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$ZrCl_4$-catalyzed one-pot multi-component synthesis of hexahydropyrano pyrimidinone derivatives

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Abstract: In this study, zirconium tetrachloride is used as a highly efficient catalyst for the one-pot three component reaction of 3,4-dihydro(2*H*)-pyran, urea and benzaldehyde in ethanol, producing corresponding hexahydropyrano pyrimidinone derivatives in good yields, with excellent diastereoselectivity. This method has various benefits such as easy availability of starting materials, lower cost, higher yield and shorter reaction time.

Keywords: Multi-component reactions; aldehydes; urea/thiourea; 3,4-dihydro(2*H*)-pyran; catalysis.

1. Introduction

There is an enormous curiosity of small molecules in the area of drug discovery which have controlling influence on various pharmacologically active functions such as antibacterials, analgesics, antipyretic medications etc.[1-2] Recent developments of technologies have paved a way for the methodical discovery of small molecules for targeted pharmacological efficiency with an aim to support the biological systems.[3] These molecules can be efficiently prepared and are economically more beneficial than commonly applied complex pharmacological relevant drugs,[4] moreover with the core moiety of the synthesized molecule proficient to target certain receptors leads to an increased pharmacological activity.[5] In this regard, the fused ring pyrimidinones have exhibited multi-spectrum pharmacological activities such as antibacterial, antitumor, anti-hypertensive, vasodilator, bronchio dilator, hepato protective cardiotonic and anti-allergic activities.[6-12]

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2. Background

Currently, the applications of green synthetic strategies to meet the conditionsof maintainable, ecologically development of pharmacologically important compounds have gained decent momentum, due to various environmental constraints.[13] Due to this, eco-friendly solvent and catalyst, based synthetic methodologies have drawnhuge interest of chemical industry, due to lower production costs along with diminished pollution, simplicity of purification process and mild conditions.[14]

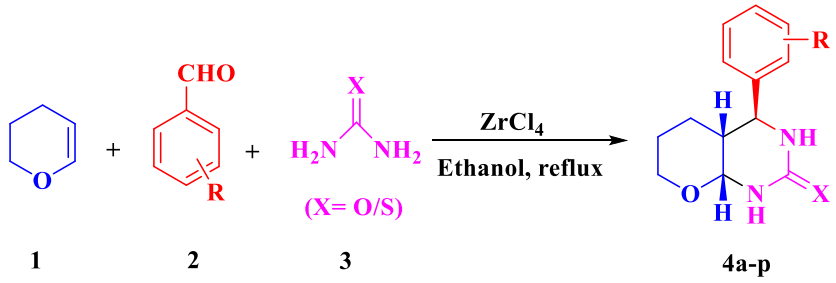
MCRs offer great potential by performing multiple reactions in one reaction step, wherein a sequence of reactions take place without the requirement of isolating the intermediates.[15] In such a process, three or more reactants are converted to the desired product in a single-pot reaction, which exhibit wide range of molecular diversity. These reactions have proven to possess excellent structural economy (structural intricacyof products), atom-economy, bond-forming efficiency, convergent synthetic ability, and the viabilityof introducing maximum chemical diversity in one chemical event.[16] Hence, considerable efforts are still being focused to customize and fine-tune the currently applied MCRs for synthesizing various organic structures that can be specifically applicable in the preparation of divergent pool of small bioactive scaffolds.[17] Particularly, multicomponent reactions (MCRs) have gained extensive attention for the synthesis of pyrimidinones.[18-19] However, only a few synthetic protocols employing TMSCl,[20-21] *p*-TSA,[22] L-proline/TFA,[23] $SbCl_3$,[24] PBBS/TBBDA,[25] and $[Hnmp]HSO_4$[26] have been developed using MCR based approaches, hence there is still a large scope for improvizing the reaction methodology, owing to the pharmacological utility of desired products.

3. Experimental

The detailed experimental procedure is given as supplementary information.

4. Present Study

In the present study, we have demonstrated a facile approach for the preparation of hexahydro pyranopyrimidinone derivatives utilizing zirconium (IV) chloride as an effective catalyst (Scheme 1). Among the materials tested, $ZrCl_4$ is found to be an ideal catalyst to promote MCR for the synthesis of pyrimidinones. It is non-toxic, inexpensive, eco-friendly and stable catalyst, which can be efficiently used for the one-pot reactions.[27] Besides, $ZrCl_2$ has also been tested as a catalyst; however, it has not yielded desired results (Table 1, entries 1 and 2). The products obtained in this study have been purified by column chromatography and analyzed by using appropriate analytical techniques.



Scheme 1. Multi-component reaction using $ZrCl_4$

Initially, we have performed the multi-component reaction of benzaldehyde, urea and 3,4-dihydro-(2*H*)–pyran in the presence of zirconium (IV) chloride for the optimization of reaction conditions. The results obtained from the optimization studies are tabulated in Table 1, the results obtained revealed that the combination of zirconium (IV)chloride and ethanol proved to be the most promising in terms of reaction time and yield (Table 1, entry 6).

The reaction was monitored by the appearance of reddish colour in the reaction mixture, indicating product formation. The optimization of catalyst amount revealed that that on raising from 5 mol% to 10 mol% the amount of catalyst, the yield of the reaction increased however an increase beyond 10 mol% in the reaction mixture, did not yield an appreciable change inthe rate as well as yield of the reaction. The stereochemistry of product **4a** was identified by spectroscopic data.

Table 1. Optimization of reaction parameters for **4a**[a]

Entry	Catalyst	Solvent	Temp (^{0}C)	Time (h)	Yield (%)[c]
1	$ZrCl_2$	Ethanol	reflux	10	NR[b]
2	$ZrCl_2$	Acetonitrile	reflux	10	NR[b]
3	$ZrCl_4$	Acetonitrile	reflux	5	45
4	$ZrCl_4$	Toluene	reflux	5	35
5	$ZrCl_4$	Dichloromethane	reflux	5	40
6	$ZrCl_4$	Ethanol	reflux	3	94

[a]Reaction conditions: Urea/Thio urea (1.2 mmol), aldehyde (1 mmol), catalyst (10 mol%), 3,4-DHP (1.5 mmol) in 5 mL solvent; [b]No reaction; [c]Pure isolated product after column chromatography

Table 2.Synthesis of 4-arylhexahydro-1*H*-pyrano[2,3-d]pyrimidin-2(8aH)-ones

Entry	Aldehyde (2a-p)	Product	Time (h)	Yield (%)
1	PhCHO (X=O)	**4a**	2.3	94
2	PhCHO (X=S)	**4b**	3	90
3	4-Me C_6H_4CHO (X=O)	**4c**	2.2	92
4	4-Me C_6H_4CHO (X=S)	**4d**	2.4	85
5	4-OMe C_6H_4CHO (X=O)	**4e**	2.1	95
6	4-OMe C_6H_4CHO (X=S)	**4f**	2.5	91
7	3,4,5-$(OCH_3)_3C_6H_2CHO$ (X=O)	**4g**	2.4	93
8	4-F C_6H_4CHO (X=O)	**4h**	3	88
9	4-Cl C_6H_4CHO (X=O)	**4i**	3	89
10	4-Br C_6H_4CHO (X=O)	**4j**	3	92
11	4-OH C_6H_4CHO (X=O)	**4k**	5	74
12	4-NO_2 C_6H_4CHO (X=O)	**4l**	2.3	78
13	4-NO_2 C_6H_4CHO (X=S)	**4m**	2.5	75
14	2-NO_2 C_6H_4CHO (X=O)	**4n**	3	81
15	2-Cl C_6H_4CHO (X=O)	**40**	2.4	88
16	3-NO_2 C_6H_4CHO (X=O)	**4p**	3	84

[a]Pure isolated product after column chromatography

Based on the optimized reaction conditions, multicomponent reaction with various electronically divergent aromatic aldehydes, urea/thiourea and dihydropyran catalyzed by $ZrCl_4$ was investigated with an intention to synthesize similar hexahydropyrano pyrimidinone scaffolds and the obtained results are shown in Table 2. It can be seen from Table 2, neither the electronic character nor the position of substituent on aromatic ring of aldehydes, alter the yield of reaction to any remarkable way. Free hydroxyl group was also tolerated under the established reaction conditions, as in **4k**. Surprisingly, only a single diastereomer was isolated from the the utilized electronically divergent aldehydes **2a-p**, despite the presence of three consecutive chiral centres. This could be postulated by the projected mechanism from the work of Wu et al.[27] Initially, urea and aldehyde undergo condensation to form *N*-acyliminium species. 2,3-Dihydropyran performs nucleophilic attack at the imine carbon to afford an oxonium intermediate. Followed by cyclization, by attack of the NH_2 group in an exo fashion due to favourable proximity of the electrophilic carbon from the amino group.

In order to display the generality and efficiency of the $ZrCl_4$ catalyzed protocol presented in this study, the results obtained have been compared with preciously reported methodologies and have been summarized in Table 3. The procedure described in this study is highly efficient and relatively better in terms of low cost, non-toxic, ecofriendly and ready availability. In instances mentioned in entries 2-4, reaction time required is longer than the one reported in the present work, although the isolated yield is comparable. Further, in case of entry 5 is reaction time reported is much lesser than the required time in the present work and the yield obtained is also comparable, however the catalyst employed is an ionic liquid based catalyst which is not easily available and expensive.

Table 3. Comparison of various catalysts on model reaction between benzaldehyde (1 mmol), urea (1.2 mmol) and 3,4-DHP (1.5 mmol) in various solvents

Entry	Reagent and conditions	Time (h/min)	Yield (%)	Reference
1	$ZrCl_4$ (10 mol%), Ethanol, reflux	2.3 h	94	Present work
2	$SbCl_3$ (10 mol%), Ethanol, reflux	5 h	88	24
3	L-Proline (10 mol%), TFA (6 mol%), CH_3CN, reflux	7 h	90	23
4	TMSCl, DMF/CH_3CN, reflux	10 h	89	20-21
5	[Hnmp]HSO_4, Solvent-free, 110 oC	10 min	90	26
6	PBBS/TBBDA, CH_3CN, reflux	-	-	25
7	*p*-TSA, DMF/CH_3CN, reflux	-	-	22

5. Conclusion

In conclusion, $ZrCl_4$ has been found to be mild Lewis acid catalyst for the purpose of synthesis of hexahydropyrano pyrimidinones in terms of atom economy, handling, ease of isolation of products, non-toxic solvent i.e. ethanol, reaction time and good to excellent yields, compared to the earlier literature.[20-26]

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Supporting Information

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