Tetrahedron xxx (2015) 1–6

Contents lists available at ScienceDirect

Tetrahedron

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

A convenient one-pot process for the synthesis of 2,4-dihydroxy-6-phenylethylenyl-8-deazapteridine derivatives

Meng Wang [a], Chao Tian [a], Xiaowei Wang [a], Junyi Liu [a,b,*], Zhili Zhang [a,*]

[a] State Key Laboratory of Natural and Biomimetic Drugs, Peking University, Beijing 100191, China
[b] Department of Chemical Biology, School of Pharmaceutical Sciences, Peking University, Beijing 100191, China

ARTICLE INFO

Article history:
Received 9 July 2015
Received in revised form 26 October 2015
Accepted 30 October 2015
Available online xxx

Keywords:
2,4-Dihydroxy-6-methylpyrido[3,2-*d*]pyrimidine
8-Deazapteridine derivatives
p-Toluenesulfonamide

ABSTRACT

We have developed an efficient one-pot reaction for the synthesis of 2,4-dihydroxy-6-phenylethylenyl-8-deazapteridine derivatives using 2,4-dihydroxy-6-methylpyrido[3,2-*d*]pyrimidine, aromatic aldehydes and *p*-toluenesulfonamide through C(sp^3)–H bond functionalization. This method is easy to operate and high-yielding, which is potentially useful for diversity-oriented synthesis.

1. Introduction

Pteridine derivatives have been well exploited because of their diverse biological activities such as anti-cancer,[1] antimicrobial,[2] anti-inflammatory,[3] immunosuppressive,[4] anti-viral,[5] antioxidant[6] and neuroprotective activities.[7] These compounds, such as aminopterin (AMT) and methotrexate (MTX), serve as one-target or multi-target antifolate agents against dihydrofolate reductase, methionine synthase, thymidylate synthase or glycinamide ribonucleotide formyltransferase (GARFT).[8] The effective biological activities of pteridine derivatives encourage researchers to explore more related compounds. New pteridine derivatives as nonclassical antifolate agents, lacking a glutamate substitution and generally containing lipophilic side chains, were developed to overcome the resistance of classic antifolate agents from metabolization by folylpoly-γ-glutamate synthetase (FPGS).[9] Among them, trimethoprim (TMP) and trimetrexate (TMQ) have been developed as active agents for the treatment of tumour and prophylaxis of opportunistic infections (Fig. 1). In particular, 6-phenylethyl and 6-phenylethylenyl 8-deazapteridine derivatives have attracted considerable attention owing to their high potential in drug discovery.[10,11] (Fig. 1) The most common synthetic approach to 6-substituted 2,4-diamino-8-deaza folate analogues is via reactions of 2,4-diamino-6-bromomethylpyrido[3,2-*d*]pyrimidine and methyl phenylacetate[10] or benzaldehyde.[11] In both methods, the activation of 6-methyl group of pteridine to 6-bromomethyl needs a multi-step procedure and the lability of bromo group often gives more inconvenience in the synthesis. Moreover, the synthesis of 2,4-dihydroxy analogues has not been reported.

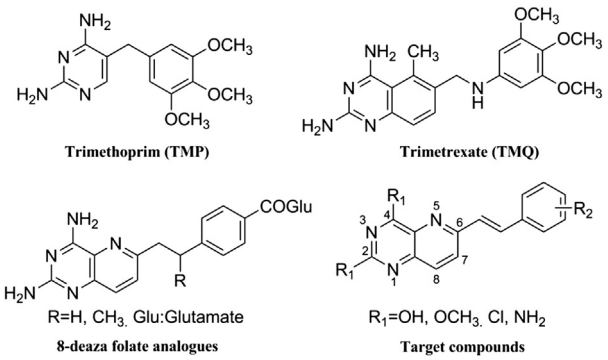


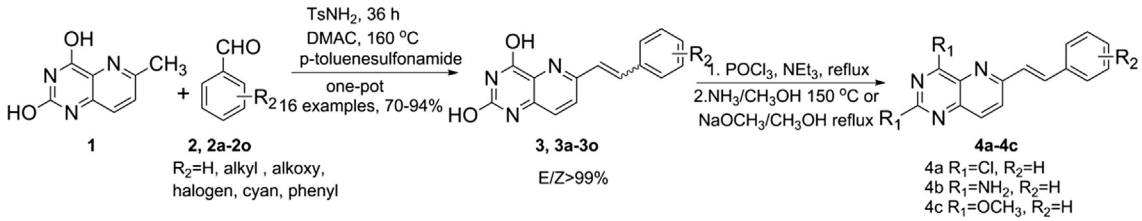
Fig. 1. Structures of TMP, TMQ, 6-phenylethyl-8-deaza folate analogues, and target compounds.

Recently, it is reported that the direct C(sp^3)–H bond functionalization of 2-methyl azaarenes can be promoted by BrØnsted acid, metal Lewis acid or microwave-assisted conditions.[12] For example, the synthesis of alkenylazaarenes was achieved through the

* Corresponding authors. Tel.: +86 10 82805203 (Z.Z.); e-mail address: lilybmu@bjmu.edu.cn (J. Liu).

http://dx.doi.org/10.1016/j.tet.2015.10.084
0040-4020/

addition of methylazaarenes to *N*-sulfonyl aldimines such as *N*-tosyl aldimines and subsequent C–N elimination in situ.[13] Herein, we report a one-pot synthesis of previously unreported 2,4-dihydroxy-6-phenylethylenyl-8-deazapteridine derivatives via C(sp^3)–H bond activation of 2,4-dihydroxy-6-methylpyrido[3,2-*d*] pyrimidine (**1**) with various benzaldehydes and *p*-toluenesulfonamide (Scheme 1). Futhermore, the products can serve as valuable precursors for the further transformation of the 2- and 4-position to obtain more diverse 8-deazapteridine derivatives.



Scheme 1. Synthesis of 6-phenylethylenyl-8-deazapteridine derivatives.

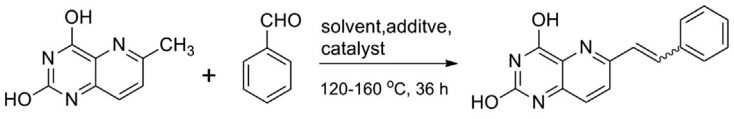
2. Results and discussion

Initially, the three-component reaction of 2,4-dihydroxy-6-methylpyrido[3,2-*d*]pyrimidine (**1**), benzaldehyde (**2**), and *p*-toluenesulfonamide was chosen as a model reaction to optimize reaction conditions (Table 1). The reaction was performed in a one-pot process. When stirred in toluene at 110 °C as reported in the literature,[13] no reaction occurred on treatment of 2,4-dihydroxy-6-methylpyrido[3,2-*d*]pyrimidine (**1**), benzaldehyde (**2**) and *p*-toluenesulfonamide (1:1.2:1.2) under argon atmosphere, even after prolonged heating for 36 h. When the reaction mixture was heated at 110 °C in DMF, a trace of 2,4-dihydroxy-6-styrylpyrido[3,2-*d*] pyrimidine (**3**) was obtained, and at 140 °C, 48% yield was obtained. We found that the formation of compound **3** is quite temperature dependent. When dimethylacetamide (DMAC) was used as solvent and heated 160 °C, the desired product was isolated in 90% yield (Table 1, entry 5). To further optimize the reaction conditions, conventionally used Lewis acids and *N*-sulfonyl aldimines were examined. We found that $Pd(OAc)_2$, $Fe(OAc)_2$, or $Sc(OTf)_3$[14] have no effect on the reaction temperature and only slight effect on the yield (Table 1, entries 6–8). And when *p*-toluenesulfonamide was replaced with *p*-nitrophenylsulfonamide (PNBSA) or *p*-toluenesulfonhydrazide (PTSH) (Table 1, entries 9 and 10), yields were low. More *p*-toluenesulfonamide was used and no better result was obtained. (Table 1, entry 11). The screening results demonstrated that the one-step alkenylation of 2,4-dihydroxy-6-methylpyrido [3,2-*d*]pyrimidine via sp^3 C–H bond activation in DMAc at 160 °C was an efficient approach to achieve 2,4-dihydroxy-6-alkenyl pteridine derivatives.

With these promising results in hand, the scope of the process with respect to the substituted benzaldehydes was subsequently explored. Generally, as summarized in Table 2, benzaldehydes bearing electron-releasing or electron-withdrawing groups were transformed into the desired 6-phenylethylenyl-8-deazapteridine derivatives (Table 2, entries 1–12) smoothly, and so were diphenyl and naphthanyl aldehyde derivatives (Table 2, entries 13–15). The electron-deficient and weakly electron-rich aldehydes **2d**–**2l** afforded the desired products **3d**–**3l** in high yields of 90–94% (Table 2, entries 4–12). In contrast, the electron-rich aldehydes **2a**–**2c** gave the corresponding products **3a**–**3c** in slightly lower yields of 70%, 77% and 86%, respectively. (1,1′-Biphenyl)-4-carboxaldehyde, 1-naphthaldehyde and 2-naphthaldehyde **2m**–**2o** (Table 2, entries 13–15) afforded the corresponding products **3m**–**3o** in 90%, 90% and 91% yields, respectively.

We subsequently investigated the reactions of 6-methylpyrido [3,2-*d*]pyrimidines with 2,4-bischloride and 2,4-bismethoxyl substituents. It was found that they were not tolerated under the optimized conditions. In order to prepare more diversely 2,4-

Table 1
Optimization of reaction condition[a]



Entry	Solvent[b]	Additive 1	Catalyst (10%)	Ratio[c] (mol)	Temp (°C)	Yield[d] (%)
1	Toluene	*p*-Toluenesulfonamide	—	1:1.2:1.2	120	nd[e]
2	DMF	*p*-Toluenesulfonamide	—	1:1.2:1.2	120	Trace
3	DMF	*p*-Toluenesulfonamide	—	1:1.2:1.2	140	48
4	DMAC	*p*-Toluenesulfonamide	—	1:1.2:1.2	140	50
5	**DMAC**	***p*-Toluenesulfonamide**	—	**1:1.2:1.2**	**160**	**90**
6	DMAC	*p*-Toluenesulfonamide	$Pd(OAc)_2$	1:1.2:1.2	120/160	Trace/94
7	DMAC	*p*-Toluenesulfonamide	$Fe(OAc)_2$	1:1.2:1.2	120/160	Trace/93
8	DMAC	*p*-Toluenesulfonamide	$Sc(OTf)_3$	1:1.2:1.2	120/160	Trace/91
9	DMAC	PNBSA	—	1:1.2:1.2	120/160	Trace/90
10	DMAC	PTSH	—	1:1.2:1.2	120/160	Trace/Trace
11	DMAC	*p*-Toluenesulfonamide	—	1:3:3	160	85

Bold indicates optimized reaction condition.
[a] 2,4-dihydroxy-6-styrylpyrido[3,2-*d*]pyrimidine **1** 5.6 mmol, reaction time for 36 h.
[b] 10 mL.
[c] **1**:**2**: *p*-toluenesulfonamide.
[d] Isolated yield.
[e] nd=not detected.

Please cite this article in press as: Wang, M.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.10.084