Tetrahedron Letters 53 (2012) 5144–5147

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Efficient palladium-mediated or base-induced 5-*endo-dig* cyclisation of C5-alkynylated pyrimidine derivatives: conventional and microwave-assisted synthesis of novel furo[2,3-*d*]pyrimidines

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ARTICLE INFO

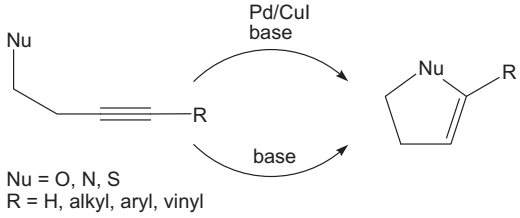
Article history:
Received 28 March 2012
Revised 29 June 2012
Accepted 12 July 2012
Available online 20 July 2012

Keywords:
5-Alkynylpyrimidines
Furo[2,3-*d*]pyrimidines
N-Methoxymethylated pyrimidine derivatives
Sonogashira cross-coupling reaction
5-*Endo-dig* cyclisation

ABSTRACT

A series of the novel 5-alkynyl- and furo[2,3-*d*]pyrimidine derivatives in which the sugar moiety is replaced by a methoxymethyl (MOM) group is synthesised using the Sonogashira cross-coupling reaction under both conventional and microwave conditions, in good to excellent yields. The 5-*endo-dig* cyclisation of 5-alkynylpyrimidine derivatives promoted by a Pd-catalyst or base gives the corresponding furo[2,3-*d*]pyrimidines in good yields.

Nucleoside analogues continue to dominate the area of antiviral therapy and make a significant contribution to cancer chemotherapy. Furthermore, the structural diversity and biological importance of pyrimidines have made them attractive targets for synthesis. For this reason, numerous analogues and derivatives of pyrimidines have been synthesised and developed as pharmacologically active compounds or drugs.[1] In particular, a number of pyrimidine nucleoside analogues with potent biological properties have been prepared by substitution at the 5-position of the pyrimidine ring.[2] Moreover, functionalised alkynes are found to be important building blocks for the synthesis of biologically active pyrimidine derivatives.[3] Bicyclic pyrimidine nucleosides such as oxazole-, thieno- or imidazopyrimidines have demonstrated pronounced antiviral and antileukemic activities.[4,5] Based on the potent bioactivities of compounds with a furo[2,3-*d*]pyrimidine core, the development of efficient syntheses of novel *N*-alkylated furo[2,3-*d*]pyrimidine derivatives has attracted our attention. We considered position C6 of the furopyrimidine scaffold an interesting target for the synthesis of the corresponding *N*-MOM derivatives, and employed the Sonogashira cross-coupling reaction under both conventional and microwave conditions[6] as the key step.



Scheme 1. Overview of the 5-*endo-dig* mode of cyclisation.

Intramolecular 5-*endo-dig* cyclisation of 5-alkynylpyrimidines is a powerful strategy for the construction of furo[2,3-*d*]pyrimidines and other heterocycles (Scheme 1).[7] Only limited examples of the *endo*-mode of cyclisation under basic conditions using KO*t*-Bu, Bu_4NOAc, Et_3N or K_2CO_3, and in the absence of transition metals, have led to functionalised cyclised products.[8]

As part of our ongoing research directed towards economical and environmentally friendly cyclisations of acetylenic compounds, we investigated the *O*-heteroannulation of 5-ethynylpyrimidine derivatives using microwave irradiation. Herein, we describe the K_2CO_3-mediated cyclisation of 5-alkynylpyrimidine

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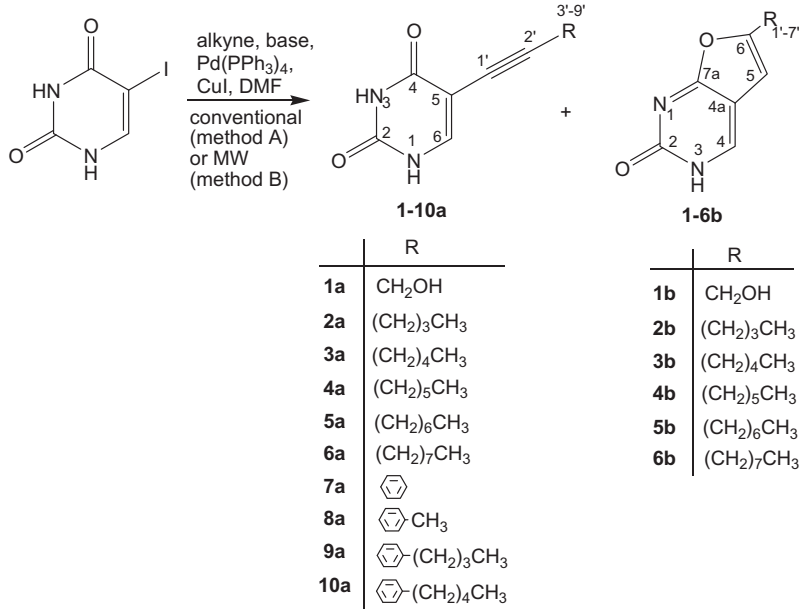
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.068



	R
1a	CH_2OH
2a	$(CH_2)_3CH_3$
3a	$(CH_2)_4CH_3$
4a	$(CH_2)_5CH_3$
5a	$(CH_2)_6CH_3$
6a	$(CH_2)_7CH_3$
7a	
8a	
9a	
10a	

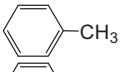
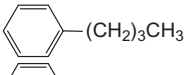
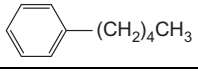
	R
1b	CH_2OH
2b	$(CH_2)_3CH_3$
3b	$(CH_2)_4CH_3$
4b	$(CH_2)_5CH_3$
5b	$(CH_2)_6CH_3$
6b	$(CH_2)_7CH_3$

Scheme 2. Conventional and microwave-assisted Sonogashira cross-coupling reactions.

derivatives, as the first example of base-induced 5-*endo-dig* cyclisation of simple unactivated alkynes in the absence of activating reagents towards the alkynyl π bond. A simple and general approach for the synthesis of *N*-methoxymethylated furo[2,3-*d*]pyrimidine derivatives **11**–**16** and 5-alkynylpyrimidine derivatives **17**–**20** is presented. Sonogashira cross-couplings[9] of 5-iodouracil with various alkylacetylenes and (*p*-alkylaryl)acetylenes in the presence of catalytic amounts of tetrakistriphenylphosphine palladium(0) [$Pd(PPh_3)_4$], and copper(I) iodide (CuI) as the co-catalyst and a base (Et_3N) in DMF at room temperature overnight gave the corresponding 5-alkynylated pyrimidine derivatives **1**–**10a** in good yields and furo[2,3-*d*]pyrimidines **1**–**6b** as the products of *5-endo-dig* cyclisation (Scheme 2).[10]

To the best of our knowledge, microwave-assisted Sonogashira cross-coupling to introduce long alkynyl and (*p*-alkylaryl)ethynyl groups at position C5 of the pyrimidine moiety has never been reported. Both conventional (method A) and microwave-assisted (method B) Sonogashira reactions gave the 5-alkynylated **1**–**10a** and furo[2,3-*d*]pyrimidines **1**–**6b** (Scheme 2). In general, the microwave-assisted Sonogashira reaction gave 5-alkynylated **1**–**10a** and furo[2,3-*d*]pyrimidines **1**–**6b** in good to excellent yields in short reaction times. The reaction conditions and yields for the conventional and microwave-assisted syntheses of compounds **1**–**10** are summarised in Table 1. In comparison to reactions under microwave irradiation, conventional syntheses provided 5-alkynylated pyrimidine derivatives **1**–**10a** in higher yields, while microwave synthesis gave increased yields (2- to 28-fold) of bicyclic products **1**–**6b** (Table 1). The only exception was the reaction of 5-iodouracil with propargyl alcohol (entry 1, Table 1). It should be noted that the microwave-assisted reaction of 5-iodouracil with (*p*-alkylaryl)acetylenes gave only the 5-alkynylated pyrimidine derivatives **7**–**10a**. The 5-*endo-dig*-cyclisation of **7**–**10a** under both conventional and microwave conditions was not detected. In contrast, the one-step palladium-copper catalysed reaction of 5-iodouracil with terminal alkylacetylenes gave both C5-alkynylated **1**–**6a** and bicyclic products **1**–**6b** (Scheme 2).

Table 1
Conventional and microwave-assisted syntheses of compounds **1**–**10**

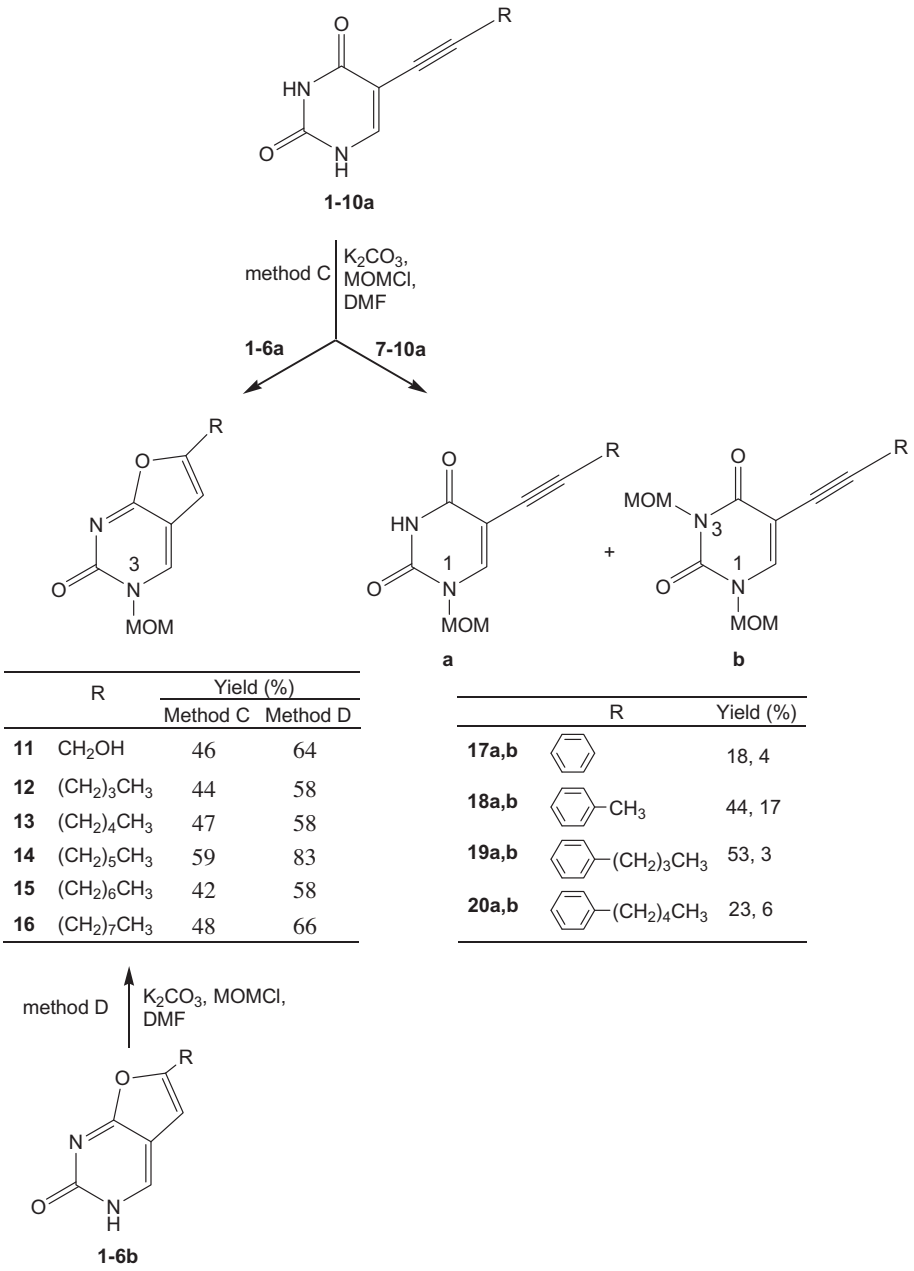
Compd.	R	Conventional synthesis				Microwave-assisted synthesis			
		Base	Time (h)	Yield (%)		Base	Time (h)	Yield (%)	
				a	b			a	b
1	CH_2OH	Et_3N	15	56	–	Et_3N	0.5	71	2
		$(iPr)_2EtN$	15	29	58	$(iPr)_2Et$	2	37	–
2	$(CH_2)_3CH_3$	Et_3N	15	76	1	Et_3N	0.5	25	3
3	$(CH_2)_4CH_3$	Et_3N	15	85	1	Et_3N	0.5	32	25
4	$(CH_2)_5CH_3$	Et_3N	15	33	23	Et_3N	2	18	52
5	$(CH_2)_6CH_3$	Et_3N	15	42	2	Et_3N	2	33	7
6	$(CH_2)_7CH_3$	Et_3N	15	68	12	Et_3N	2	8	52
7		Et_3N	24	55	–	Et_3N	10	14	–
8		Et_3N	24	60	–	Et_3N	10	29	–
9		Et_3N	24	78	–	Et_3N	10	48	–
10		Et_3N	24	64	–	Et_3N	10	34	–

Compounds **1**–**10a** were subsequently submitted to *N*-methoxymethylation reactions. As the literature attests, there are only a few reports on the MOM protection of nitrogen in a pyrimidine ring,[11] and no reports of *N*-MOM pyrimidines with long 5-alkynyl side chains or 6-alkylfuro[2,3-*d*]pyrimidines. *N*-methoxymethylation reactions of 5-alkynylated pyrimidine derivatives **1**–**10a** were performed with K_2CO_3 (2.5 equiv) and methoxymethyl chloride (MOMCl, 2 equiv) in DMF at room temperature. We found that 5-alkynylpyrimidines **1**–**6a** underwent smooth base-catalysed 5-*endo*-*dig* cyclisation, leading to the formation of furo[2,3-*d*]pyrimidines **11**–**16** in good yields (42–59%, method C). On the other hand, the methoxymethylation reaction of 5-[(*p*-alkylaryl)ethynyl]pyrimidines **7**–**10a** gave *N*-1-MOM **17**–**20a** and *N*,*N*-1,3-diMOM **17**–**20b** 5-alkynylated pyrimidine derivatives (method C, Scheme 3).[12] Pyrimidine derivatives **7**–**10a** bearing (*p*-alkylaryl)acetylenes at C5 did not afford bicyclic products, even after prolonged reaction times (method C, Scheme 3). *N*-3-MOM-furo[2,3-*d*]pyrimidine derivatives **11**–**16** were also obtained from the corresponding furopyrimidines **1**–**6b** in methoxymethylation reactions with K_2CO_3 in good to excellent yields (58–83%) (method D, Scheme 3).[12]

Moreover, *N*,*N*-1,3-diMOM 5-alkynylated pyrimidine derivatives (**22**–**25**) were prepared by Sonogashira cross-coupling reactions of aliphatic acetylenes with 5-iodo-1,3-bis(methoxymethyl)pyrimidine (**21a**) using both conventional and microwave conditions (see Supplementary data).

The structures of the newly synthesised compounds **1**–**20** were deduced by analysis of their ^{1}H and ^{13}C NMR and mass spectra as well as elemental analyses. The assignments of the ^{1}H NMR spectra were performed on the basis of the chemical shifts, signal intensities and the magnitudes and multiplicities of H–H coupling constants (see Supplementary data).

The 5-alkynylated and furo[2,3-*d*]pyrimidine derivatives **1**–**20** were evaluated for their cytostatic activities against human



	R	Yield (%) Method C	Method D
11	CH_2OH	46	64
12	$(CH_2)_3CH_3$	44	58
13	$(CH_2)_4CH_3$	47	58
14	$(CH_2)_5CH_3$	59	83
15	$(CH_2)_6CH_3$	42	58
16	$(CH_2)_7CH_3$	48	66

	R	Yield (%)
17a,b		18, 4
18a,b		44, 17
19a,b		53, 3
20a,b		23, 6

Scheme 3. *N*-Methoxymethylation reactions.

malignant tumour cell lines: cervical carcinoma (HeLa), breast epithelial adenocarcinoma, metastatic (MCF-7), hepatocellular carcinoma (HepG2), colorectal adenocarcinoma (SW620), pancreatic carcinoma (MiaPaCa-2) and normal human fibroblasts (WI38). However, the results indicated that the evaluated compounds did not significantly inhibit any of the tested malignant tumour cell lines.

In conclusion, we have described an efficient, experimentally simple and attractive one-pot syntheses of 5-alkynylated pyrimidines **1**–**10a** and furo[2,3-*d*]pyrimidine derivatives **1**–**6b** *via* a Sonogashira cross-coupling/heteroannulation approach under conventional and microwave conditions. While conventional synthesis provided 5-alkynylpyrimidines **1**–**10a** as the major products, synthesis under microwave irradiation afforded bicyclic products **1**–**6b** in considerably increased yields. We found that pyrimidine derivatives with alkynyl side chains at C5, **1**–**6a**, underwent smooth base-promoted 5-*endo*-*dig* cyclisation during methoxymethylation reactions leading to good yields of furo[2,3-*d*]pyrimidines **11**–**16**. However, pyrimidine derivatives bearing (*p*-alkylaryl)acetylenes at C5 did not undergo the *O*-heteroannulation, thus affording *N*-1-MOM **17**–**20a** and *N*,*N*-1,3-diMOM **17**–**20b** 5-[(*p*-alkylaryl)ethynyl]pyrimidine derivatives. We believe this is the first report of an alternative procedure for the synthesis of *N*-alkylated 5-alkynyl- and furo[2,3-*d*]pyrimidine derivatives promoted by K_2CO_3. Furthermore, this synthetic procedure is potentially suitable for the preparation of a variety of *N*-alkylated heterocyclic structural analogues that could be developed as potential biologically active compounds.

Acknowledgements

Support of this study by the Ministry of Science, Education and Sports of the Republic of Croatia (projects #125-0982464-2925 and #335-0000000-3532) is gratefully acknowledged.

Supplementary data

Supplementary data (^{1}H and ^{13}C NMR, mass spectrometry and elemental analysis data of compounds **1**–**20**, synthesis and experimental procedures of compounds **21**–**25**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.068.

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10. *General procedure for the preparation of **1**–**10a** and **1**–**6b***. To a solution of 5-iodopyrimidine (0.84 mmol) in anhydrous DMF (7 mL) were added the terminal alkyne (2.5 mmol), $Pd(PPh_3)_4$ (0.08 mmol), CuI (0.08 mmol) and Et_3N [or $(iPr)_2EtN$] (1.68 mmol). *Method A:* The reaction mixture was stirred at room temperature overnight. The extent of the reaction was monitored by TLC and the solvent was evaporated in vacuo and the residue purified by column chromatography (initial eluent CH_2Cl_2, then CH_2Cl_2/MeOH = 40:1) to afford **1**–**10a** and **1**–**6b**. *Method B:* The synthesis was carried out at 50 °C for 30 min under microwave irradiation (300 W, 1 bar, Milestone start S microwave oven). Purification by column chromatography (initial eluent CH_2Cl_2, then CH_2Cl_2/MeOH = 40:1) afforded compounds **1**–**10a** and **1**–**6b**.
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12. *Method C:* a solution of 5-alkynylpyrimidine derivative **1**–**10a** (0.4 mmol) and K_2CO_3 (1 mmol) in anhydrous DMF (5 mL) was cooled to 0 °C, and after 10 min, methoxymethyl chloride (MOMCl) (1.2 mmol) was added. The obtained mixture was additionally stirred at room temperature overnight and the solvent was then evaporated. Purification by column chromatography (CH_2Cl_2/MeOH = 40:1) afforded compounds **11**–**20**. *Method D:* a solution of furo[2,3-*d*]pyrimidine derivative **1**–**6b** (0.08 mmol) and K_2CO_3 (0.16 mmol) in anhydrous DMF (1 mL) was cooled to 0 °C, and after 10 min, MOMCl (0.16 mmol) was added. The obtained mixture was additionally stirred at room temperature overnight and the solvent was then evaporated. Further purification by column chromatography (CH_2Cl_2/MeOH = 40:1) afforded **11**–**16**.