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A novel multicomponent synthesis of polyfunctionalized bicyclic tetrahydropyrimidinone derivatives via mercaptoacetylative ring transformations

Lal Dhar S. Yadav *, Ankita Rai

Green Synthesis Lab, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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ABSTRACT

A novel K-10 clay (nanoclay)-catalyzed expeditious synthesis of polyfunctionalized bicyclic pyrimidines using unprotected aldoses, 2-methyl-2-phenyl-1,3-oxathiolan-5-one and amidines/guanidine is reported. These polyfunctionalized bicyclic pyrimidines were obtained in excellent yields (72–93%) with high cis diastereoselectivity (>94%) at the ring junction via tandem condensation, mercaptoacetylative ring transformation and cyclization reactions. The process presents an excellent illustration of use of carbohydrates as renewable resources for the formation of pharmaceutically relevant fine chemicals employing solvent-free microwave irradiation conditions in a one-pot procedure.

1. Introduction

Many naturally occurring thiosugars are potential targets for the carbohydrate-based therapeutics, such as Thiolactomycin, Salacinol, Kotalonol, Tagetioxin and Mycothiol.[1] Sugars incorporating intracyclic sulfur atom (thiosugars) are of considerable interest. For example, 5-thio-D-glucose (Fig. 1) is an α-glycosidase inhibitor,[2] and some 5-thioglycosidases have antithrombotic effect[3] and other useful medicinal properties.[1] The biological interest in thiosugars has expanded the studies on diabetes enzyme inhibitor, antiviral and antitumour activities.[4–9]

Pyrimidines are found widely as a core structure in a large variety of compounds that exhibit important biological activities.[10–12] Pyrimidines and their derivatives as a class of extremely important heterocyclic compounds are used in a wide array of synthetic and industrial applications. They not only are an integral part of the genetic materials, namely, DNA and RNA as nucleotides and nucleosides, but also play critical roles especially in pharmaceutical fields.[13,14] For example, L-lathyrine, a naturally occurring 2-aminopyrimidine, shows a wide range of biological activities such as pollen growth inhibition and antitumour and hypoglycemic activities (Fig. 1).[15] Furthermore, some pyrimidine derivatives can give stable and good quality nanomaterials having many important electrical and optical properties,[16,17] and they can also be used as functional materials.[18–20] Thus, development of a convenient and efficient methodology for the synthesis of thiosugar-fused bicyclic pyrimidines is an interesting target of investigation.

Amongst the various general procedures available for the synthesis of pyrimidines, the most general method is based on the bis-nucleophile plus bis-electrophile methods[21–27] or cross-coupling reactions[28,29] and is restricted to methods involving Pinner synthesis via 3,4- and 1,6- (I);[21–27] 1,2- and 2,3- (II);[30] 1,2- and 3,4- (III);[31] 4,5- and 1,6- (IV);[32] 2,3- and 4,5- (V)[33–35] and 3,4- and 4,5- (VI)[36] bond-forming original reactions (Scheme 1). Recently, we have disclosed a synthesis of pyrimidine via novel 1,2- and 1,6- bond-forming reactions (VII, Scheme 1).[37] Lewis acid-promoted multicomponent organic transformations are gaining increasing popularity due to their economic and ecological efficacy. Also, in situations where a premium is put on speed, diversity and efficiency, multicomponent reactions (MCRs) are of

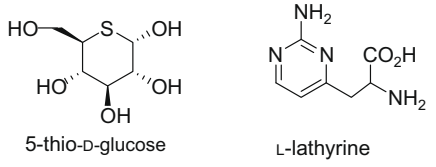

Figure 1.

* Corresponding author. Tel.: +91 5322500652; fax: +91 5322460533.
E-mail address: ldsyadav@hotmail.com (L. D. S. Yadav).

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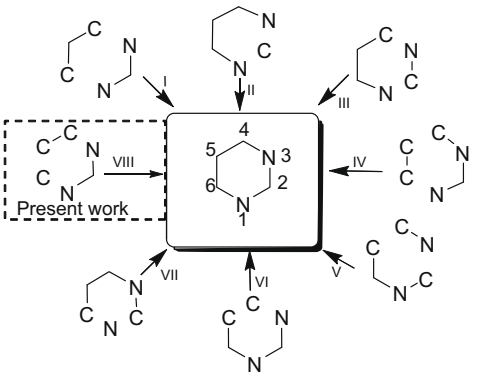


Scheme 1. Various routes for pyrimidine synthesis.

increasing importance. Again, due to interest in the preparation of 5-thiosugar derivatives many 5-thiosugars were synthesized from sugars,[38–41] instead, however these methods generally require multisteps. Thus, we have devised a novel K-10 clay (nanoclay)-catalyzed multicomponent reaction for the annulation of the pharmaceutically important thiosugars with a pyrimidine moiety, which would afford attractive scaffolds for exploiting their chemical diversity. Also, the presence of free polyhydroxyl groups would enhance water solubility and biodegradability of the target molecules.

This article reports a conceptually new route for the synthesis of polyfunctionalized pyrimidines via 3,4-, 4,5- and 1,6 bond-forming reaction (VIII, Scheme 1) using a [3+1+2] coupling protocol starting from unprotected aldoses **1**, N-unsubstituted amidines/guanidine **2** and activated mercaptoacetic acid **3** (Scheme 2). The present unprecedented synthesis of functionalized bicyclic pyrimidines **4** and **5** is an outcome of our continued interest in solvent-free heterocyclization strategies,[42–47] especially using carbohydrates as raw materials.[48,49] Furthermore, the present synthetic protocol is in accord with 'renewable resources', a new and rapidly developing concept in environmental and chemical sciences that concerns the wide use of biorenewable materials for industry.[50]

2. Results and discussion

In our initial experiment we optimized the catalyst for the present reaction. We have examined various mineral catalysts for the formation of **4a** (R = Me). Among the catalysts tested, K-10 clay gave the best result (Table 1, entry 1). $CeCl_3{\cdot}7H_2O$/NaI-system and $CeCl_3{\cdot}7H_2O$ afforded the product **4a** in moderate to good yields (Table 1, entries 2 and 3), while poor yields of product **4a** were obtained in the case of silica gel and neutral or acidic alumina (Table 1, entries 4–6). Moreover, the reaction did not take place when basic alumina was used as the catalyst. It was also observed that significantly lower yield of **4a** was obtained using oil-bath heating rather than the MW-activated method with all the catalyst systems (Table 1). After optimization of the reaction conditions, the polyfunctionalized bicyclic pyrimidines **4** and **5** were efficiently synthesized by microwave (MW) irradiation of an intimate solvent-free mixture of D-xylose/D-glucose **1**, amidines/guanidine **2**, 2-methyl-2-phenyl-1,3-oxathiolone-5-one **3** and the nanoclay, Montmorillonite K-10 (particle size 32.7 nm), at 80 °C for 7–12 min in a Chemical Laboratory Microwave Oven (Model: BP-310/50, 230 V, 50 Hz power input) (Scheme 2).

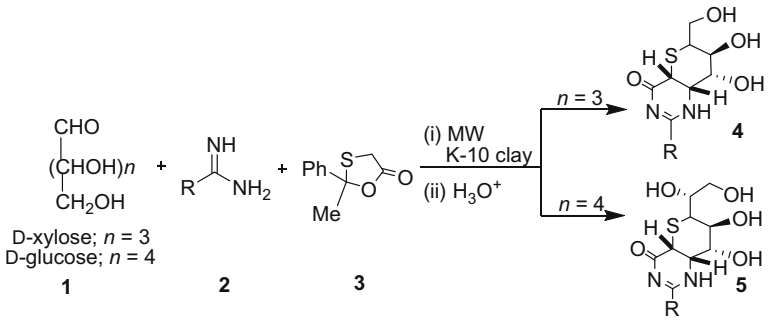
Table 1
Optimization of reaction conditions for compound **4a** (R = Me)

Entry	Catalyst system	MW		Oil-bath	
		Time[a] (min)	Yield[b] (%)	Time[a] (h)	Yield[b] (%)
1	K-10 clay	10	91	7	56
2	$CeCl_3{\cdot}7H_2O$	12	53	7	22
3	$CeCl_3{\cdot}7H_2O$/NaI	11	62	8	31
4	Silica gel	13	25	10	19
5	Neutral alumina	16	17	10	11
6	Acidic alumina	16	20	9	13

[a] Time for the completion of the reaction at 80 °C as indicated by TLC.
[b] Yield of isolated and purified product **4a**.

Isolation and purification by recrystallization from ethanol afforded **4** and **5** in 72–93% yields with >94% diastereoselectivity (Table 2) in favor of the isomer with cis ring junction as determined by ^{1}H NMR spectroscopy.[47,51–55] The crude isolates were checked by ^{1}H NMR for their diastereomeric ratios to note any inadvertent alteration of these ratios during subsequent purification. In products **4** and **5**, the rings are cis fused as indicated by the coupling constants of ring junction protons 4a-H and 8a-H ($J_{4a,8a}$ = 4.9 Hz). It is also supported by NOE interaction experiments. For example, 11.6% and 12.3% NOEs were observed between 4a-H and 8a-H in products **4a** and **5a**, respectively, indicating that 4a-H and 8a-H are located on the same face of the molecule, hence confirming the cis fusion of the rings.

The chiral carbons of the precursor carbohydrates retain their configuration in the product if they are not involved in any bond breaking/formation. This fact is supported by the observation that there was no change in the absolute configuration of any chiral carbon of D-xylose or D-glucose when an intimate solvent-free mixture of D-xylose or D-glucose (2.0 mmol) and K-10 clay (0.20 g) was subjected to MW irradiation at 80 °C for 15 min, that is, under the present reaction conditions. The formation of **4** and **5** may be tentatively rationalized by intramolecular attack of the nitrogen atom of the amidine/guanidine moiety at the carbonyl carbon (C-5) of the 2-methyl-2-phenyl-1,3-oxathiolan-5-one **3** to yield the target compounds **4** and **5**. This conclusion is based on the observation that the representative intermediate compounds **7a** and **7g** have been isolated in 52% and 59% yields, respectively, and that



Scheme 2. Synthesis of bicyclic pyrimidines **4** and **5**.