DIB and $[NMM]^+[HSO4]^-$ catalyzed one-pot three component synthesis of novel glycosyl dihydropyrimidin-2-one/thione derivatives

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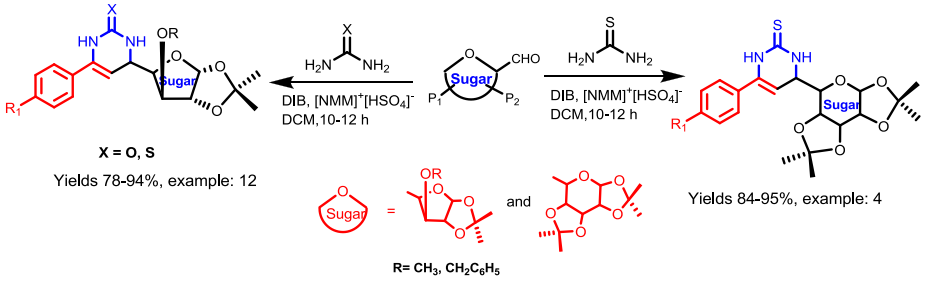
Abstract

A novel one-pot diacetoxyiodobenzne (DIB) and N-methylmorpholinium hydrogen sulphate catalyzed three component protocol has been developed for the synthesis of novel carbohydrate based dihydropyrimidin-2-ones/thiones at room temperature. This approach provides a new access to a diverse multifunctionalized glycosyl-heterocycle compounds from glycosyl ulose, acetophenone and urea/thiourea. The developed synthetic approach is simple, clean and environmentally benign in comparison to conventional methods.



INTRODUCTION

Dihydropyrimidin-2-ones/thiones, a class of useful and interesting heterocyclic compounds have found increasing applications in organic synthesis as important building blocks of heterocyclic compounds of great medicinal values.[1] Multi-functionalized dihydropyrimidine skeleton is often considered as privileged skeleton to identify the novel and potential leads in drug discovery as it displays a wide spectrum of biological activities such as antiviral, antitumor, antibacterial, anti-inflammatory,[2] and mitotic kinesin inhibition. [3] and dihydropyridine calcium channel modulators.[4] (*S*)-L-771688 (**1**) is a more potent and selective R1a receptor antagonist for the treatment of benign prostatic hyperplasia (BPH) than the (*R*)-enantiomer.[5] (*R*)-enantiomer of SQ 32926 (**2**), a calcium channel blocker, exhibits >400-fold more potent antihypertensive activity in vitro than the other enantiomer,[6] and α-1a receptor antagonists (**3**) and neuropeptide Y (NPY) antagonists which made them the most attractive targets for synthetic chemists.[7] The interest in this heterocyclic core has been further increased by the identification of monastrol (**4**) as a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest. [(8)]

Monastrol specifically inhibits the mitotic kinesin Eg5 motor protein and can be considered as a new lead for the development of anticancer drug, antihypertensive agents.[9] Recently, marine natural products with core dihydropyrimidine-5-carboxylate shown significant multifaceted biological profile,[10] among them are the batzelladine alkaloids A (**5**), and their analogues which inhibit the binding of HIV envelope protein gp-120 to human CD4 cells therefore which proved new potential leads for AIDS therapy. Thus, the diverse range of biological activities of these moieties has stimulated considerable interest to synthesize these heterocyclic scaffolds using new and efficient routes. [11]

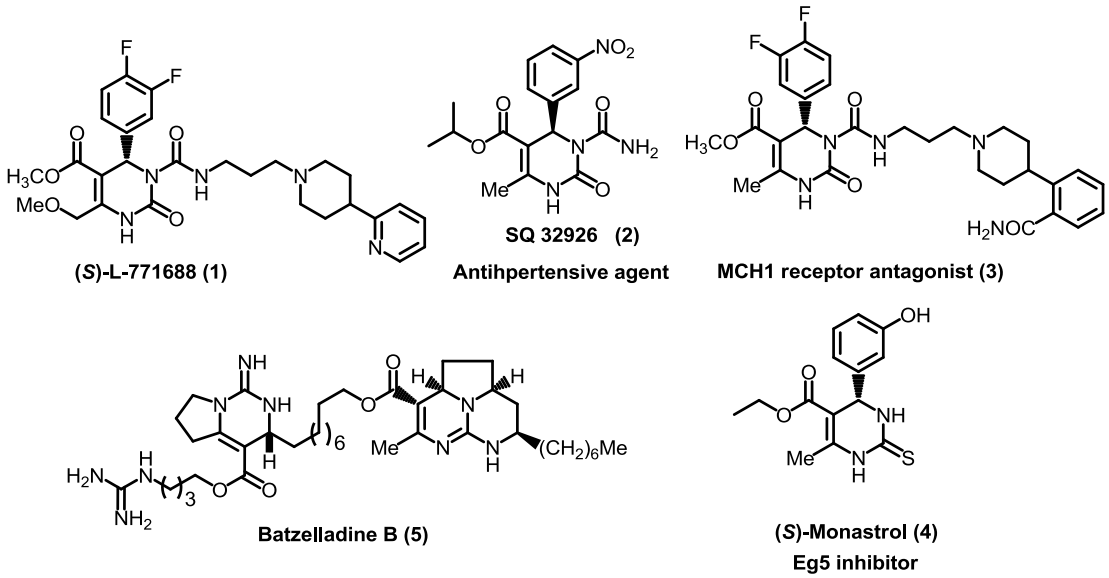
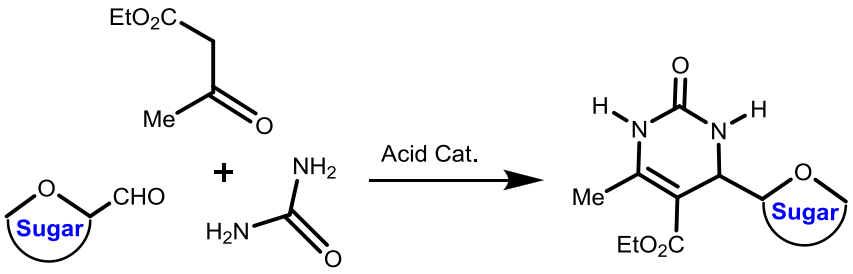


Figure 1: Biologically active dihydropyrimidin-2-one/thione derivatives.

Multicomponent one-pot synthesis rapidly furnish diverse new chemical entities needed for the discovery of new lead compounds therefore method undoubtedly has enticed the great deal of attention in the realm of modern drug discovery and synthetic organic chemisty. [12] Recently, carbohydrate derived therapeutically important molecules enticed the major focus in chemical biology and medicinal chemistry and thus resulted the huge efforts to search the efficient synthetic methodologies to access carbohydrate based heterocyclic privileged structures. Carbohydrates derived scaffolds emerged as "privileged" combinatorial scaffolds due to their unraveled structural diversity, arising from a high chiral density, variable branching pattern, and polyfunctionality,[12] for example, guanidinoglycosides shown better biological properties (anti-influenza and anti-HIV activities) against the nonglycosylated guanidino derivatives.[13] Therefore synthetic modification and structurally diverse carbohydrate building blocks can be breakthrough in finding novel drug molecules or novel biochemical tools with structural and stereochemical diversities.[13]

The common synthetic methods for dihydropyrimidinone (DHPM) and their derivatives are generally based on the reaction of aldehyde-ketoester-urea, i.e. biginelli condensation. Using this conventional route several protocols have been developed to synthesize DHPM's on the basis of Biginelli multicomponent chemistry.[14] Dondoni and coworker reported the synthesis of dihydropyrimidinone glycoconjugates using the aldehyde-ketoester-urea cyclocondensation reaction, in which they used various acids and transitional metal catalyst for the desired conversion and overall yield was 36-41%. In addition, few methods are reported using glycosyl ulose (2,3-*O*-isopropylidene-D-glyceraldehyde, 2,4-*O*ethylidene-D-threose and D-erythrose, 2,5-anhydro-*aldehydo*-D-xylose) in the Biginelli reaction.[15]



Scheme 1. Biginelli reaction for carbohydrate based dihydropyrimidin-2-one derivatives

It is worth to note that, very few efforts have been made to develop the synthesis of carbohydrate based dihydropyridinone derivatives but still date there is no report for the mild and efficient synthesis of carbohydrate based dihydropyrimidin-2-one/thione skelton in good yields. Literature survey revealed that, optically pure DHPMs are accessed via resolution [16] and chiral auxiliary methods.[17] Only a few reports so far in the literature for the synthesis of optically pure DHPMs by employing organocatalysts.[18] The exploration of these above mentioned methods have serious limitations for synthesis of glycosyl dihydropyrimidin-2-one/thione derivatives considering with respect to stability of carbohydrate derivatives, use of acid-sensitive prone reagents to yield and scope, high temperature or strong acidic condition in which glycosidic bond is fragile and often chances to cleave under harsh conditions. It is pertinent to note that hypervalent iodine reagents are emerging as efficient mild oxidants for metal free oxidative transformations in organic syntheses and their application as reagents in carbohydrate chemistry would be of great relevance to meet the environmental considerations and may lead the development of more simpler, non-polluting synthetic approaches for the synthesis of bioactive molecules with carbohydrate scaffolds.[19] The huge therapeutic potential to construct the glycosyl dihydropyrimidin-2-one/thione derivatives drove our interest to develop a simple, new and high yielding protocol for the synthesis of a diverse range of novel glycosyl dihydropyrimidin-2-one/thione derivatives under mild reaction condition.

Herein we report a novel high yielding diacetoxyiodobenzne (DIB) and N-methylmorpholinium hydrogen sulphate $[NMM]^+[HSO_4]^-$ promoted multicomponent reaction (MCR) involving glycosyl ulose, acetophenone and urea/thiourea for the synthesis of a diverse range of glycosyl dihydropyrimidin-2-one/thione derivatives at room temperature. To the best of our knowledge, there are no reports on DIB and N-methylmorpholinium hydrogen sulphate catalyzed one-pot three component reaction for the synthesis of glycosyl dihydropyrimidin-2-one/thione derivatives.

EXPERIMENTAL SECTION

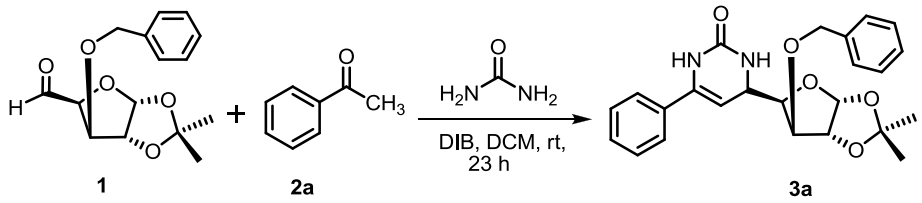
General experimental procedure for glycosyl dihydropyrimidin-2-one/thione derivatives

A mixture of glycosyl ulose (1.0 equivalent), acetophenone (1.0 equivalent), urea / thiourea (1.0 equivalent) and DIB (1.5 equivalent) and $[NMM]^+[HSO_4]^-$ (10 mol%) were added in anhydrous CH_2Cl_2 (10 mL) under N_2 atmosphere and stirred at room temperature for 10 h. The progress of reaction was monitored on TLC using ethyl acetate/n-hexane (40:60) solvent system. On completion of reaction, the reaction mixture was treated with 20% $Na_2S_2O_3$ (20 mL) and saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with two portions of CH_2Cl_2. The collected organic phases were then washed with brine, dried over MgSO4, filtered, and concentrated *in vacuo.* The residue was purified by flash column chromatography over SiO_2 (230–400 mesh) using ethyl acetate-n-hexane (70:30) as eluent gave the pure corresponding glycosyl dihydropyrimidin-2-one/thione derivatives.

6-(3‘-O-Benzyl-1,2-O-isopropylidene-α-D-xylotetrafuranos-4‘-yl)-4-phenyl-1,2,3,5, 6-tetrahydropyrimidin-2-one (**3a**): It was obtained by the multicomponent reaction of glycosyl ulose (**1**) (0.90 g, 3.23 mmol), acetophenone (**2a**) (0.376 mL, 3.23 mmol), urea (0.194 g, 3.23 mmol), DIB (1.56 g, 4.85 mmol) and $[NMM]^+[HSO_4]^-$ (0.064 g, 10 mmol%) in 90 % yield as a brown colour mass :($C_{24}H_{26}N_2O_5$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.32 and 1.48 [each s, each 3H, 2 x >C(CH_3)$_2$], 3.68 (dd, J = 5.4 Hz, methyne 1H), 3.79 (d, J = 11.4 Hz, vinylic proton, 1H), 4.10 (d, J = 2.7 Hz, 1H, C_3-H), 4.56 (d, J = 12 Hz, OCH_APh, C_2-H, 2H), 4.75 (d, J = 12 Hz, 1H, OCH_BPh), 4.63 (d, J = 3.6 Hz, 1H, C_4-H), 5.94 (d, J = 3.9 Hz, 1H, C_1-H), 7.28-7.34 (m, 10H, Ar-H), 8.08 (bs, 1H, NH), 8.29 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.15, 26.65, 64.24, 69.15, 72.13, 79.93, 81.92, 82.08, 105.07, 111.79, 125.06, 125.26, 127.80, 128.12, 128.42, 128.61, 136.19, 137.18, 138.40, and 155.06 ppm.

RESULT AND DISCUSSION

At the outset of this study, we focused our attention on developing a multicomponent reaction of glycosyl uloses, urea/thiourea and acetophenones to synthesis novel glycosyl dihydropyrimidinones. Thus glycosyl ulose (**1**) was reacted with acetophenone and urea in anhydrous CH_2Cl_2 at room temperature using DIB as catalyst to afford the corresponding glycosyl dihydropyrimidin-2-one derivative (**3a**) and to our delight the reaction was successful and product was obtained in low yield. In the light of this success, we believed that under the optimized condition the yield of the product would increase significantly.



Scheme 2. DIB catalyzed synthesis of glycosyl dihydropyrimidin-2-one derivative

Therefore, to optimize the reaction parameters, we set above reaction as a model reaction and briefly studied the effect of various solvents on the reaction time and yield. The results illustrated the poor performance of toluene, THF, DMF, DCE, benzene and acetonitrile in terms of yield and reaction time. The reaction in methanol failed to afford the desire product. Chloroform performed well with respect to yield but required slightly longer reaction time. This MCR was eventually found to be facile only in CH_2Cl_2 with good yield in a considerably shorter reaction time, and hence anhydrous CH_2Cl_2 was established as the solvent of choice for this reaction (entry 4, Table 1).

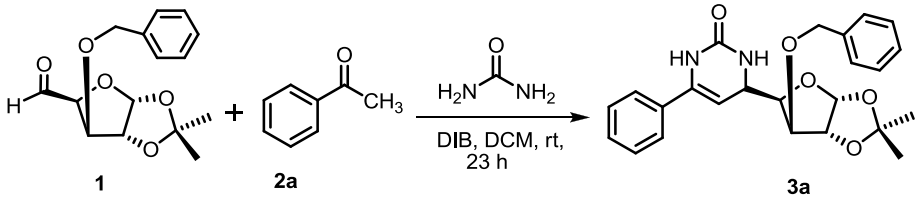


Table 1. Optimization of MCR of glycosyl ulose (**1**), acetophenone and urea in various solvents

Entry	Solvents	Time (h)	Yield (%)
1	MeOH	-	-
2	DCE	30	40

3	MeCN	30	35
4	CH_2Cl_2	23	40
5	$CHCl_3$	27	40
6	DMF	30	30
7	THF	30	30
8	Toluene	30	35
9	Benzene	30	30

Molar ratios of reactants: glycosyl ulose (furanose form) (1.0 mmol), acetophenone (1.0 mmol), urea (1.0 mmol) and DIB (1.5 mmol).

Since the yield of the final compound was still not encouraging, we examined the reaction under the catalysis of molecular iodine instead of DIB by considering the general similarity between DIB and iodine mediated cyclization, but reaction did not occur smoothly even with the increased molar ratio of iodine and only trace amount (20%) of desired product was obtained after 25 h of reaction time. Then, we studied the various combinations of DIB-iodine on model reaction and results are summarized in Table 2. The 0.5 equivalent of each DIB and iodine offered the better yield in comparison to yield offered by either DIB or molecular iodine alone. After intensive screenings of various combinations of catalyst we found that 1.5 and 0.5 equivalent molar ratios of DIB and iodine respectively are the most effective combination to get the desired glycosyl dihydropyrimidin-2-one derivative in high yield (Table 2, entry 9). Our literature survey revealed that TBAB has been used in combination with DIB therefore we add the TBAB as an additive with aim to improve the yield further but it failed to provide the significant result in terms of yield as well as reaction time.

Table 2. Screening of catalysts for synthesis of dihydropyrimidin-2-one.

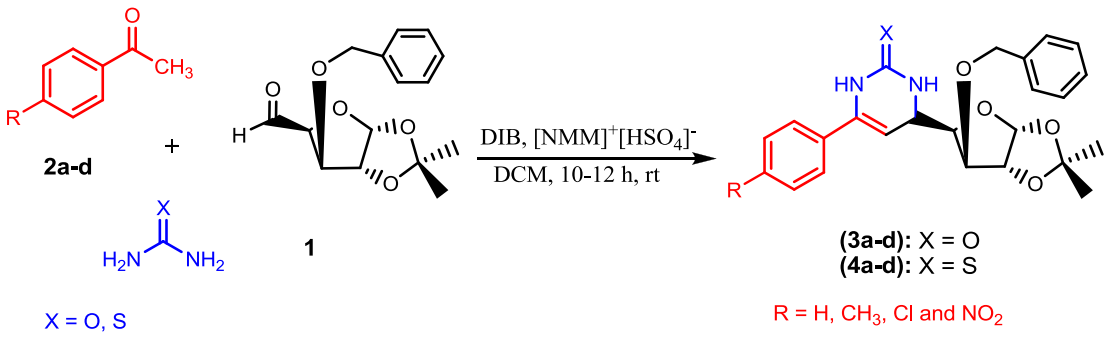
Entry	DIB	I_2	TBAB	$[NMM]^+[HSO4]^-$ (mol %)	Time (h)	Yield (%)
1.	1.0	-	-	-	23	30
2.	1.5	-	-	-	23	40
3.	2.0	-	-	-	23	40
4.	-	0.5	-	-	24	ta
5.	-	1.0	-	-	26	ta
6.	-	1.5	-	-	25	20
7.	0.5	0.5	-	-	25	48

8.	0.5	1.0	-	-	24	50
9.	1.5	0.5	-	-	20	68
10.	1.5	-	1.0	-	22	40
11.	1.5	-	-	0.5	12	80
12.	1.5	-	-	10	10	90
13	-	-	-	10	25	-

ta = trace amount

The thermal instability of glycosyl ulose being the main challenge in accelerating the reaction rate by heat treatment prompted us to evaluate some other catalyst to enhance the yield. In recent years, room temperature ionic liquids (RTILs) capable of catalyzing the one-pot, multicomponent reactions of carbonyl compounds have emerged as promising environmentally benign reaction media in carbohydrate chemistry [20] Their high polarity and ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and can provide higher selectivity compared to conventional solvents. Keeping this in view, we evaluated the catalytic performance of *N*-methylmorpholinium hydrogen sulphate along with 1.5 equiv of DIB and to our surprise the yield of the desired compound was enhanced up to 80% in case of 5 mol% of ionic liquid. When the molar percent of $[NMM]^+[HSO4]^-$ was doubled the yield of the product was further increased and reached up to 90% (Table 2, entry 12). It is important to note that the application of ionic liquid as co-catalyst along with DIB not only improved the yield but also reduced the reaction time from 26 h to 10 h. After screening the various mole % of $[NMM]^+[HSO4]^-$ and DIB, we arrived at optimized condition where 1.0 equivalent of each glycosyl ulose, acetophenone, urea/thiourea, 1.5 equivalent of DIB and 10 mol% of ionic liquid were found the optimum ratios for the best result. The enormous improvement in both yields of product as well as the reaction time after introducing the ionic liquid may be due the offering of required acidity by ionic liquid to activate the reaction.

Scheme 3. Synthesis of diverse glycosyl dihydropyrimidin-2-one/thione in furanose form

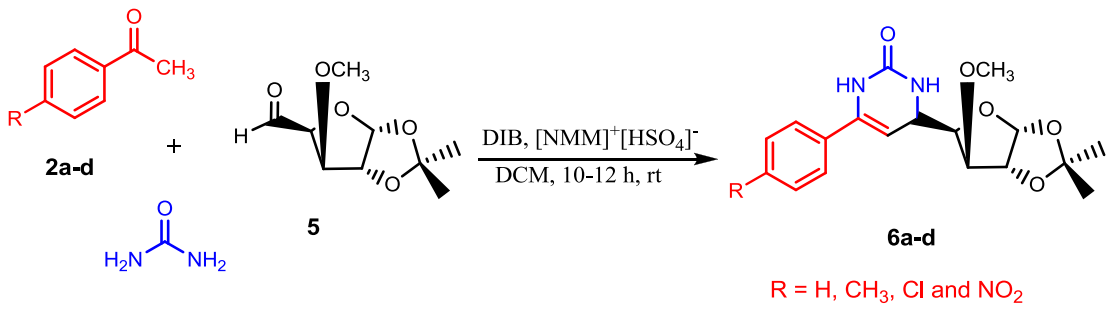


Entry	Acetophenone	Urea/ thiourea	Product	Yield (%)
1.	Acetophenone	urea	**3a**	90
2.	*p*-Methylacetophenone	urea	**3b**	92
3.	*p*-Chloroacetophenone	urea	**3c**	85
4.	*p*-Nitroacetophenone	urea	**3d**	78
5.	Acetophenone	thiourea	**4a**	90
6.	*p*-Methylacetophenone	thiourea	**4b**	94
7.	*p*-Chloroacetophenone	thiourea	**4c**	85
8.	*p*-Nitroacetophenone	thiourea	**4d**	80

Molar ratios of reactants: glycosyl ulose (furanose form) (1.0 mmol), acetophenone (1.0 mmol), urea/thiourea (1.0 mmol) DIB (1.5 mmol) and $[NMM]^+[HSO_4]^-$ (10 mol %). Reaction time 10 h.

With optimized reaction condition in hand, the glycosyl uloses (**1, 5)** was reacted with urea/thiourea and various acetophenones such as acetophenone (**2a**), *p*-methylacetophenone (**2b**), *p*-chloroacetophenone (**2c**) and *p*-nitroacetophenone (**2d**)) in anhydrous CH_2Cl_2 at room temperature to prepare a series of glycosyl dihydropyrimidin-2-one/thione derivatives (**3a-d, 4a-d and 6a-d**) in good yields (Scheme 2 & 3). Notably, this method is compatible with a number of functional groups such as halogen and nitro giving their corresponding dihydropyrimidin-2-one/thione in good yields. The yields of the final products revealed that the *para*-substituent of acetophenone impacted the performance of the reaction. Increasing electron withdrawing potential of the substituent diminished the reaction rate gradually which resulted in the lower yield, whereas the electron donating group accelerated the pace of the reaction and led to the formation of product in high yield.

Scheme 4. Synthesis of diverse glycosyl dihydropyrimidin-2-one in furanose form



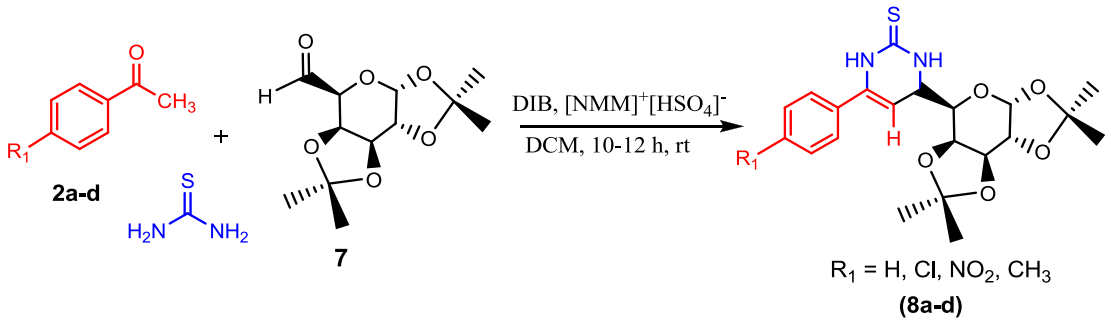
Entry	Acetophenone	Urea	Product	Yield (%)
1.	Acetophenone	urea	**6a**	90
2.	*p*-Methylacetophenone	urea	**6b**	92

3.	*p*-Chloroacetophenone	urea	**6c**	85
4.	*p*-Nitroacetophenone	urea	**6d**	78

Molar ratios of reactants: glycosyl ulose (furanose form) (1.0 mmol), acetophenone (1.0 mmol), urea (1.0 mmol) DIB (1.5 mmol) and $[NMM]^+[HSO_4]^-$ (10 mol %). Reaction time 10 h.

The generality of this multicomponent reaction was investigated for galactose based aldehyde (**7**) scheme 4. The reaction of aldehyde (**7**) with thiourea and acetophenones (**2a-d**) went smoothly and afforded the corresponding products (**8a-d**) in good to high yields. The substituents on the aldehyde had very little effect on the performance of reaction. We believe that this synthetic protocol would applicable to a wide range of aldehyde. The structures of all the novel dihydropyrimidin-2-one/thione were deduced from their spectral studies (IR, ^{1}H, and ^{13}C NMR) and elemental analysis. The diastereoselctive formation of C5 can be explained by considering the transition state models newly formed chiral centre confuguartion

Scheme 5. Synthesis of diverse glycosyl dihydropyrimidin-2-thione in pyranose form

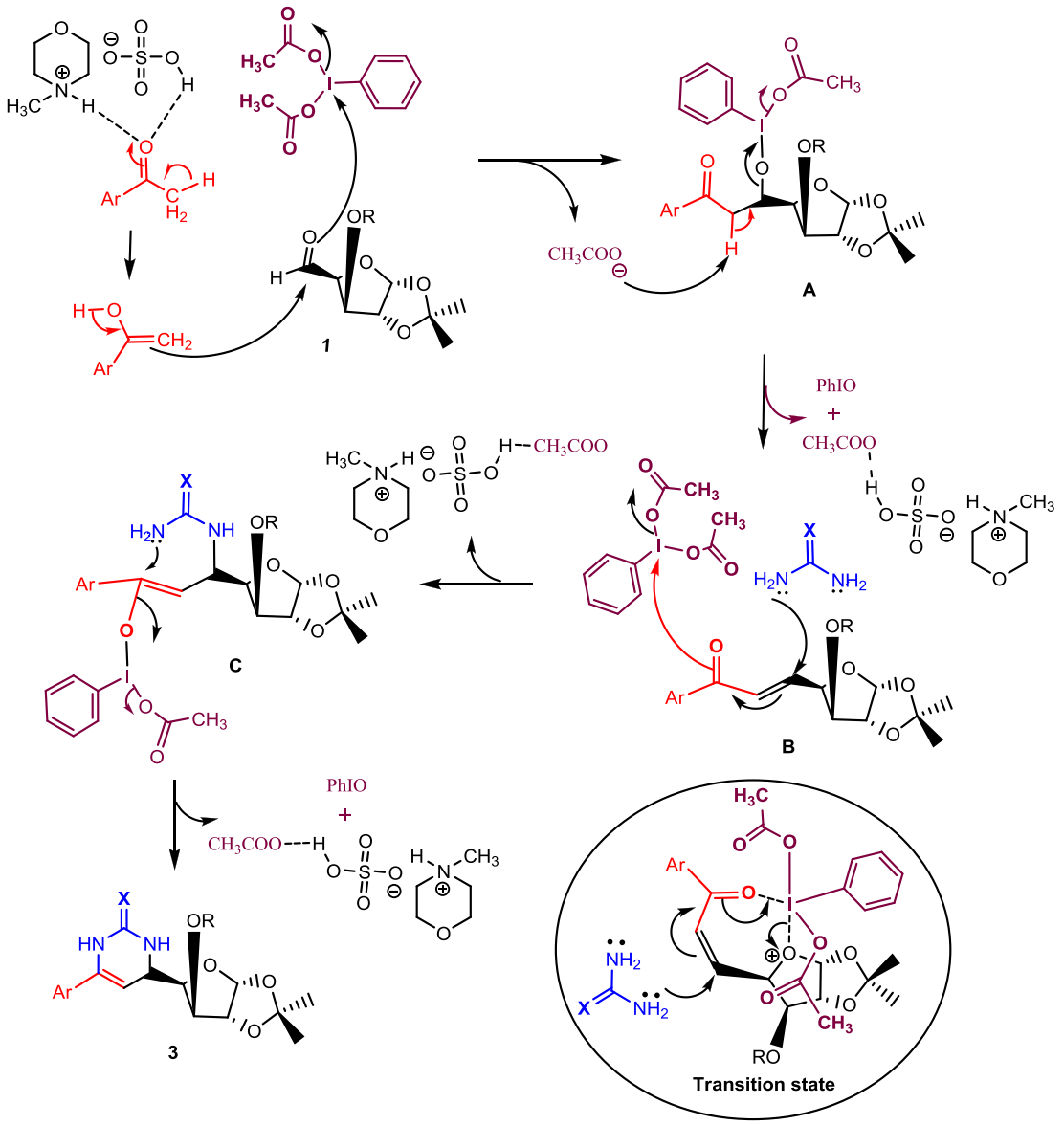


Entry	Acetophenone	Urea/ thiourea	Product	Yield (%)
1.	Acetophenone	thiourea	**8a**	89
2.	*p*-Methylacetophenone	thiourea	**8b**	95
3.	*p*-Chloroacetophenone	thiourea	**8c**	87
4.	*p*-Nitroacetophenone	thiourea	**8d**	84

Molar ratios of reactants: glycosyl ulose (pyranose form) (1.0 mmol), acetophenone (1.0 mmol), thiourea (1.0 mmol) DIB (1.5 mmol) and $[NMM]^+[HSO_4]^-$ (10 mol %). Reaction time 10 h.

Although a detailed understanding of the mechanism for this three component reaction will require additional studies, we assume that synthesis of dihydropyrimidin-2-one/thione from glycosyl aldehyde, acetophenone and urea/thiourea under the catalysis of DIB and *N*-methylmorpholinium hydrogen sulphate may proceed through the pathway outlined in **Scheme 6**. The reaction begins with

ionic liquid catalyzed formation of enol form of acetophenone whose pi electrons attack at electron-deficient carbonyl carbon of glycosyl ulose **1**, simultaneously, nucleophilic attack of lone pair electrons of oxygen of carbonyl carbon to iodine atom of DIB, as iodine in DIB acts as a good electrophilic center, and leads to the formation of intermediate **A**. Subsequently, the abstraction of α-proton by the acetate ion facilitates the formation of intermediate **B** by leaving behind iodosylbenzene. The nucleophilic attack of amino group of urea/thiourea at the *β*-carbon of intermediate **B** affords intermediate **C** which finally on nucleophilic attack by another amino group of urea/thiourea and then ionic liquid assisted subsequent dehydration paves the way for the formation of desired dihydropyrimidine-2-one/thione. The configuration at C-5 was determined from the 1H NMR spectra based on the coupling constant values as well from our earlier reported ^{1}H NMR investigation. Our literature survey revealed that 1,4 conjugate addition of amine with olefinic ester with conventional process without any catalyst reported with the diastereomeric mixture.[21] Interestingly, this one-pot, three-component transformation fetch the single diastereomer . Although the detail mechanistic investigation have not established experimentally, a plausible reaction pathways discussed in **Scheme 6**. The diastereospecific formation of 3**a** can be explained by considering the transition states state model (Fig. 1). Indeed, it's very well known that the stereoelectronic and steric factors often play an pivotal role in guiding the stereochemical outcome in the intramolecular Michael addition reactions.[22] We believe that the DIB chelation with α-β unsaturated carbonyl sugar is responsible for the stereochemical control in intramolecular conjugate addition reactions which controlled by stereoelectronic and steric factors and this constricts the nucleophilic attack of amino group of urea/thiourea at the *β*-carbon through only one fashion. We believe that, under the reaction conditions of DIB and in situ conjugate addition, complexation of the Iodine of DIB by the carbonyl carbon and 'O' of furanose and pyranose ring determines the amine addition stereosepecifically in transition states. Thus, the complexation of Iodine with the carbonyl carbon and 'O' of furanose and pyranose ring in such a way that the amine preferred Si face attack (TS A, Fig. 2), which results only 'S' configuration as a diastereospecific product. Favoured transition state model.



Scheme 6. Proposed mechanism of the DIB-$[NMM]^{+}[HSO4]^{-}$ catalyzed synthesis of DHP and plausible transition state model responsible for the single diastereomer.

CONCLUSION

In conclusion, we have developed a high yielding one-pot three component novel protocol for an easy access of diverse multi-functionalized carbohydrate based dihydropyrimidin-2-one/thione derivatives, which are of great importance in drug discovery/medicinal chemistry. To the best of our knowledge, this is the first example that uses the combination of DIB-$[NMM]^{+}[HSO4]^{-}$ catalyst for one pot three component synthesis of carbohydrate dihydropyrimidin-2-one/thione derivatives, which offers facile

approach to medicinally useful glycosyl-heterocyclic compounds. Advantages of the developed protocol are (a) the synthetic protocol is simple and does not require heating or refluxing; (b) procedure is high yielding and environmentally benign; (c) It does not require expensive and toxic metal catalysts etc. Further studies into the mechanism and their applications are currently under investigation.

ACKNOWLEDGEMENTS

The authors thank CISC, BHU for providing spectroscopic and analytical data of synthesized compounds. Department of Chemistry, MVP's, K.R.T. Arts B.H. Commerce and A.M. Science College, Gangapur Road, Nashik for providing necessary infrastructure and facility.

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