Tetrahedron xxx (2013) 1–13

Contents lists available at SciVerse ScienceDirect

Tetrahedron

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

Condensation reactions of guanidines with bis-electrophiles: formation of highly nitrogenous heterocycles☆

David M. Arnold, Matthew G. LaPorte, Shelby M. Anderson, Peter Wipf*

University of Pittsburgh, Center for Chemical Methodologies and Library Development, Pittsburgh, PA 15260, USA

ARTICLE INFO

Article history:
Received 3 March 2013
Received in revised form 24 April 2013
Accepted 26 April 2013
Available online xxx

Keywords:
Guanidines
Pyrimidines
Quinazolines
Atwal–Biginelli reaction
Screening library

ABSTRACT

2-Amino-1,4-dihydropyrimidines were reacted with bis-electrophiles to produce novel fused bipyrimidine, pyrimidoaminotriazine, and pyrimidosulfonamide scaffolds. In addition, a quinazoline library was constructed using a guanidine Atwal–Biginelli reaction with 1-(quinazolin-2-yl)guanidines. The product heterocycles have novel constitutions with high nitrogen atom counts and represent valuable additions to screening libraries for the discovery of new modulators of biological targets.

1. Introduction

Diversity Oriented Synthesis (DOS) inspires chemists to design or apply chemical methodologies that result in the synthesis of structurally diverse, functionally rich and often architecturally complex small molecule scaffolds.[1,2] In many cases, new biological targets can be explored more effectively with DOS-derived probes and natural products than traditional aromatic 'drug-like' heterocycles.[3] Novel molecular scaffolds are therefore valuable additions to high throughput screening libraries and improve the odds of identifying lead compounds in drug discovery initiatives.[4,5]

As a continuation of our efforts in the preparation of rare heterocyclic scaffolds,[6] we became interested in developing a convergent synthetic route to 4*H*-pyrimido[1,2-*a*]pyrimidines. While there is evidence in the literature demonstrating melanin-concentrating hormone receptor (MCH1R) antagonistic effects,[7] protein kinase inhibition,[8] treatment of atherosclerosis and restenosis,[9] antiviral activities,[10] inhibition of platelet aggregation,[11] and anti-MRSA dihydrofolate reductase activity[12] of 4*H*-pyrimido[1,2-*a*]pyrimidines **1**, their synthesis and application is strikingly rare compared to the structurally and pharmacologically related ring-contracted imidazo[1,2-*a*]pyridines **2** (Fig. 1). The latter

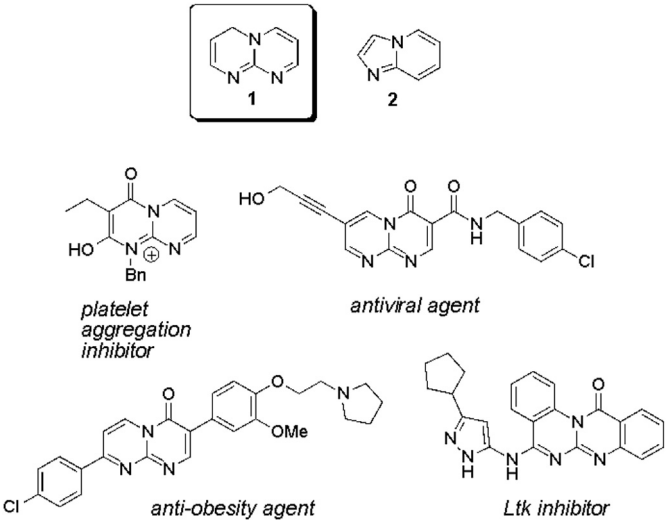


Fig. 1. The 4*H*-pyrimido[1,2-*a*]pyrimidine and imidazo[1,2-*a*]pyridine scaffolds **1** and **2**, and selected biologically active derivatives.

heterocycle is an abundant pharmacophore in medicinal chemistry and has been used in antiviral, antibacterial, anti-inflammatory, analgesic, antipyretic, and anxioselective indications. Derivatives of **2** are β-amyloid formation inhibitors and constitute a novel class of orally active nonpeptide bradykinin B2 receptor antagonists.[13] Several imidazo[1,2-*a*]pyridines are already clinically used,

☆ Submitted in honor of Prof. Paul Wender, the recipient of the 2012 Tetrahedron Prize for Creativity in Organic Chemistry.

* Corresponding author. Tel.: +1 412 624 8606; fax: +1 412 624 0787; e-mail address: pwipf@pitt.edu (P. Wipf).

0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.04.127

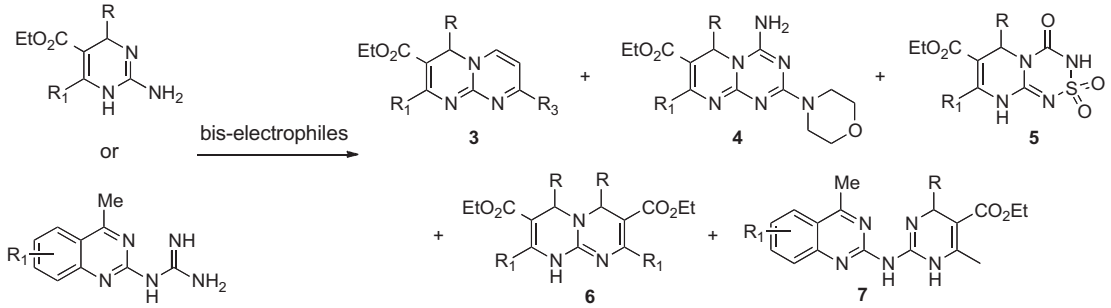
including zolimidine (an anti-ulcer drug), zolpidem (a hypnotic drug), and alpidem (a nonsedative anxiolytic). Imidazo[1,2-*a*]pyrimidine moieties are also important as benzodiazepine receptor agonists, antiviral agents, antibacterials, antifungal agents, and calcium channel blockers.[13]

Using a variant of the Biginelli three-component reaction for the preparation of cyclic guanidines,[14,15] we were able to develop efficient strategies for a tandem condensation with bis-electrophiles to give bipyrimidines **3**, pyrimidoaminotriazines **4**, cyclic pyrimidosulfonamides **5**, and pyrimidopyrimidines **6** (Scheme 1). In addition, a small sub-library of quinazoline-containing heterocycles **7** was assembled using Atwal–Biginelli conditions.[16,17]

Table 1
Conversion of thioureas (**8a**, R=CH_3; **8b**, R=$(CH_2)_2Ph$; **8c**, R=$CH(CH_3)_2$) to thioimidates **9a–c** and 2-aminopyrimidines **10a–c** according to Scheme 2

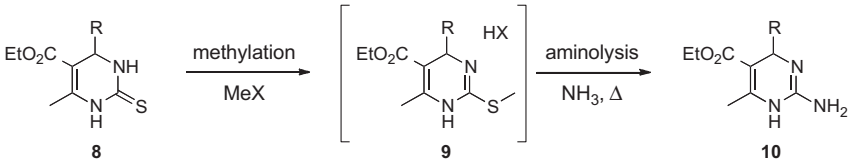
Entry	**8**/Conditions	**9**/Additive/time	**10**/Yield[a] %
1	**8a**/MeOTf, THF, 1.5 h	**9a**/NH_4OAc/20 h	**10a**/77
2	**8a**/MeOTf, $ClCH_2CH_2Cl$, 0.75 h	**9a**/NH_4OAc/15 h	**10a**/30
3	**8a**/MeOTf, PhCl, 3.5 h	**9a**/NH_4OAc/17 h	**10a**/61
4	**8a**/MeOTf, PhCl, 15 h	**9a**/NH_4Cl/21 h	**10a**/51
5	**8a**/$(MeO)_2SO_2$, THF, 60 h	**9a**/NH_4OAc/17 h	**10a**/57
6	**8b**/MeOTf, PhCl, 3.5 h	**9b**/NH_4OAc/17 h	**10b**/39
7	**8c**/MeOTf, PhCl, 3.5 h	**9c**/NH_4OAc/20 h	**10c**/33

[a] Isolated yield of purified product.



Scheme 1. Overview of heterocycles obtained by condensation of guanidines with bis-electrophiles.

New strategies for accessing structurally diverse guanidine-based Biginelli products have previously been reported by the Overman group.[18] Specifically, triazone-protected guanidines were found to endure the harsh acidic conditions frequently used for the Biginelli cyclization.[18] In order to access C-4 alkyl-substituted cyclic guanidines **10**, we first envisioned using thioureas **8** as starting materials followed by an aminolysis of the corresponding methylthioureas **9**, in a manner similar to that reported by Kappe (Scheme 2).[19]



Scheme 2. Thiourea methylation followed by aminolysis of the thioimidate provides access to 2-aminodihydropyrimidines.

2. Results and discussion

Thioureas **8** with R=methyl, phenethyl, and isopropyl were prepared through Biginelli multicomponent condensations from β-ketoesters, aldehydes, and thiourea under standard acid-catalyzed conditions.[20] The reaction parameters for the one-pot methylation/aminolysis were optimized on substrate **8a** (R=Me) (Table 1, entries 1–5). Initial investigations using methyl iodide resulted in dealkylation of the newly formed methylthiourea **9a**, most likely due to the presence of nucleophilic iodide ions in the vigorously heated aminolysis reaction mixture.[21] Accordingly, methyl triflate was used as an alternative electrophile for the *S*-alkylation and proved effective for the formation of the desired guanidine **10a** in good isolated yields. The use of dimethyl sulfate also provided **10a** in 57% yield but required prolonged reaction times (entry 5). High yields of product **10a** were achieved when THF was used as the reaction solvent. However, the methylation step was problematic due to the propensity of methyl triflate to polymerize THF.[22] The optimal solvent for this two-step reaction sequence was found to be chlorobenzene (PhCl), which was both inert to the reaction conditions and could safely be heated to 95–100 °C under sealed tube conditions (Table 1, entry 3). The aminolysis step was found to proceed smoothly on multigram scale (2.5 g) with ammonium acetate or ammonium chloride as additives in the presence of ammonia. Following this one-pot reaction, the hydrochloride salts of **10a–c** were prepared and subsequently used as substrates for further cyclization reactions (vide infra).

The 4-arylated 2-aminopyrimidine **13**·**TFA** was obtained in a two-step sequence starting from PMB–guanidine **11** (Scheme 3).[23] Treatment of a solution of **11** in hexafluoroisopropanol with enone **12** and sodium bicarbonate at 90 °C provided the PMB-protected **13** in 42% yield. Deprotection of the PMB group was accomplished in 70% yield in TFA buffered with water, triethylsilane, and thioanisole.[24] A three-component Biginelli reaction with guanidine hydrochloride **14**·**HCl**, ethyl 3-oxo-3-phenylpropanoate **15**, and aldehydes **16** and **17** was performed to access heterocycles **18**, **19**, and the hydrochloride salt **18**·**HCl** (Scheme 4).

Cyclization reactions of guanidines with the bis-electrophile 1,1,3,3-tetramethoxypropane (**20**) were explored under microwave conditions (Scheme 5 and Table 2).[25,26] We found that these reactions proceeded smoothly in 42–76% yield when the hydrochloride salts of **10a–c** or **18** were combined with **20** in a microwave vial and heated to 160 °C in trifluoroethanol (**21**) (entries 1–4). The use of the hydrochloride salts was essential since the corresponding reactions with free amines did not afford the cyclocondensation products. We also briefly explored the reaction of **18** with 4-methoxybut-3-enone **26** to give 8-methyl 4*H*-pyrimido[1,2-*a*]pyrimidine **27** in 64% yield (Table 2, entry 5).

Please cite this article in press as: Arnold, D. M.; et al., Tetrahedron (2013), http://dx.doi.org/10.1016/j.tet.2013.04.127