive conditions (Table 1). The best results were obtained using secondary amines, such as diethylamine, pyrrolidine, or piperidine in methanol and performing reduction by hydrogen in the presence of 10% palladium on charcoal (entries 4, 6, 7).



Scheme 1 Our previous work. *Reagents and conditions*: i) secondary amine (1 equiv), CH_2Cl_2, r.t., 20 min; ii) primary amine (1 equiv), CH_2Cl_2, r.t., 48 h; iii) R^2SNa (1 equiv), MeOH, r.t., 30 min.

Other solvents (dichloromethane, ethylacetate) under the same reductive conditions were also investigated and proved to be far less effective (entries 1–3, 10, 11). Moreover, using of primary amines (benzylamine, propylamine) resulted in longer reaction times (entries 3, 8, 9). The latter three results can be explained by much more slower reaction of starting compound **1a** with primary amines and also by stabilization of intermediate enamines (**2**, **3**) by intramolecular hydrogen bond between NH moiety and nitrogen of the pyrimidine ring.



5a

Figure 1 Structure of dimeric side-product **5a**

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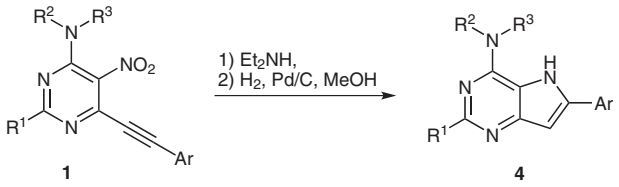
Table 1 Reaction Conditions for Nucleophilic Reductive Cyclization of 4-Amino-5-nitro-6-phenylethynylpyrimidine (**2a**)

Entry	Solvent	Amine	Reductant	Time (h)	Yield of **4a** (%)
1	CH_2Cl_2	Et_2NH	H_2, Pd/C	24	35[a]
2	CH_2Cl_2	$(CH_2)_4NH$	H_2, Pd/C	24	33[a]
3	CH_2Cl_2	$PhCH_2NH_2$	H_2, Pd/C	60	20[a]
4	MeOH	Et_2NH	H_2, Pd/C	2	98
5	MeOH[b]	Et_2NH	$NH_2NH_2{\cdot}H_2O$	1	30[c]
6	MeOH	$(CH_2)_4NH$	H_2, Pd/C	2	90
7	MeOH	$(CH_2)_5NH$	H_2, Pd/C	2	94
8	MeOH	$PrNH_2$	H_2, Pd/C	10	85
9	MeOH	$PhCH_2NH_2$	H_2, Pd/C	12	81
10	THF	Et_2NH	H_2, Pd/C	15	78
11	EtAc	Et_2NH	H_2, Pd/C	48	41
12	EtAc	Et_2NH	$SnCl_2$	48	30
13	DMF	Et_2NH	$SnCl_2$	3	58

[a] Incomplete reduction of **2a** was observed by TLC.
[b] Reaction was performed at reflux temperature.
[c] Formation of dimeric side product **5a** was observed.

Changing the reductant into hydrazine hydrate in boiling methanol (either in the presence of Pd/C or without the catalyst), resulted in formation of side dimeric product **5a** (Table 1, entry 5, Figure 1). Using tin(II) chloride in ethyl acetate or dimethylformamide at room temperature also decreased the yield of final 4-amino-6-phenylpyrrolo[3,2-*d*]pyrimidine (**4a**, Table 1, entries 12, 13). It is noteworthy that better yields of final product were achieved when the starting material was refluxed with an equivalent of secondary amine in methanol for 10–15 minutes, and after the formation of enamine **2** was complete (observed by TLC as deep-red spot), the nitro group was subsequently reduced in the same flask by hydrogen, using 10% Pd/C at the room temperature. Upon reduction, the intermediate **3** rapidly cyclized via intramolecular 1,5-electrocyclic reaction to give the target pyrrolo[3,2-*d*]pyrimidine (**4a**). It should be noted, that we did not find any evidence about the reduction of intermediate enamines C=C bond.

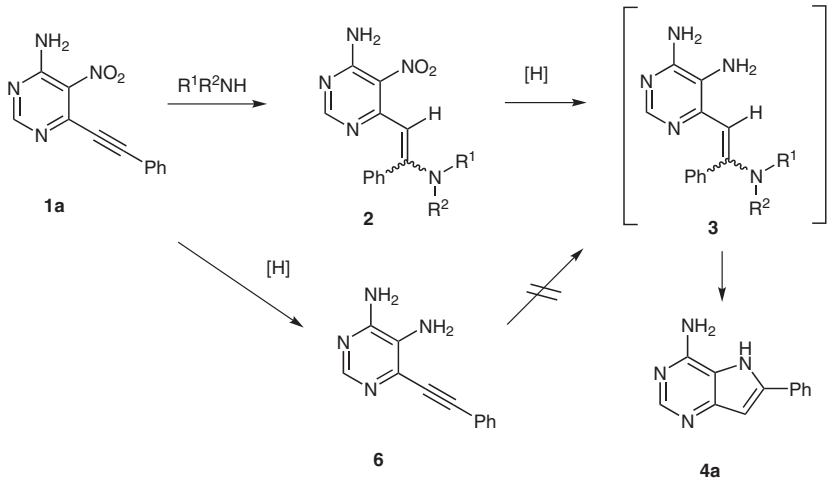
Table 2 Synthesis of 2,4-Disubstituted 6-Arylpyrrolo[3,2-*d*]pyrimidines **4a**–**p** by the Presented Method[11,12]



1 **4**

Entry	Starting compound	R^1	NR^2R^3	Ar	Product	Yield (%)
1	**1a**	H	NH_2	Ph	**4a**	98
2	**1b**	H	NH_2	4-MeC_6H_4	**4b**	80
3	**1c**	H	NH_2	4-EtC_6H_4	**4c**	83
4	**1d**	H	NH_2	4-FC_6H_4	**4d**	79
5	**1e**	SCH_3	NH_2	Ph	**4e**	82
6	**1f**	SCH_3	NH_2	4-MeC_6H_4	**4f**	85
7	**1g**	SCH_3	NH_2	4-EtC_6H_4	**4g**	78
8	**1h**	H	$NHCH_2C_6H_5$	Ph	**4h**	84[a]
9	**1k**	SCH_3	$NHCH_2C_6H_5$	Ph	**4k**	86[a]
10	**1l**	H	$N(CH_2)_4$	Ph	**4l**	88
11	**1m**	SCH_3	$N(CH_2)_4$	Ph	**4m**	90
12	**1n**	H	$N(CH_2)_4$	4-MeC_6H_4	**4n**	92
13	**1o**	H	$N(CH_2)_5$	Ph	**4o**	91
14	**1p**	H	$N(CH_2)_4O$	Ph	**4p**	88

[a] Reductive N-debenzylation of final compounds was not observed.



Scheme 2 Study on the one-pot preparation of pyrrolo[3,2-*d*]pyrimidine framework

Also, it is important to start the reduction of the nitro group only after the complete formation of enamine **2**. Otherwise, the formation of 2,5-diamino-6-phenylethynylpyrimidine (**6**) stops the reaction in the first step, because of inactivation of the triple bond by electron-donating 5-amino group (Scheme 2).

So, according to the present methodology, we have prepared various 2,4-disubstituted 6-arylpyrrolo[3,2-*d*]pyrimidines **4a**–**p** via consequent conjugative addition of secondary amine to 6-arylethynyl-5-nitropyrimidines **1a**–**p** and reductive cyclization reaction of intermediate enamines. The results are summarized in Table 2.

In conclusion, we have developed a novel, simple, and high-yielding synthetic method of pyrrolo[3,2-*d*]pyrimidine framework via one-pot reaction of 2,4-disubstituted 6-arylethynyl-5-nitropyrimidines with secondary amines followed by reductive cyclization. We believe that the present methodology extends promise for the convenient synthetic protocol for the preparation of pyrrolo[3,2-*d*]pyrimidine derivatives of biological interest.

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(11) **Typical Procedure for the Preparation of 2,4-Disubstituted 6-Arylpyrrolo[3,2-*d*]pyrimidines 4a–o**
To a solution of the corresponding 6-arylethynyl-5-nitropyrimidine **1a**–**p** (0.3 mmol) in MeOH (5 mL) freshly distilled Et_2NH (21,9 mg, 0.3 mmol) was added. The resulting reaction mixture was refluxed for 15 min, then deeply red solution was cooled to r.t., 10% Pd/C (0.33 mg, 0.03 mmol) was added, and the resulted mixture was stirred under H_2 atmosphere for 2 h. After the completion of the reaction, the catalyst was filtered off, the mother liquid was evaporated under reduced pressure, the residue washed with H_2O, filtered, and recrystallized to give compounds **4a**–**p**.
4-Amino-6-phenylpyrrolo[3,2-*d*]pyrimidine (4a)
Yield 98%; mp 226–227 °C (from DMF–H_2O). IR (KBr): ν_{max} = 3444, 3441, 3396 (NH, NH_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 6.81 (br s, 2 H, NH_2), 6.86 (s, 1 H, C7H), 7.38 (t, *J* = 7.5 Hz, 1 H, ArH), 7.51 (t, *J* = 7.5 Hz, 2 H, ArH), 7.87 (d, *J* = 7.5 Hz, 2 H, ArH), 8.11 (s, 1 H, C2H), 11.64 (br s, 1 H, NH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ = 98.6, 114.7, 125.1, 128.3, 129.0, 131.1, 131.4, 139.4, 150.2, 150.7 ppm. Anal. Calcd for $C_{12}H_{10}N_4$: C, 68.56; H, 4.79; N, 26.65. Found: C, 68.37; H, 4.51; N, 26.88.
4-Amino-2-methylthio-6-phenylpyrrolo[3,2-*d*]pyrimidine (4e)
Yield 82%; mp 235–237 °C (from DMF–H_2O). IR (KBr): ν_{max} = 3446, 3443, 3398 (NH, NH_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 2.45 (s, 3 H, SCH_3), 6.77 (s, 1 H, C7H), 7.14 (br s, 2 H, NH_2), 7.36 (t, *J* = 7.5 Hz, 1 H, ArH), 7.49 (t, *J* = 7.5 Hz, 2 H, ArH), 7.91 (d, *J* = 7.5 Hz, 2 H, ArH), 12.19 (br s, 1 H, NH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ = 13.4, 98.8, 112.9, 125.2, 127.4, 128.1, 131.5, 139.5, 148.8, 150.3, 160.6 ppm. Anal. Calcd for $C_{13}H_{12}N_4S$: C, 60.91; H, 4.72; N, 21.86. Found: C, 60.77; H, 4.66; N, 21.99.
4-Morpholino-6-phenylpyrrolo[3,2-*d*]pyrimidine (4p)
Yield 88%; mp >230 °C (dec.; from MeOH). IR (KBr): ν_{max} = 3341 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.87 (br s, 8 H, morpholino), 6.86 (s, 1 H, C7H), 7.41–7.48 (m, 3 H, ArH), 7.72 (d, *J* = 7.2 Hz, 2 H, ArH), 8.52 (s, 1 H, C2H), 9.23 (br s, 1 H, NH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ = 46.8, 66.6, 100.9, 116.4, 125.9, 129.1, 129.2, 131.2, 142.1, 150.8, 150.9, 151.4 ppm. Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.50; H, 5.66; N, 20.08.

(12) Compounds **4b**–**d**,**f**–**o** and **5a** were also fully characterized by IR, ^1H NMR, ^{13}C NMR spectroscopic and microanalytical data.