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Tandem reactions of 6-phenylethynylpyrimidine-5-carbaldehydes with alcohols: regioselective synthesis of 5-alkoxy-(7*Z*)-7-benzylidene-5,7-dihydrofuro[3,4-*d*]-pyrimidines and 5-alkoxy-7-phenyl-5*H*-pyrano[4,3-*d*]pyrimidines

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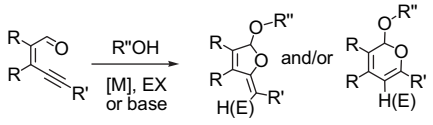
ABSTRACT

An efficient and versatile tandem processes of acetalisation and cycloisomerization reactions have been developed for the reactions of 6-phenylethynylpyrimidine-5-carbaldehydes. The influence of the catalyst and role of the substituent in the position 4 of the pyrimidine ring have been studied. Regioselective synthesis of 5,7-dihydrofuro[3,4-*d*]pyrimidine and pyrano[4,3-*d*]pyrimidine cores is described.

1. Introduction

Functionally substituted alkynes are versatile intermediates in the synthesis of heterocyclic or carbocyclic compounds.[1] A literature survey revealed that cyclization of the carbonyl group on alkynes could undergo transition metal-catalyzed or electrophile-induced 5-*exo*-dig and/or 6-*endo*-dig cyclization reactions (Scheme 1). Thus, Yamamoto et al. reported reactions of acetylenic aldehydes with alcohols catalyzed by palladium.[2] The Pd(II) salt employed was claimed to exhibit a dual role both as a Lewis acid and a transition metal catalyst. In a more recent study, the analogous cyclization of the same acetylenic carbonyl precursors with nucleophiles was achieved in the presence of Cu(I),[3] Cu(II),[3] Ag(I),[4] Au(I),[4] Au(III)[4] salts, bis(pyridine) iodonium tetrafluoroborate (IPy_2BF_4)[5] and HBF_4.[5] Recently, the Larock group found that *o*-(1-alkynyl)-substituted arene carbonyl compounds treated with electrophiles, such as NBS, I_2, ICl, PhSeBr, 4-$NO_2C_6H_4SCl$ and various alcohols or carbon-based nucleophiles underwent smooth three-component reaction to form high-substituted oxygen heterocycles.[6] It was shown that electrophiles attacked the triple bond of the starting compounds, therefore nucleophilic attack of neighbouring carbonyl oxygen became more favourable. Base-catalyzed transformations of aromatic or heteroaromatic aldehydes having an *o*-alkynyl substituent leading mainly to the 5-*exo*-dig cyclization reactions were also reported.[7]



Scheme 1. Literature results overview.

Recently we have studied novel, transition metal catalyst- and initiator-free tandem acetalisation/5-*exo*-dig cyclization reactions of 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehydes to 5-alkoxy-(7*Z*)-7-benzylidene-5,7-dihydrofuro[3,4-*d*]pyrimidines.[8] We showed that transformations of 4-dialkylamino-6-phenylethynylpyrimidine-5-carbaldehydes proceeded smoothly and provided high yields of the 5,7-dihydrofuro[3,4-*d*]pyrimidine derivatives when 1 equiv of sodium or potassium alkoxides in the appropriate primary alcohol at reflux were used. Moreover, we observed that 6-phenylethynylpyrimidine-5-carbaldehydes bearing an alkylamino or arylamino substituent in the position 4 of the pyrimidine ring did not undergo acetalisation/cyclization reactions. Due to limitations of this methodology we searched for methods with an extended scope including the investigation of substituent effects on the regioselectivity of the reactions.

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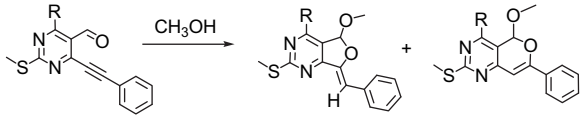
2. Results and discussion

The starting compounds **1a**-**h** were synthesized by the palladium-catalyzed Sonagashira coupling of the corresponding 2,4-disubstituted 6-chloropyrimidine-5-carbaldehydes with phenylacetylene according to procedure described earlier.[8,9]

As we have found recently,[8] 4-dialkylamino-6-phenylethynyl pyrimidine-5-carbaldehydes undergo smooth base-catalyzed acetalisation/5-*exo*-dig cyclization reactions with primary alcohols, leading to the high-yielding formation of 5-alkoxy-(7*Z*)-7-benzylidene-5,7-dihydrofuro[3,4-*d*]pyrimidines. On the other hand, 6-phenylethynylpyrimidine-5-carbaldehydes bearing amino-, alkylamino- or arylamino groups in position 4 of the pyrimidine ring did not undergo the same process. In order to study the generality and regioselectivity of the acetalisation/cyclization reaction two starting compounds bearing morpholino (as *N*,*N*-dialkylamino group, compound **1a**) and anilino (as arylamino group, compound **1b**) in position 4 of the pyrimidine ring were chosen and their reactions with methanol under the different conditions were studied. The results are summarized in Scheme 2 and Table 1.



1-3a: R = $N(CH_2)_4O$;
1-3b: R = NHC_6H_5

Scheme 2.

First of all, we studied the reactivity of 2-methylthio-4-morpholino-6-phenylethynylpyrimidine-5-carbaldehyde (**1a**) with methanol under the different conditions. During heating a solution of the starting compound in methanol in the presence of bases, the regioselective formation of (7*Z*)-7-benzylidene-5-methoxy-4-morpholino-5,7-dihydrofuro[3,4-*d*]pyrimidine (**2a**) took place.[8] Reaction proceeded smoothly and provided high yields of **2a** when 1 equiv of sodium or potassium methoxide were used (entries 2, 3). Then we tried to change the regioselectivity of ring-closure and for this purpose we used catalytic amounts of different transition metals salts in order to form π-complexes between triple bond and metal ion.[10] As shown in Table 1, CuI and $AuCl_3$ (entries 4, 8) were ineffective. After the long heating and work up of the reaction mixtures, the initial compound was recovered. Using 5 mol % of palladium (II) chloride or silver (I) oxide led to the formation of only 5-*exo*-dig cyclization product **2a** (entries 6, 9). However, the reaction of **1a** with methanol in the presence of $Cu(OTf)_2$, $PdCl_2(PPh_3)_2$, $AgNO_3$ or CF_3CO_2Ag proceeded with poor regioselectivity and the formation of mixtures of **2a** and **3a** was observed in these cases (entries 5, 7, 10, 11). We were pleasantly surprised when during heating of solution of **1a** in 1,2-dichloroethane in the presence of 3 equiv of methanol and 5 mol % of $AgNO_3$ in microwave oven after 5 min a high-yielding regioselective formation of 6-*endo*-dig cyclization product **3a** was observed (entry 12). Using CF_3CO_2Ag at the same conditions provided slightly lower regioselectivity (entry 13). However, irradiation of the reaction mixture in the presence of a catalytic amount of silver (I) nitrate together with an equivalent of potassium methoxide completely reversed the regioselectivity—a high-yielding formation of **2a** was observed (entry 14).

The next compound that we chose was 4-anilino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde (**1b**). As we have found recently, compound **1b** treated by sodium methoxide in methanol did not undergo acetalisation/cyclization reactions (entries 15, 16). Moreover silver (I) oxide also did not catalyzed the formation of furo[3,4-*d*]pyrimidine **2b** or pyrano[4,3-*d*]pyrimidine **3b** (entry 17). In all these cases after the work up of the reaction mixtures the initial compound **1b** was recovered. On the other hand, using a catalytic amount of silver (I) salts together with potassium methoxide gave slow but regioselective acetalisation/5-*exo*-dig cyclization (entries 18, 19). Interestingly, when we used

Table 1
Optimization of the acetalisation/5-*exo*-dig or 6-*endo*-dig cyclization reactions of 4-substituted 2-methylthio-6-phenylethynylpyrimidine-5-carbaldehydes (**1a**,**b**) with methanol (Scheme 2)

Entry	Start. comp.	Base	Catalyst	Conditions	*5-exo*-dig product (**2**)	*6-endo*-dig product (**3**)
1	**1a**	K_2CO_3	—	CH_3OH, reflux, 2 h	72%[a]	—
2	**1a**	$NaOCH_3$	—	CH_3OH, reflux, 1 h	92%[a]	—
3	**1a**	$KOCH_3$	—	CH_3OH, reflux, 0.5 h	93%[a]	—
4	**1a**	—	CuI	CH_3OH, reflux, 20 h	No reaction[b]	
5	**1a**	—	$Cu(OTf)_2$	CH_3OH, reflux, 5 h	0.73[c]	0.27[c]
6	**1a**	—	$PdCl_2$	CH_3OH, reflux, 5 h	60%[a]	—
7	**1a**	—	$PdCl_2(PPh_3)_2$	CH_3OH, reflux, 5 h	0.26[c]	0.74[c]
8	**1a**	—	$AuCl_3$	CH_3OH, reflux, 5 h	No reaction[b]	
9	**1a**	—	Ag_2O	CH_3OH, reflux, 40 h	39%[a]	—
10	**1a**	—	$AgNO_3$	CH_3OH, reflux, 4 h	0.41[c]	0.59[c]
11	**1a**	—	CF_3CO_2Ag	CH_3OH, reflux, 4 h	0.49[c]	0.51[c]
12	**1a**	—	$AgNO_3$	CH_3OH/DCE, MW, 610 W, 5 min	—	96%[a]
13	**1a**	—	CF_3CO_2Ag	CH_3OH/DCE, MW, 610 W, 5 min	0.4[c]	0.96[c]
14	**1a**	$KOCH_3$	$AgNO_3$	CH_3OH/DCE, MW, 610 W, 5 min	98%[a]	—
15	**1b**	$KOCH_3$	—	CH_3OH, reflux, 20 h	No reaction[b]	
16	**1b**	$KOCH_3$	—	CH_3OH, MW, 610 W, 30 min	No reaction[b]	
17	**1b**	—	Ag_2O	CH_3OH, reflux, 24 h	No reaction[b]	
18	**1b**	$KOCH_3$	$AgNO_3$	CH_3OH/DCM, rt, 48 h	79%[a]	—
19	**1b**	$KOCH_3$	CF_3CO_2Ag	CH_3OH/DCM, rt, 48 h	82%[a]	—
20	**1b**	—	$AgNO_3$	CH_3OH, reflux, 4 h	—	85%[a]
21	**1b**	—	CF_3CO_2Ag	CH_3OH, reflux, 4 h	—	87%[a]
23	**1b**	—	$AgNO_3$	CH_3OH/DCE, MW, 610 W, 10 min	—	96%[a]
24	**1b**	—	CF_3CO_2Ag	CH_3OH/DCE, MW, 610 W, 10 min	—	98%[a]

[a] Isolated yield.
[b] Starting material recovered.
[c] Ratio estimated by ^1H NMR analysis.

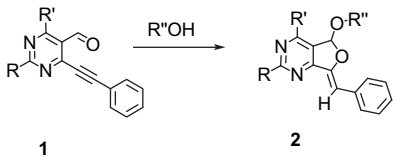
only silver catalysts without addition of bases, we observed regioselective formation of 6-*endo*-dig cyclization product **3b**. The same result was obtained even during convectional or microwave heating (entries 20–24).

So, we have found that the optimal acetalisation/5-*exo*-dig cyclization of 4-*N*,*N*-dialkylamino-6-phenylethynylpyrimidine-5-carbaldehydes conditions are: an equivalent of potassium alkoxides in alcohols, convectional or microwave heating. The best conditions for the acetalisation/5-*exo*-dig cyclization of 6-phenylethynylpyrimidine-5-carbaldehydes bearing amino, alkylamino or arylamino groups in position 4 of the pyrimidine ring are: an equivalent of potassium alkoxide, alcohol (3 equiv), 5 mol % of silver (I) nitrate or silver (I) trifluoroacetate in dichloromethane at room temperature. The optimal acetalisation/6-*endo*-dig cyclization of 4-*N*,*N*-dialkylamino-6-phenylethynylpyrimidine-5-carbaldehydes conditions are: alcohol (3 equiv), 1,2-dichloroethane, 5 mol % of silver (I) nitrate, irradiation of the reaction mixture in microwave oven (610 W) for 5 min. The best conditions for the acetalisation/6-*endo*-dig cyclization of 6-phenylethynylpyrimidine-5-carbaldehydes bearing amino, alkylamino or arylamino groups in position 4 of the pyrimidine ring are: alcohol (3 equiv), 1,2-dichloroethane, 5 mol % of silver (I) nitrate or silver (I) trifluoroacetate convectional heating for 4 h or irradiation of the reaction mixture in microwave oven (610 W) for 10 min. We have also found, that in the presence of silver (I) salts, addition of water to the triple bond of 6-phenylethynylpyrimidine-5-carbaldehydes takes place,[11] so use of anhydrous solvents is strongly recommended.

According to the presented methodologies, we have prepared various 5,7-dihydrofuro[3,4-*d*]pyrimidines (**2**) (Scheme 3) and 5*H*-pyrano[4,3-*d*]pyrimidines (**3**) (Scheme 4). The results are summarized in Tables 2 and 3. It is noteworthy that use of sterically hindered 2-propanol or *tert*-butanol resulted in an incomplete reaction even after prolonged reflux.[8] (Table 2, entry 7). However, using a microwave induced methodology, secondary and tertiary alcohols promote the nucleophilic cyclization effectively (Table 2, entries 7, 9, 15).

From these results we can propose three possible mechanistic pathways for the acetalisation/cyclization reactions. We believe that base-induced acetalisation/5-*exo*-dig cyclization proceeds by a tandem type reaction—formation of an intermediate hemiacetal and immediate nucleophilic cyclization to form the 5,7-dihydrofuran ring. We speculate, that 6-phenylethynylpyrimidine-5-carbaldehydes bearing an NHR′ moiety in the position 4 of the pyrimidine ring, exist in an unfavourable conformation where the carbonyl group is turned towards the NHR′ moiety to form an intramolecular hydrogen bond and directed away from the C≡C bond,[12] therefore tandem reactions become impossible. Using a catalytic amount of silver nitrate or silver trifluoroacetate resulted the complexation of Ag^{+} with C≡C bond (intermediate **4**), thus making rotation of C=O to the activated triple bond more favourable (Scheme 5).

Two of our investigated catalysts—silver (I) oxide and palladium (II) chloride also led to the acetalisation/5-*exo*-dig cyclizations, so we suppose that these species coordinate with the oxygen of the carbonyl moiety of the starting compounds. Thus, intermediate acetal derivative **5** cyclizes to give complex **6** and,



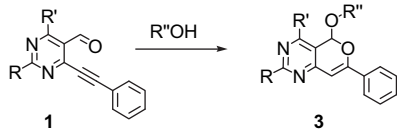
Scheme 3.

Table 2
Data of the synthesis of 2,4-disubstituted 5-alkoxy-(7*Z*)-7-benzylidene-5,7-dihydrofuro[3,4-*d*]pyrimidines **2a**–**r** (Scheme 3)

Entry	Starting comp.	R	R′	R″	Product	Method	Yield, %
1	**1a**	SCH_3	$N(CH_2)_4O$	CH_3	**2a**	A[a]	93
2	**1a**	SCH_3	$N(CH_2)_4O$	CH_3	**2a**	B[b]	100
3	**1b**	SCH_3	NHC_6H_5	CH_3	**2b**	C[c]	82
4	**1a**	SCH_3	$N(CH_2)_4O$	C_2H_5	**2c**	A	90
5	**1a**	SCH_3	$N(CH_2)_4O$	C_2H_5	**2c**	B	97
6	**1a**	SCH_3	$N(CH_2)_4O$	C_4H_9	**2d**	B	78
7	**1a**	SCH_3	$N(CH_2)_4O$	$CH(CH_3)_2$	**2e**	B	89
8	**1a**	SCH_3	$N(CH_2)_4O$	$C(CH_3)_3$	**2f**	A	5[d]
9	**1a**	SCH_3	$N(CH_2)_4O$	$C(CH_3)_3$	**2f**	B	90
10	**1b**	SCH_3	NHC_6H_5	C_2H_5	**2g**	C	76
11	**1c**	SCH_3	NH_2	CH_3	**2h**	C	82
12	**1d**	SCH_3	$N(CH_2)_4$	CH_3	**2i**	A	95
13	**1d**	SCH_3	$N(CH_2)_4$	C_2H_5	**2j**	A	93
14	**1d**	SCH_3	$N(CH_2)_4$	C_4H_9	**2k**	A	79
15	**1d**	SCH_3	$N(CH_2)_4$	$CH(CH_3)_2$	**2l**	B	71
16	**1e**	SCH_3	$N(CH_2)_5$	CH_3	**2m**	A	90
17	**1e**	SCH_3	$N(CH_2)_5$	C_2H_5	**2n**	B	85
18	**1e**	SCH_3	$N(CH_2)_5$	C_4H_9	**2o**	B	89
19	**1f**	H	$N(CH_2)_4$	CH_3	**2p**	A	92
20	**1f**	H	$N(CH_2)_4$	C_2H_5	**2q**	A	94
21	**1g**	H	$N(CH_2)_4O$	C_2H_5	**2r**	A	89

[a] Method A: potassium alkoxide (1 equiv), alcohol, reflux, 0.5–3 h.
[b] Method B: potassium alkoxide (1 equiv), alcohol (3 equiv), 1,2-dichloroethane, microwave oven, 610 W, 5 min.
[c] Method C: potassium alkoxide (1 equiv), alcohol (3 equiv), CF_3CO_2Ag (5 mol %), dichloromethane, rt 24–48 h.
[d] Starting material was recovered.

after catalyst recycling, yields the 5-*exo*-dig product **2**. Moreover, it is important to note again, that 6-phenylethynylpyrimidine-5-carbaldehydes bearing an NHR′ moiety in the position 4 of the pyrimidine ring adopt an unfavourable conformation[12] and do

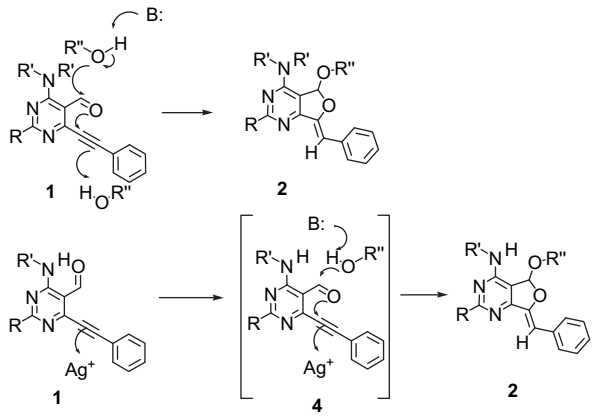


Scheme 4.

Table 3
Data of the synthesis of 2,4-disubstituted 5-alkoxy-7-phenyl-5*H*-pyrano[4,3-*d*]pyrimidines **3a**–**k** (Scheme 4)

Entry	Starting comp.	R	R′	R″	Product	Method	Yield, %
1	**1a**	SCH_3	$N(CH_2)_4O$	CH_3	**3a**	D[a]	49[c]
2	**1a**	SCH_3	$N(CH_2)_4O$	CH_3	**3a**	E[b]	96
3	**1b**	SCH_3	NHC_6H_5	CH_3	**3b**	D	85
4	**1b**	SCH_3	NHC_6H_5	CH_3	**3b**	E	96
5	**1a**	SCH_3	$N(CH_2)_4O$	C_2H_5	**3c**	E	88
6	**1a**	SCH_3	$N(CH_2)_4O$	C_4H_9	**3d**	E	85
7	**1a**	SCH_3	$N(CH_2)_4O$	$CH_2C\equiv CH$	**3e**	E	98
8	**1b**	SCH_3	NHC_6H_5	C_2H_5	**3f**	D	78
9	**1b**	SCH_3	NHC_6H_5	C_4H_9	**3g**	E	84
10	**1c**	SCH_3	NH_2	CH_3	**3h**	E	79
11	**1d**	SCH_3	$N(CH_2)_4$	CH_3	**3i**	D	39[c]
12	**1d**	SCH_3	$N(CH_2)_4$	CH_3	**3i**	E	89
13	**1f**	H	$N(CH_2)_4$	CH_3	**3j**	D	44[c]
14	**1f**	H	$N(CH_2)_4$	CH_3	**3j**	E	82
15	**1h**	H	$NHCH_2C_6H_5$	CH_3	**3k**	D	87

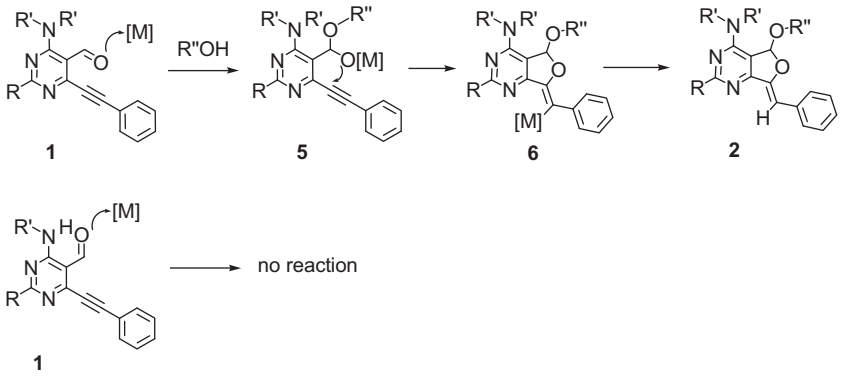
[a] Method D: alcohol, $AgNO_3$ (5 mol %), reflux, 4–6 h.
[b] Method E: alcohol (3 equiv), $AgNO_3$ (5 mol %), 1,2-dichloroethane, microwave oven, 610 W, 5–10 min.
[c] Mixture of **2** and **3** was formed.



Scheme 5. Mechanistic path A.

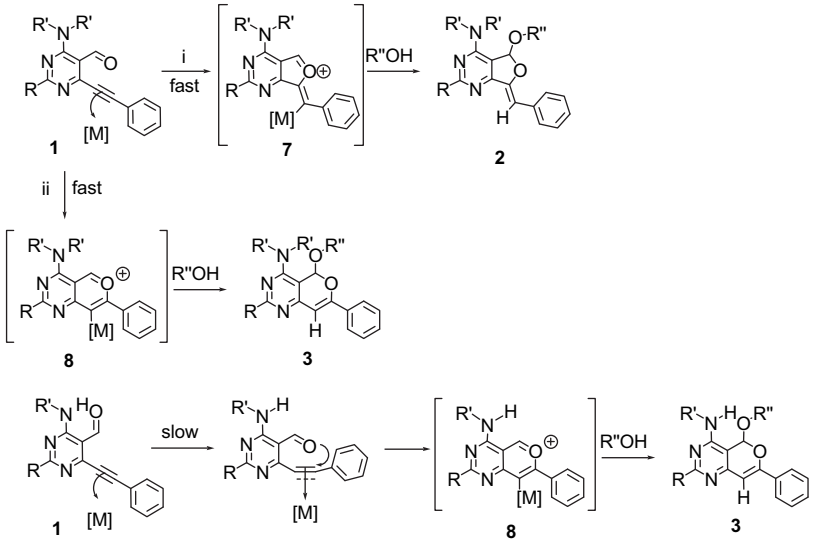
not undergo acetalisation/5-*exo*-dig cyclizations without formation of π-complexes between the triple bond and catalysts (Scheme 6).

of the triple bond of **1**, the enhancement of electrophilicity of the alkyne gives rise to subsequent nucleophilic attack of the carbonyl oxygen atom on the electron deficient alkyne to yield the intermediate complexes **7** and/or **8**. The solvent/nucleophile alcohol can then attack intermediates **7** and **8** and lead to catalyst recycling and liberation of the products **2** and/or **3**. It is noteworthy that 4-dialkylamino-6-phenylethynylpyrimidine-5-carbaldehydes during refluxing in alcohols in the presence of catalysts gave mixture of 5-*exo*-dig and 6-*endo*-dig cyclization products **2** and **3**. This could be explained by the conformation of starting compounds, we believe that carbonyl group is turned away from *N*,*N*-dialkylamino moiety and it is close to the C≡C bond.[12] So, after the complexation the nucleophilic attack by the carbonyl oxygen occurs very quickly and control of regioselectivity is lost. Fortunately, microwave heating of the reaction mixture led to better 6-*endo*-dig regiochemistry. On the other hand, 6-phenylethynylpyrimidine-5-carbaldehydes bearing NHR′ moiety in the position 4 of the pyrimidine ring exist in a different conformation where the carbonyl group is turned towards the NHR′ moiety to form an intramolecular hydrogen bond and directed away from the C≡C bond.[12] Thus, after the complexation



Scheme 6. Mechanistic path B.

The path C (Scheme 7) accounts for the $Cu(OTf)_2$, $PdCl_2(PPh_3)_2$, $AgNO_3$ and CF_3CO_2Ag catalysts without using bases (Table 1, entries 5, 7, 10–13, 20–24), for which upon coordination the carbonyl group rotates to the triple bond slowly and only after the rotation the cyclization process can take place. During this slower process we obtain high regioselectivity.



Scheme 7. Mechanistic path C.

3. Conclusions

In summary, we have developed a novel, concise and regioselective synthetic methods of 5,7-dihydrofuro[3,4-*d*]pyrimidine and 5*H*-pyrano[4,3-*d*]pyrimidine frameworks via acetalisation/cyclization reactions of 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehydes. We have demonstrated the influence of the substituent of the 4—position of the pyrimidine ring on the compound's reactivity and regioselectivity of the reaction. The microwave-induced cycloizomerisation allows use of sterically hindered alcohols. Silver nitrate or silver trifluoroacetate were found to be effective catalysts for the cyclization processes and it was shown that we can control the regiochemistry depending on microwave or convectionl heating, on the presence or absence of base, as well as on the type of catalyst. Three possible mechanisms of the cyclizations were proposed. We believe that the present methodologies enables efficient synthetic protocols for the preparation of furo[3,4-*d*]pyrimidines and pyrano[4,3-*d*]pyrimidines.

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} aluminium plates (Merck). Visualization was accomplished by UV light.

Data for compounds **2a**,**i**,**m** have been published in the previous paper.[8]

4.2. Typical procedures for the preparation of 2,4-disubstituted 5-alkoxy-(7*Z*)-7-benzylidene-5,7-dihydrofuro[3,4-*d*]pyrimidines 2a–r

Method A: To a solution of the corresponding 6-phenylethynylpyrimidine-5-carbaldehyde **1a**,**d**–**g** (0.3 mmol) in an alcohol (5 mL) a solution of potassium alkoxide (0.3 mmol) in the appropriate alcohol (2 mL) was added. The resulting reaction mixture was refluxed for 0.5–2 h. The solvent was evaporated under reduced pressure, the residue washed with water, filtered and recrystallized to give compounds **2a**,**c**–**f**,**i**–**r**.

Method B: A solution of the corresponding 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehyde **1a**,**d**–**g** (0.3 mmol), alcohol (0.9 mmol) and potassium alkoxide (0.3 mmol) in 1,2-dichloroethane (3 mL) was placed in closed 15 mL vessel and irradiated in a microwave oven at 610 W for 5 min. After the heating, the solution was cooled to room temperature, filtered through a silica gel layer, concentrated and the solid residue was recrystallized or purified by flash column chromatography to give **2a**,**c**–**f**,**i**–**r**.

Method C: A solution of the corresponding 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehyde **1b**,**c** (0.3 mmol), alcohol (0.9 mmol), silver trifluoroacetate (5 mol %) and potassium alkoxide (0.3 mmol) in dichloromethane (3 mL) was stirred at room temperature for 24–48 h. After the reaction was complete, the solution filtrated through a silica gel layer, concentrated and the solid residue was recrystallized or purified by flash column chromatography to give **2b**,**g**,**h**.

4.2.1. 4-Anilino-(7Z)-7-benzylidene-5-methoxy-2-methylthio-5,7-dihydrofuro[3,4-d]pyrimidine ***2b***. White solid, yield: 82% (method C), mp 174–176 °C (from MeOH). IR (KBr): ν_{max}=3437 (NH) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.64 (3H, s, SCH_3), 3.48 (3H, s, OCH_3), 6.51 (1H, s, CH), 6.53 (1H, s, CH), 6.84 (1H, br s, NH), 7.20 (1H, t, *J*=7.2 Hz, ArH), 7.28–7.31 (1H, m, ArH), 7.38–7.44 (4H, m, ArH), 7.66 (2H, d, *J*=7.2 Hz, ArH), 7.82 (2H, d, *J*=7.2 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.5, 53.6, 102.5, 104.8, 106.8, 121.5, 124.5, 127.1, 128.5, 128.9, 129.3, 134.5, 137.7, 150.0, 155.3, 161.5, 175.0 ppm. Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13. Found: C, 66.95; H, 5.16; N, 11.07.

4.2.2. (7Z)-7-Benzylidene-5-ethoxy-2-methylthio-4-morpholin-4-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2c***. White solid, yield 90% (method A), 97% (method B), mp 173–174 °C (from EtOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.29 (3H, t, *J*=7.2 Hz, CH_3), 2.60 (3H, s, SCH_3), 3.75–3.87 (8H, m, $N(CH_2)_4O$), 3.80 (2H, q, *J*=7.2 Hz, CH_2), 6.51 (1H, s, CH), 6.66 (1H, s, CH), 7.26 (1H, t, *J*=7.5 Hz, ArH), 7.40 (2H, t, *J*=7.5 Hz, ArH), 7.82 (2H, d, *J*=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.1, 20.6, 45.4, 66.3, 68.6, 100.9, 105.5, 106.4, 126.8, 128.4, 129.1, 132.9, 156.5, 157.7, 162.5, 172.6 ppm. Anal. Calcd for $C_{20}H_{23}N_3O_3S$: C, 62.32; H, 6.01; N, 10.90. Found: C, 62.55; H, 5.99; N, 11.09.

4.2.3. (7Z)-7-Benzylidene-5-butoxy-2-methylthio-4-morpholin-4-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2d***. White solid, yield 78% (method B), mp 163–164 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (3H, t, *J*=7.2 Hz, CH_3), 1.39–1.43 (2H, m, CH_2), 1.52–1.54 (2H, m, CH_2), 2.60 (3H, s, SCH_3), 3.76–3.87 (8H, m, $N(CH_2)_4O$), 3.80–3.84 (2H, m, CH_2), 6.52 (1H, s, CH), 6.64 (1H, s, CH), 7.26 (1H, t, *J*=7.5 Hz, ArH), 7.41 (2H, t, *J*=7.5 Hz, ArH), 7.82 (2H, d, *J*=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.9, 14.1, 22.6, 29.3, 45.4, 66.3, 67.6, 99.9, 105.4, 106.2, 126.5, 128.4, 129.2, 130.9, 155.5, 157.3, 162.0, 174.6 ppm. Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found: C, 64.05; H, 6.59; N, 10.07.

4.2.4. (7Z)-7-Benzylidene-5-isopropoxy-2-methylthio-4-morpholin-4-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2e***. White solid, 89% (method B), mp 155–156 °C (from 2-PrOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (3H, d, *J*=6.0 Hz, CH_3), 1.31 (3H, d, *J*=6.0 Hz, CH_3), 2.59 (3H, s, SCH_3), 3.77–3.85 (8H, m, $N(CH_2)_4O$), 4.15 (1H, sept, *J*=6.0 Hz, CH_2), 6.51 (1H, s, CH), 6.71 (1H, s, CH), 7.23 (1H, t, *J*=7.5 Hz, ArH), 7.39 (2H, t, *J*=7.5 Hz, ArH), 7.81 (2H, d, *J*=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 22.5, 22.7, 45.4, 66.6, 70.5, 101.7, 104.6, 106.7, 126.8, 128.4, 129.1, 134.9, 150.0, 157.3, 162.2, 173.1 ppm. Anal. Calcd for $C_{21}H_{25}N_3O_3S$: C, 63.13; H, 6.31; N, 10.52. Found: C, 63.35; H, 6.29; N, 10.49.

4.2.5. (7Z)-7-Benzylidene-5-tert-butoxy-2-methylthio-4-morpholin-4-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2f***. White solid, yield 5% (method A), yield 90% (method B), mp 189–190 °C dec (from butanol). ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.91 (9H, s, $(CH_3)_3$), 2.29 (3H, s, SCH_3), 3.48–3.58 (8H, m, $N(CH_2)_4O$), 6.14 (1H, s, CH), 6.62 (1H, s, CH), 6.97 (1H, t, *J*=7.5 Hz, ArH), 7.05 (2H, t, *J*=7.5 Hz, ArH), 7.50 (2H, d, *J*=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ=13.5, 28.4, 44.8, 65.7, 72.0, 100.3, 100.8, 107.1, 126.0, 127.7, 128.1, 134.2, 149.5, 156.5, 161.2, 171.8 ppm. Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found: C, 63.98; H, 6.57; N, 10.27.

4.2.6. 4-Anilino-(7Z)-7-benzylidene-5-ethoxy-2-methylthio-5,7-dihydrofuro[3,4-d]pyrimidine ***2g***. White solid, 76% (method C), mp 148–149 °C (from 2-PrOH). IR (KBr): ν_{max}=3438 (NH) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ=1.19 (3H, t, *J*=6.9 Hz, CH_3), 2.56 (3H, s, SCH_3), 3.71–3.73 (1H, m, OCH_2), 3.83–3.87 (1H, m, OCH_2), 6.35 (1H, s, CH), 6.68 (1H, s, CH), 7.16 (1H, t, *J*=7.2 Hz, ArH), 7.27 (1H, t, *J*=7.5 Hz, ArH), 7.38–7.44 (4H, m, ArH), 7.67 (2H, d, *J*=7.2 Hz, ArH), 7.82 (2H, d, *J*=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ=13.6, 15.1, 63.6, 100.5, 105.3, 108.5, 121.8, 123.8, 126.9, 128.5, 128.7, 128.9, 134.4, 138.3, 150.2, 154.8, 160.0, 173.0 ppm. Anal. Calcd for

$C_{22}H_{21}N_3O_2S$: C, 67.50; H, 5.41; N, 10.73. Found: C, 67.45; H, 5.36; N, 10.66.

4.2.7. 4-Amino-(7Z)-7-benzylidene-5-methoxy-2-methylthio-5,7-dihydrofuro[3,4-d]pyrimidine ***2h***. White solid, 82% (method C), mp 175–176 °C. IR (KBr): ν_{max}=3443, 3440 (NH_2) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.47 (3H, s, SCH_3), 3.48 (3H, s, OCH_3), 6.26 (1H, s, CH), 6.52 (1H, s, CH), 6.88 (2H, br s, NH_2), 7.24 (1H, t, J=7.2 Hz, ArH), 7.38–7.44 (2H, m, ArH), 7.80 (2H, d, J=7.2 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 54.6, 101.5, 103.8, 104.8, 121.5, 124.6, 128.1, 132.5, 151.0, 155.2, 162.5, 173.2 ppm. Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 59.90; H, 4.98; N, 13.90.

4.2.8. (7Z)-7-Benzylidene-5-ethoxy-2-methylthio-4-pyrrolidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2j***. White solid, yield 93% (method A), mp 152–154 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.30 (3H, t, J=6.9 Hz, CH_3), 1.96–2.05 (4H, m, $(CH_2)_2$), 2.60 (3H, s, SCH_3), 3.48–3.59 (2H, m, OCH_2), 3.71–3.93 (4H, m, $N(CH_2)_2$), 6.46 (1H, s, CH), 6.67 (1H, s, CH), 7.28 (1H, t, J=7.8 Hz, ArH), 7.39 (2H, t, J=7.8 Hz, ArH), 7.81 (2H, d, J=7.8 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.5, 15.2, 22.9, 25.6, 47.8, 48.9, 63.2, 100.1, 105.8, 107.1, 126.8, 128.6, 128.7, 134.6, 150.5, 155.0, 160.0, 171.9 ppm. Anal. Calcd for $C_{20}H_{23}N_3O_2S$: C, 65.01; H, 6.27; N, 11.37. Found: C, 65.05; H, 6.39; N, 11.26.

4.2.9. (7Z)-7-Benzylidene-5-butoxy-2-methylthio-4-pyrrolidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2k***. White solid, yield 79% (method A), mp 138–140 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=0.93 (3H, t, J=7.2 Hz, CH_3), 1.37–1.45 (4H, m, $(CH_2)_2$), 2.00–2.05 (4H, m, $(CH_2)_2$), 2.61 (3H, s, SCH_3), 3.61–3.85 (6H, m, $N(CH_2)_2$, OCH_2), 6.47 (1H, s, CH), 6.71 (1H, s, CH), 7.25 (1H, t, J=7.5 Hz, ArH), 7.39 (2H, t, J=7.5 Hz, ArH), 7.80 (2H, d, J=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 19.5, 27.0, 31.9, 48.2, 49.3, 67.7, 100.9, 106.7, 107.7, 127.5, 129.3, 129.4, 135.3, 151.2, 155.8, 160.4, 172.6 ppm. Anal. Calcd for $C_{22}H_{27}N_3O_2S$: C, 66.47; H, 6.85; N, 10.57. Found: C, 66.35; H, 6.79; N, 10.48.

4.2.10. (7Z)-7-Benzylidene-5-isopropoxy-2-methylthio-4-pyrrolidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2l***. White solid, yield 71% (method B), mp 144–145 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.24 (3H, d, J=6.0 Hz, CH_3), 1.27 (3H, d, J=6.0 Hz, CH_3), 1.99–2.05 (4H, m, $(CH_2)_2$), 2.55 (3H, s, SCH_3), 3.62–3.70 (6H, m, $N(CH_2)_2$,), 4.16 (1H, sept, J=6.0 Hz, CH_2), 6.29 (1H, s, CH), 7.02 (1H, s, CH), 7.22 (1H, t, J=7.5 Hz, ArH), 7.39 (2H, t, J=7.5 Hz, ArH), 7.77 (2H, d, J=7.5 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 22.5, 22.7, 24.6, 49.3, 69.7, 101.9, 104.7, 105.7, 127.6, 129.4, 129.4, 135.3, 151.3, 155.8, 161.4, 173.8 ppm. Anal. Calcd for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.85; H, 6.51; N, 10.99.

4.2.11. (7Z)-7-Benzylidene-5-ethoxy-2-methylthio-4-piperidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2n***. White solid, yield 85% (method B), mp 122–124 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.30 (3H, t, J=6.9 Hz, CH_3), 1.67–1.70 (6H, m, $(CH_2)_3$), 2.60 (3H, s, SCH_3), 3.70–3.78 (4H, m, $N(CH_2)_2$), 3.80–3.85 (2H, m, OCH_2), 6.48 (1H, s, CH), 6.66 (1H, s, CH), 7.25 (1H, t, J=7.8 Hz, ArH), 7.39 (2H, t, J=7.8 Hz, ArH), 7.81 (2H, d, J=7.8 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 15.2, 24.6, 25.9, 46.5, 43.1, 101.3, 105.4, 106.3, 126.7, 128.4, 129.2, 134.9, 150.4, 156.8, 161.9, 173.1 ppm. Anal. Calcd for $C_{21}H_{25}N_3O_2S$: C, 65.77; H, 6.57; N, 10.96. Found: C, 65.55; H, 6.44; N, 11.02.

4.2.12. (7Z)-7-Benzylidene-5-butoxy-2-methylthio-4-piperidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2o***. White solid, yield 89% (method B), mp 124–126 °C (from 2-PrOH). ^1H NMR (300 MHz, $CDCl_3$): δ=0.94 (3H, t, J=7.2 Hz, CH_3), 1.30–1.28 (4H, m, $(CH_2)_2$), 1.67–1.61 (6H, m, $(CH_2)_3$), 2.60 (3H, s, SCH_3), 3.62–3.65 (2H, m, OCH_2), 3.78–3.79 (4H, m, $N(CH_2)_2$), 6.48 (1H, s, CH), 6.65 (1H, s, CH), 7.25 (1H, t, J=7.8 Hz, ArH), 7.38 (2H, t, J=7.8 Hz, ArH), 7.81 (2H, d, J=7.8 Hz, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 19.5, 27.0, 30.2, 31.9, 48.2, 49.3, 67.7, 100.3, 105.4, 106.6, 126.8, 128.4, 129.4, 134.7, 150.4, 156.8, 161.9, 172.1 ppm. Anal. Calcd for $C_{23}H_{29}N_3O_2S$: C, 67.12; H, 7.10; N, 10.21. Found: C, 67.15; H, 6.99; N, 10.28.

4.2.13. (7Z)-7-Benzylidene-5-methoxy-4-pyrrolidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2p***. White solid, yield 92% (method A), mp 145–147 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.05 (4H, br s, CH_2CH_2), 3.56 (3H, s, OCH_3), 3.80 (4H, br s, $N(CH_2)_2$), 6.50 (1H, s, CH), 6.70 (1H, s, CH), 7.25 (1H, t, J=7.8 Hz, ArH), 7.39 (2H, t, J=7.8 Hz, ArH), 7.80 (2H, d, J=7.8 Hz, ArH), 8.61 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=24.1, 46.9, 53.9, 101.7, 106.4, 109.7, 126.9, 128.4, 129.2, 134.8, 150.7, 156.3, 159.6, 160.3 ppm. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.80; H, 6.01; N, 13.44.

4.2.14. (7Z)-7-Benzylidene-5-ethoxy-4-pyrrolidin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2q***. White solid, yield 94% (method A), mp 134–136 °C (from EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.33 (3H, t, J=6.9 Hz, CH_3), 2.05 (4H, br s, CH_2CH_2), 3.75 (4H, br s, $N(CH_2)_2$), 3.77–3.82 (1H, m, OCH_2), 3.92–4.02 (1H, m, OCH_2), 6.49 (1H, s, CH), 6.70 (1H, s, CH), 7.25 (1H, t, J=7.8 Hz, ArH), 7.39 (2H, t, J=7.8 Hz, ArH), 7.80 (2H, d, J=7.8 Hz, ArH), 8.60 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=15.3, 25.8, 46.9, 63.2, 101.5, 105.7, 110.1, 126.8, 128.4, 129.1, 134.9, 150.8, 156.3, 159.5, 160.2 ppm. Anal. Calcd for $C_{19}H_{21}N_3O_2$: C, 70.57; H, 6.55; N, 12.99. Found: C, 70.70; H, 6.49; N, 13.03.

4.2.15. (7Z)-7-Benzylidene-5-ethoxy-4-morpholin-1-yl-5,7-dihydrofuro[3,4-d]pyrimidine ***2r***. White solid, yield 89% (method A), mp 141–142 °C (from EtOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.32 (3H, t, J=6.9 Hz, CH_3), 3.74–3.78 (2H, m, OCH_2), 3.75 (8H, br s, $N(CH_2)_2O$), 6.54 (1H, s, CH), 6.70 (1H, s, CH), 7.27 (1H, t, J=7.5 Hz, ArH), 7.41 (2H, t, J=7.5 Hz, ArH), 7.81 (2H, d, J=7.8 Hz, ArH), 8.63 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=15.3, 46.9, 58.9, 63.3, 101.0, 105.2, 110.5, 126.1, 128.4, 129.5, 134.9, 151.8, 156.3, 159.5, 161.2 ppm. Anal. Calcd for $C_{19}H_{21}N_3O_3$: C, 67.24; H, 6.24; N, 12.38. Found: C, 67.33; H, 6.40; N, 12.13.

4.3. Typical procedures for the preparation of 2,4-disubstituted 5-alkoxy-7-phenyl-5*H*-pyrano[4,3-*d*]pyrimidines 3a–k

Method D: To a solution of the corresponding 6-phenylethynylpyrimidine-5-carbaldehyde **1a–d**, **f–g** (0.3 mmol) in an alcohol (5 mL) silver nitrate (2.54 mg, 0.015 mmol) was added. The resulting reaction mixture was refluxed for 4–6 h. The solvent was evaporated under reduced pressure, the residue was dissolved in chloroform, filtered through a silica gel layer, concentrated and the solid residue was recrystallized or purified by flash column chromatography to give **3a–k**.

Method E: A solution of the corresponding 2,4-disubstituted 6-phenylethynylpyrimidine-5-carbaldehyde **1a–d**, **f–g** (0.3 mmol), alcohol (0.9 mmol) and silver nitrate (2.54 mg, 0.015 mmol) in 1,2-dichloroethane (3 mL) was placed in closed 15 mL vessel and irradiated in a microwave oven at 610 W for 5–10 min. After the heating, the solution was cooled to room temperature, filtered through a silica gel layer, concentrated and the solid residue was recrystallized or purified by flash column chromatography to give **3a–k**.

4.3.1. 5-Methoxy-2-methylthio-4-morpholin-4-yl-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3a***. Yellowish solid, yield 49% (method D), 96% (method E), mp 175–177 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.61 (3H, s, SCH_3), 3.57 (3H, s, OCH_3), 3.79–3.82

(8H, m, $N(CH_2)_4O$), 6.13 (1H, s, CH), 6.99 (1H, s, CH), 7.43–7.46 (3H, m, ArH), 7.89–7.93 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=16.2, 48.4, 54.9, 66.6, 96.7, 100.5, 101.3, 125.8, 128.8, 130.7, 132.1, 156.6, 157.7, 160.0, 168.9 ppm. Anal. Calcd for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.31. Found: C, 61.56; H, 5.91; N, 11.19.

4.3.2. 4-Anilino-5-methoxy-2-methylthio-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3b***. Yellowish solid, yield 85% (method D), 96% (method E), mp 115–117 °C. IR (KBr): ν_{max}=3441 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.56 (3H, s, SCH_3), 3.61 (3H, s, OCH_3), 6.48 (1H, s, CH), 6.54 (1H, s, CH), 7.00 (1H, br s, NH), 7.15 (1H, t, *J*=7.5 Hz, ArH), 7.39–7.49 (5H, m, ArH), 7.60 (2H, d, *J*=7.5 Hz, ArH), 7.82–7.83 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.2, 56.9, 99.7, 100.4, 101.3, 122.5, 125.8, 126.7, 128.8, 129.2, 129.8, 130.7, 132.1, 156.6, 157.7, 160.0, 169.9 ppm. Anal. Calcd for $C_{21}H_{19}N_3O_2S$: C, 66.82; H, 5.07; N, 11.13. Found: C, 66.85; H, 5.06; N, 11.27.

4.3.3. 5-Ethoxy-2-methylthio-4-morpholin-4-yl-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3c***. Yellowish solid, yield 88% (method E), mp 157–158 °C (from 2-PrOH-octane). ^1H NMR (300 MHz, $CDCl_3$): δ=1.22 (3H, t, *J*=7.2 Hz, CH_3), 2.56 (3H, s, SCH_3), 3.53–3.60 (2H, m, OCH_2), 3.69–3.82 (8H, m, $N(CH_2)_4O$), 6.29 (1H, s, CH), 6.68 (1H, s, CH), 7.44–7.46 (3H, m, ArH), 7.82–7.85 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.0, 14.9, 48.9, 63.4, 66.7, 96.0, 101.2, 102.3, 125.4, 128.6, 130.1, 133.1, 156.4, 157.0, 161.4, 171.0 ppm. Anal. Calcd for $C_{20}H_{23}N_3O_3S$: C, 62.32; H, 6.01; N, 10.90. Found: C, 62.51; H, 5.89; N, 11.01.

4.3.4. 5-Butoxy-2-methylthio-4-morpholin-4-yl-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3d***. Yellowish solid, yield 85% (method E), mp 134–135 °C (from octane). ^1H NMR (300 MHz, $CDCl_3$): δ=0.86 (3H, t, *J*=7.2 Hz, CH_3), 1.27–1.30 (2H, m, CH_2), 1.50–1.54 (2H, m, CH_2), 2.56 (3H, s, SCH_3), 3.56–3.60 (1H, m, OCH), 3.78–3.83 (8H, m, $N(CH_2)_4O$), 4.00–4.07 (1H, m, OCH), 6.23 (1H, s, CH), 6.89 (1H, s, CH), 7.42–7.45 (3H, m, ArH), 7.86–7.89 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.6, 14.9, 19.2, 31.4, 48.6, 66.7, 67.6, 95.9, 101.0, 101.9, 125.6, 128.6, 130.3, 132.7, 156.9, 157.1, 160.7, 170.2 ppm. Anal. Calcd for $C_{22}H_{27}N_3O_3S$: C, 63.90; H, 6.58; N, 10.16. Found: C, 63.95; H, 6.44; N, 10.25.

4.3.5. 2-Methylthio-4-morpholin-4-yl-7-phenyl-5-(prop-2-ynyloxy)-5H-pyrano[4,3-d]pyrimidine ***3e***. Yellow solid, yield 98% (method E), mp 115–117 °C. IR (KBr): ν_{max}=2118 (C≡C) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.56 (3H, s, SCH_3), 2.60 (1H, t, J^4=2.4 Hz, ≡CH), 3.78–3.83 (8H, m, $N(CH_2)_4O$), 4.30 (1H, dd, J^2=16.2 Hz, J^4=2.4 Hz, OCH), 4.60 (1H, dd, J^2=16.2 Hz, J^4=2.4 Hz, OCH), 6.62 (1H, s, CH), 6.72 (1H, s, CH), 7.44–7.47 (3H, m, ArH), 7.82–7.85 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=14.0, 48.8, 53.1, 66.8, 76.1, 77.7, 92.9, 101.5, 101.6, 125.2, 128.7, 130.2, 132.5, 155.7, 157.0, 161.4, 171.3 ppm. Anal. Calcd for $C_{21}H_{21}N_3O_3S$: C, 63.78; H, 5.35; N, 10.63. Found: C, 63.87; H, 5.42; N, 10.75.

4.3.6. 4-Anilino-5-ethoxy-2-methylthio-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3f***. Yellowish solid, yield 78% (method D), mp 122–123 °C. IR (KBr): ν_{max}=3442 (NH) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=1.22 (3H, t, *J*=7.2 Hz, CH_3), 2.49 (3H, s, SCH_3), 3.59–3.64 (2H, m, OCH_2), 6.79 (1H, s, CH), 6.91 (1H, s, CH), 7.18 (1H, t, *J*=7.5 Hz, ArH), 7.39–7.47 (5H, m, ArH), 7.60 (2H, d, *J*=7.5 Hz, ArH), 7.82–7.84 (2H, m, ArH), 8.99 (1H, br s, NH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ=14.2, 15.2, 58.9, 99.7, 100.2, 101.5, 122.5, 125.8, 126.7, 128.8, 129.2, 129.9, 130.7, 132.1, 156.7, 157.7, 162.0, 170.9 ppm. Anal. Calcd for $C_{22}H_{21}N_3O_2S$: C, 67.50; H, 5.41; N, 10.73. Found: C, 67.47; H, 5.40; N, 10.66.

4.3.7. 4-Anilino-5-butoxy-2-methylthio-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3g***. Yellowish solid, yield 84% (method E), mp 108–109 °C. IR (KBr): ν_{max}=3445 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=0.97 (3H, t, *J*=6.8 Hz, CH_3), 1.27–1.30 (2H, m, CH_2), 1.50–1.54 (2H, m, CH_2), 2.60 (3H, s, SCH_3), 3.68 (2H, t, *J*=6.8 Hz, OCH_2), 6.55 (1H, s, CH), 6.58 (1H, br s, NH), 6.59 (1H, s, CH), 7.19 (1H, t, *J*=7.5 Hz, ArH), 7.39–7.47 (5H, m, ArH), 7.60 (2H, d, *J*=7.5 Hz, ArH), 7.66–7.69 (2H, m, ArH), ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.6, 14.4, 19.2, 31.6, 64.1, 85.9, 99.7, 103.2, 122.5, 125.8, 126.9, 128.9, 129.2, 129.9, 131.7, 132.1, 156.7, 156.7, 162.0, 173.9 ppm. Anal. Calcd for $C_{24}H_{25}N_3O_2S$: C, 68.71; H, 6.01; N, 10.02. Found: C, 68.77; H, 6.09; N, 10.11.

4.3.8. 4-Amino-5-methoxy-2-methylthio-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3h***. Yellowish solid, yield 79% (method E), mp 178–180 °C (from MeOH). IR (KBr): ν_{max}=3442, 3439 (NH_2) cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=2.49 (3H, s, SCH_3), 3.54 (3H, s, OCH_3), 6.44 (1H, s, CH), 6.66 (1H, s, CH), 7.18 (2H, br s, NH_2), 7.48–7.50 (3H, m, ArH), 7.88–7.91 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, DMSO-d_6): δ=14.4, 55.2, 96.7, 98.1, 100.3, 126.2, 129.5, 131.1, 133.6, 154.7, 157.1, 159.9, 171.2 ppm. Anal. Calcd for $C_{15}H_{15}N_3O_2S$: C, 59.78; H, 5.02; N, 13.94. Found: C, 60.00; H, 5.09; N, 14.02.

4.3.9. 5-Methoxy-2-methylthio-4-pyrrolidin-4-yl-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3i***. Yellowish solid, yield 39% (method D), 89% (method E), mp 117–118 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ=1.95–1.98 (4H, br s, $(CH_2)_2$), 2.51 (3H, s, SCH_3), 3.55 (3H, s, OCH_3), 3.60–3.67 (4H, m, $N(CH_2)_2$), 6.50 (1H, s, CH), 6.58 (1H, s, CH), 7.40–7.44 (3H, m, ArH), 7.79–7.83 (2H, m, ArH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.2, 25.4, 48.6, 54.1, 97.5, 98.2, 101.3, 125.3, 128.6, 129.8, 133.2, 155.2, 155.7, 156.7, 170.4 ppm. Anal. Calcd for $C_{19}H_{21}N_3O_2S$: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.36; H, 5.90; N, 11.69.

4.3.10. 5-Methoxy-4-pyrrolidin-4-yl-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3j***. Yellowish solid, yield 44% (method D), 82% (method E), mp 112–113 °C (from MeOH). ^1H NMR (300 MHz, $CDCl_3$): δ=2.02 (4H, br s, CH_2CH_2), 3.59 (3H, s, OCH_3), 3.80 (4H, br s, $N(CH_2)_2$), 6.56 (1H, s, CH), 6.79 (1H, s, CH), 7.40–7.44 (3H, m, ArH), 7.79–7.83 (2H, m, ArH), 8.54 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=25.1, 46.9, 53.9, 101.7, 106.4, 109.9, 126.5, 128.4, 129.6, 134.8, 150.7, 157.3, 159.6, 162.3 ppm. Anal. Calcd for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 69.82; H, 6.09; N, 13.45.

4.3.11. 4-Benzylamino-5-methoxy-7-phenyl-5H-pyrano[4,3-d]pyrimidine ***3k***. Yellowish solid, yield 87% (method D), mp 129–130 °C. IR (KBr): ν_{max}=3440 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=3.55 (3H, s, OCH_3), 4.78 (2H, t, *J*=4.5 Hz, CH_2), 5.55 (1H, br s, NH), 6.42 (1H, s, CH), 6.57 (1H, s, CH), 7.32–7.42 (8H, m, ArH), 7.82–7.84 (2H, m, ArH), 8.59 (1H, s, CH) ppm. ^{13}C NMR (75 Hz, $CDCl_3$): δ=44.7, 53.6, 96.6, 98.4, 125.5, 127.5, 128.2, 128.7, 129.3, 130.4, 138.6, 146.8, 157.3, 158.3 ppm. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.03; H, 5.54; N, 12.17. Found: C, 72.98; H, 5.43; N, 12.16.

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References and notes

1. (a) *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, Germany, 1995; (b) *Chemistry of Triple-Bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, NY, 1994.
2. (a) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764; (b) Nakamura, H.; Ohtaka, M.; Yamamoto, Y. *Tetrahedron Lett.* **2002**, 7631.
3. Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5193.

4. Godet, T.; Vaxelaire, C.; Michel, C.; Milet, A.; Belmont, P. *Chem.— Eur. J.* **2007**, *13*, 5632.
5. Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028.
6. (a) Yue, D.; Della Ca, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581; (b) Yue, D.; Della Ca, N.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3381.
7. (a) Godet, T.; Bosson, J.; Belmont, P. *Synlett* **2005**, 2786; (b) Kanazawa, C.; Ito, A.; Terada, M. *Synlett* **2009**, 638.
8. Cikotiene, I.; Morkunas, M.; Motiejaitis, D.; Rudys, S.; Brukstus, A. *Synlett* **2008**, 1693.
9. Cikotiene, I.; Kairys, V.; Buksnaitiene, R.; Morkunas, M.; Motiejaitis, D.; Rudys, S.; Brukstus, A.; Fernandes, M. X. *Tetrahedron* **2009**, *65*, 5752.
10. (a) Lewandos, G. S.; Gregston, D. K.; Nelson, F. R. *J. Organomet. Chem.* **1976**, *118*, 363; (b) Jong, T.-T.; Leu, S.-J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 423; (c) Sun, J.; Kozmin, S. A. *Angew. Chem.* **2006**, *118*, 5113; (d) Hashmi, A. S. K.; Hutchings, G. J. *Angew. Chem.* **2006**, *118*, 8064; (e) Hashmi, A. S. K. *Angew. Chem.* **2005**, *117*, 7150; (f) Chen, L.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1459; (g) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, *104*, 2285; (h) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.
11. Representative procedure of addition of water to the triple bond of 6-phenylethynylpyrimidine-5-carbaldehydes. Synthesis of 4-anilino-6-[(*Z*)-2-hydroxy-2-phenylvinyl]-2-methylthiopyrimidine-5-carbaldehyde (**9**). A solution of 4-anilino-2-methylthio-6-phenylethynylpyrimidine-5-carbaldehyde (**1b**) (0.1 g, 0.29 mmol) and silver (I) nitrate (2.45 mg, 0.0145 mmol) in 95% ethanol (3 mL) was irradiated in a microwave oven at 610 W for 10 min. After heating, the solution was cooled to room temperature, the solvent was evaporated under reduced pressure, and the residue was purified by flash column chromatography. Yellow solid, yield 79%, mp 162–163 °C (from ethanol). IR (KBr): ν_{max}=3468 (broad) (OH, NH), 1624 (C=O) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=2.51 (3H, s, SCH_3), 6.63 (1H, s, CH), 7.08 (1H, t, J=8.7 Hz, ArH), 7.26–7.32 (2H, m, ArH), 7.36–7.39 (3H, m, ArH), 7.56–7.59 (2H, m, ArH), 7.82–7.85 (2H, m, ArH), 10.30 (1H, s, CH), 11.61 (1H, br s, NH), 16.09 (1H, s, OH) ppm ^{13}C NMR (75 Hz, $CDCl_3$): δ=13.4, 85.6, 98.9, 121.6, 121.9, 124.3, 125.8, 127.9, 128.1, 130.4, 134.9, 136.7, 156.7, 164.8, 171.9, 187.6 ppm. Anal. Calcd for $C_{20}H_{17}N_3O_2S$: C 66.10, H 4.71, N 11.56. Found: C 66.29, H 4.89, N 11.65. This compound in chloroform solution exists as a tautomeric mixture of enol (79%) and keto form (21%).
12. The structures of several starting compounds were optimized using Density Functional Theory (DFT) methods. It was observed, that the carbonyl group is turned towards to the NHR′ moiety (in 6-phenylethynylpyrimidine-5-carbaldehydes bearing primary amino, alkylamino or aniline group in the position 4 of the pyrimidine ring) or turned towards to the triple bond (in 6-phenylethynylpyrimidine-5-carbaldehydes bearing *N*,*N*-dialkylamino group in the position 4 of the pyrimidine ring).