SYNTHESIS OF NOVEL YLIDES VIA A CASCADE PROCESS: UGI 4CR/YLIDE INITIATED MICHAEL/CHROMONE RING OPENING.

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Abstract

The development of efficient methods for the synthesis of heterocyclic compounds is always of great importance for chemists. In this perspective, we describe a general approach for the synthesis of functionalized heterocyclic compounds via Ugi MCR with 3-formyl chromone, amine, 2-chloro acetic acid and isocyanide followed by intramolecular ylide initiated Michael reaction. In this case, the reaction proceeds via in-situ generated phosphonium salt that give scope in formation of novel stable heterocyclic ylides. We especially emphasize the importance of tuning the Ugi adduct for the points of molecular diversity by designing intramolecular ylide initiated Michael reaction with chromone based moiety as Michael acceptor, 2-chloro acetic acid in Ugi reaction that helps for in situ generation of phosphonium salt that allows formation of a different class of heterocyclic compounds.

Keywords: Ugi reaction, 3-formyl chromone, Phosphorous ylides, Michael reaction.

Introduction

Functionalized heterocycle moieties are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. Recently for obtaining the highly functionalized heterocycles many strategies were used, in that point of
view MCR approach has great impact in organic synthesis of complex molecules. In this context, we selected Ugi-MCR reaction as primary platform for our synthesis. The Ugi four component reaction (Ugi 4CR) is one of the milestones in this field, and great efforts devoted to the exploration of the potential of this transformation. The ability to incorporate high levels of molecular functionality in a single step continues to be an attractive feature of the Ugi-multi-component condensation reaction. In order to increase “biological attractiveness” of the Ugi adducts, many groups have recently reported examples of post reaction manipulation focusing on substrate cyclization. These transformations include Diels-Alder reaction, amino-cyclization, lactonization, radical cyclization, Micheal reaction, Aza- Micheal reaction. However, the most potent strategy involves the coupling of the Ugi and Passerini reactions with post-condensation transformations. Our interest in the efficient generation of interesting nitrogen containing motifs has led us to investigate a new strategy, which relies on the sequential use of Ugi MCR with post transformation process. In this project, we emphasized a synthesis of novel phosphorus containing compounds via Ugi MCR followed by intramolecular ylide initiated Michael addition reaction that results in a stable novel heterocyclic phosphorus ylides. In the present project, we have taken 3-formyl chromone as aldehyde component and 2-chloroacetic acid as acid component in Ugi MCR that help for the post transformation.

Scheme:1 Stable ylides via Ugi 4CR/ylide initiated Michael reaction sequence.
The importance of choosing these heteroaromatic aldehydes because in past decades there few reports in the literature based on heteroaromatic aldehydes in MCR's another main reason in the point of diversity of structure based on each aldehyde. In this point of view 3-formylchromone is a highly reactive and well examined compound containing three electronic centers: unsaturated keto function, a conjugated second carbonyl group at C-3 and a very reactive electrophilic center at C-2 are present in the structure of this compound, for this reason 3-formylchromone 1 often used as a starting material for the synthesis of different heterocycles. By this methodology we obtain stable phosphorous ylides, those also have great importance like efficient synthons for organic reactions.

Results and Discussion:

The present methodology explains the formation of stable heterocyclic ylides. Here in this methodology we describe a general approach for the synthesis of functionalized heterocycles via Ugi MCR followed by intramolecular ylide initiated Michael reaction, in this case, the reaction proceeds via in-situ generated phosphonium salts.

The Ugi reaction with 3-formyl chromone, amine, isocyanide and 2-chloro acetic acid with equimolar quantity at classical Ugi conditions in methanol 1M at room temperature for 24h give Ugi adduct which subsequently used for obtaining stable phosphonium salt
under conventional heat in presence of triphenyl phosphine and toluene but unfortunately we
unable to isolate the phosphonium salt. According to the reaction strategy we expected to
obtain phosphonium salt 7 instead of final product stable heterocyclic ylide 6 obtained, but
this can be explained by the reactivity of chromone towards nucleophiles. Chromone has
good reactivity towards nucleophiles when 3\textsuperscript{rd} position of the chromone ring was engaged.
The conditions for conduction Ugi reaction is followed according to literature procedure that
was reported by Marcaccini, S.\textsuperscript{9}

We also studied the efficiency of the reaction of chromone based Ugi adduct with
triphenyl phosphine under variable conditions. Later we developed a microwave conditions
for Ugi reactions here for this we took a substrates for model reaction. 3-formyl chromone 1,
p-methoxy aniline 2\textsubscript{a}, 2-chloro acetic acid 3 and \textit{tert}-butyl isocyanide 4\textsubscript{a}. The reaction was
conducted with equimolar quantities of 3-formyl chromone 1, 4-methoxy aniline 2\textsubscript{a}, 2-chloro
acetic acid 3 and \textit{tert}-butyl-isocyanide 4\textsubscript{a} is added sequentially to a microwave tube charged
with magnetic stirring bar in 1M methanol as solvent.
The reaction was irradiated at 85 Watts with duration of 10 min, and the reaction completion was checked by thin layer chromatography (TLC) with 6:4 v/v hexane : ethyl acetate. The product obtained was purified by column chromatography and confirmed by $^1$H NMR.

After having the Ugi adduct 5a we started looking for expected but we while experiencing experimentally we found something interesting the results which has mentioned here in following Table 1.

**Table 6: Reaction optimization for the formation of products**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Condition</th>
<th>Product 7a</th>
<th>Product 6a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5equiv PPh₃, Toluene, 60 ºC, 12h</td>
<td>65%</td>
<td>10%</td>
</tr>
<tr>
<td>2</td>
<td>1equiv PPh₃, Toluene, 120 ºC 12h</td>
<td>55%</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>1.2equiv PPh₃, Toluene, 100W, MW, 120 ºC, 60 min</td>
<td>35%</td>
<td>35%</td>
</tr>
<tr>
<td>4</td>
<td>1.2equiv PPh₃, MeOH, rt, 24h</td>
<td>44%</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>1.2equiv PPh₃, DMF, rt, 24h</td>
<td>65%</td>
<td>5%</td>
</tr>
<tr>
<td>6</td>
<td>1.2equiv PPh₃, MeOH, reflux, 12h</td>
<td>60%</td>
<td>17%</td>
</tr>
<tr>
<td>7</td>
<td>1.2equiv PPh₃, DMF, reflux, 12h</td>
<td>20%</td>
<td>45%</td>
</tr>
<tr>
<td>8</td>
<td>1.2equiv PPh₃, DMF, 100W, MW, 120 ºC, 30 min</td>
<td>25%</td>
<td>45%</td>
</tr>
</tbody>
</table>

As if we observe the table initial experiments we conducted according to literature procedure. The reaction involves in nucleophilic substitution in formation of chromone based phosphonium salt 7 and from this *in-situ* generation of carbon centered nucleophile which enhances the Michael reaction with chromone at 2\(^{nd}\) position which was considered to be the reactivity electrophilic center. The table represents the formation of product and study
of control in formation of product 6 in different conditions. The first condition regarding when we started to obtain phosphonium salt we observed a new compound which was confirmed to be product (6a), instead of phosphonium salt (7a). These products were confirmed by brief analysis of \(^1\text{H},^{13}\text{C} \& ^{31}\text{P}\) NMR. The analysis of the above products formation gave an idea about formation of salt and ylide initiated Michael reaction product. The salt formation is justified by simple way because we are observing a quaternary organic derivative ,that represents a Menshutkin reaction \(^{11}\) type in the formation of phosphonium salt 7a. The reaction can also be explained by substitution nucleophilic bimolecular (SN\(^2\)). The factors that influence the reaction is mostly groups that attached to phosphorous. Apart from this solvent also influences the drastic change in reaction sequence, the most recommended solvents for the formation phosphonium salts are polar aprotic. That’s the reason where we have changed the solvents in different entries which gave drastic change in yields (Table 1: entries 3, 4, 5) of phosphonium salt 7a. we found major yield with 1.2equiv PPh\(_3\), DMF, rt, 24h, is 65 % which explains the influence of polar aprotic solvents in SN\(^2\) reaction in formation of phosphonium salt 7a. The reason for the lower to moderate yields is because of bulky group phenyl on phosphorous atom in the reaction may hinders and decreases the possibility of formation of phosphonium salt 7a. In the same reaction mixture we found another un expected product that was obtained due to the continuation of reaction after formation of phosphonium salt 7a. Here in this reaction the stable phosphonium salt generated a stable carbon centered nucleophile which initiates the Michael addition at 2\(^{nd}\) position of the chromone group. The gave scope in ring opening followed by 1,5 proton shift which results the product in good to moderate yields. As if we observe in table we reduced the yield and increased yield of the stable heterocyclic ylide 6a by changing the solvent. Finally we obtained 45 % yield for the model reaction we selected. But the yield is
independent of their electronic structure and different groups. We also found scope and formation of stable heterocyclic ylides by varying different isocyanides and amines.

We report here in that Ugi MCR followed by intermolecular ylide initiated Michael reaction which was explained clearly by possible mechanism, in this case, the reaction proceeds via in-situ generated phosphorus ylides.

Possible mechanism for formation of heterocyclic stable ylide.
In-situ generated phosphonium salt contains a stable α-carbanion (A) which attacks at 2nd position of the chromone which is well known electrophilic reactivity center and chromone is good Michael acceptor that enhances the Michael addition with α-carbanion results an intermediate B, then after 1,5 proton shift results the stable ylide 6 with ring opening of chromone adduct. The series of ten heterocyclic ylide based tetrahydropyridine carboxamides derivatives (6a) confirmed by $^1H$, $^{13}C$, $^{31}P$ NMR, HRMS and X-ray.

Conclusions:

In this methodology we developed a synthesis of novel stable heterocyclic ylides via Ugi/ylide initiated Michael and ring opening reaction in moderate to good yields. This methodology gave scope in ring opening of 3-formyl chromone and that explains the reactivity towards the nucleophile. The present methodology give a good future scope in generation of novel heterocyclic Wittig reagents.

References


