A new protocol for synthesis of α,β-unsaturated ketones using zirconium tetrachloride under microwave irradiation

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A facile one-pot synthesis of α,β-unsaturated carbonyl compound has been accomplished from ZrCl₄ mediated condensation of α-bromo ketones with aryl aldehydes under microwave irradiation.

Key words: α-Bromoketone, arylaldehyde, α,β-unsaturated enone, microwave, Claisen-Schmidt condensation, zirconium tetrachloride

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The synthesis of α,β-unsaturated carbonyl compounds is of great importance as this bifunctional unit is one of the main structural components in various naturally occurring and biologically essential substances. Moreover, α,β-unsaturated enones are important intermediates in many addition reactions of nucleophiles due to inductive polarization of carbonyl group at the β-position. Several strategies for the synthesis of these systems based on the formation of carbon-carbon bond have been reported, and among them the direct aldol condensation and Claisen-Schmidt condensation still occupy prominent positions. In aldol condensation the preparation of α,β-unsaturated ketones requires at least two-steps – aldol formation and dehydration. Since aldol addition is reversible, Mukaiyama or Claisen-Schmidt condensation approach of using enol ether has emerged as an alternative pathway. However, it lowers atom economy as silylation of ketones introduces another step. Moreover, Claisen-Schmidt condensation of cycloalkanones are not straightforward, as these reactions proceed beyond monoocondensation. In addition, many of these methods require harsh reaction condition, expensive and toxic reagents, poor yields and low selectivity. Although, several modifications have been made to counter these problems, there is still a need for the development of selective and better strategies for the one-step generation of α,β-unsaturated carbonyl compounds.

Zirconium (IV) chloride, as transition metal catalysis in organic synthesis, is gaining importance because of its low toxicity, ease of handling and high catalytic activity. In spite of relatively weak Lewis acid character, it has shown high potential in a large number of organic transformation reactions. However, preparation of zirconium enolates involve complex processes. On the other hand, we have utilized aluminium triiodide for aldol condensation of α-halo carbonyl compounds via an intermediate of aluminium enolate. Our continued interests on the chemistry of α-halo ketones led us to report here an efficient one-pot synthesis of α,β-unsaturated carbonyl compounds from α-bromo ketones and aryl aldehydes promoted by zirconium tetrachloride in a solventless condition under microwave irradiation (Scheme I).

Results and Discussion

The objective of the present study is to explore the role of microwave energy for the facile and in situ generation of zirconium enolate and its application in Claisen-Schmidt reaction. In a typical experiment, 2-bromoacetophenone 1a, benzaldehyde 2a and ZrCl₄ were intimately mixed in acidic alumina and irradiated in a Synthwave 402 Prolabo focussed microwave unit at a frequency of 2450 MHz and 80% power for 6 min, the product 1,3-diphenyl-prop-2-ene-1-one 3a was isolated in 90% yield (Table I, Scheme I).
entry 1). This led to investigate the behaviour of a number of α-bromoketones and aromatic aldehydes under the similar reaction conditions. As shown in Table I, this facile methodology could be successfully applied to acyclic and cyclic α-bromoketones 1a-c for condensation with aromatic 2a-d, hetero 2e-f and conjugated aldehydes 2g to afford α,β-unsaturated ketones 3a-k (entries 2-11). In contrast to an early observation, the reaction even did not proceed beyond mono-condensation even when excess of arylaldehydes 2a-b were allowed to react with α-bromocyclic ketone 1b-c. Similarly, α,α'-

Table I — ZrCl₄ mediated synthesis of conjugated enones under microwave irradiation

<table>
<thead>
<tr>
<th>Entry</th>
<th>α-Bromoketone</th>
<th>Arylaldehyde</th>
<th>Product*</th>
<th>Yield</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>PhCOCH₂Br 1a</td>
<td>PhCHO 2a</td>
<td>PhCOCH=CHPh 3a</td>
<td>90</td>
<td>17a</td>
</tr>
<tr>
<td>2.</td>
<td>1a</td>
<td>p-Cl-C₆H₄CHO 2b</td>
<td>PhCOCH=CHC₆H₄Cl⁻ 3b</td>
<td>87</td>
<td>17a</td>
</tr>
<tr>
<td>3.</td>
<td>1a</td>
<td>p-Me-C₆H₄CHO 2c</td>
<td>PhCOCH=CHC₆H₄Me⁻ 3c</td>
<td>88</td>
<td>17a</td>
</tr>
<tr>
<td>4.</td>
<td>1a</td>
<td>p-NO₂-C₆H₄CHO 2d</td>
<td>PhCOCH=CHC₆H₄NO₂⁻ 3d</td>
<td>78</td>
<td>17a</td>
</tr>
<tr>
<td>5.</td>
<td>1a</td>
<td>2e</td>
<td>PhCOCH=CHC₆H₄ 3e</td>
<td>85</td>
<td>17b</td>
</tr>
<tr>
<td>6.</td>
<td>1a</td>
<td>2f</td>
<td>PhCOCH=CHC₆H₄ 3f</td>
<td>80</td>
<td>17b</td>
</tr>
<tr>
<td>7.</td>
<td>1a</td>
<td>PhCH=CHCHO 2g</td>
<td>PhCOCH=CHC₆H₄ 3g</td>
<td>75</td>
<td>17b</td>
</tr>
<tr>
<td>8.</td>
<td>1b</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 3h</td>
<td>85</td>
<td>3b</td>
</tr>
<tr>
<td>9.</td>
<td>1b</td>
<td>2b</td>
<td>PhCOCH=CHC₆H₄ 3i</td>
<td>85</td>
<td>3b</td>
</tr>
<tr>
<td>10.</td>
<td>1c</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 3j</td>
<td>88</td>
<td>3b</td>
</tr>
<tr>
<td>11.</td>
<td>1e</td>
<td>2b</td>
<td>PhCOCH=CHC₆H₄ 3k</td>
<td>88</td>
<td>3b</td>
</tr>
<tr>
<td>12.</td>
<td>1d</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 3l</td>
<td>85</td>
<td>17c</td>
</tr>
<tr>
<td>13.</td>
<td>1e</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 3m</td>
<td>80</td>
<td>17c</td>
</tr>
<tr>
<td>14.</td>
<td>1f</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 4a</td>
<td>86</td>
<td>17b</td>
</tr>
<tr>
<td>15.</td>
<td>1g</td>
<td>2a</td>
<td>PhCOCH=CHC₆H₄ 4b</td>
<td>88</td>
<td>17d</td>
</tr>
</tbody>
</table>

*aThe products were characterized from their spectral (IR, NMR and MS) data. bIsolated yield of the pure products.
dibromocyclic ketone 1d-e reacted with aromatic aldehyde 2a to afford diarylidene adducts 3l-m in high yields. Products from the reactions were purified by column chromatography and identified by spectral analysis and comparison of m.p. with authentic samples3b, 17. However, an attempt to carry out the condensation reaction of 1a and 2a-g in acidic alumina without ZrCl4 failed. On the other hand, when the same reactions were carried in the absence of acidic alumina under ZrCl4 mediation, it afforded 3a-g in good yields (55-78 %) signifying the role of alumina only as a medium.

The ZrCl4 mediated reaction of conjugated α-bromoketones 1f-g with aromatic aldehyde 2a in the presence of acidic alumina failed under identical condition (entries 14-15); rather on aqueous work up it afforded benzylideneacetone 4a and 16-dehydro-pregnenolone acetate 4b exclusively as reductive dehalogenated products. This interesting phenomenon prompted us to examine the viability of reductive bromination reaction in other α-bromoketones. Accordingly, the ZrCl4 mediated reductive debromination experiments for α-bromoketones 1a-c were carried independently under microwave in the absence of arylaldehydes. In each case, the corresponding reductive debrominated keto compounds viz., acetophenone, cyclopentanone and cyclohexanone were obtained in excellent yields.

The condensation reaction is expected to proceed via a Claisen-Schmidt condensation type mechanism involving an initial formation of zirconium enolate intermediate A from the reaction of α-bromoketone 1a with ZrCl4 under microwave condition. Nucleophilic attack of enolate intermediate A on benzaldehyde 2a led to intermediate B, with subsequent rearrangement to intermediate C facilitating loss of zirconyl chloride (ZrOCl2)18 to afford product 3a. On the other hand, the formation of acetophenone from 1a on hydrolysis could be accounted due to conversion of intermediate A to intermediate D with concomitant loss of ZrOCl2. The failure of 1f (R = styryl) to react with arylaldehyde could be presumed due to delocalization of the π-electrons of the conjugated double bond of zirconium enolate intermediate A, which facilitated the α-carbon center relatively deficient to participate in nucleophilic attack (Scheme II).

In conclusion, the methodology reported herein denotes a new application of zirconium tetrachloride for the efficient preparation of α,β-unsaturated ketones under environmentally benign microwave and solventless condition. The procedure is particularly interesting because of site selective moncondensation of cyclic α-bromoketones. The methodology is facile and expected to be a general route for one-pot combinatorial synthesis of a wide range of α,β-unsaturated ketones.

**Experimental Section**

Melting points were measured in a Buchi-540 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer 1640 FT-IR spectrometer on chloroform; 1H NMR spectra on a Bruker 300 MHz spectrometer using TMS as internal standard; mass spectra on a Bruker Daltonic Data Analysis 2.0 spectrometer. Column chromatography was performed with silica gel (60-100 mesh) and TLC with silica gel G.

![Scheme II](image-url)
General procedure for ZrCl₄ mediated reaction of α-bromoketones with aldehydes under microwave irradiation

α-Bromoketone (1.0 mmole), aldehyde (1.0 mmole) and ZrCl₄ (1.12 mmole) were intimately mixed with activated acidic alumina and irradiated for 6-10 min in a Synthwave Microwave Module 402 (ProLabo) at operating frequency 2450 MHz. On completion of reaction, the reaction mixture turned deep brown in colour. After cooling down to room temperature, it was eluted with methanol/chloroform (5/95), washed with water and dried over Na₂SO₄. Removal of the solvent gave a residue which was purified by column chromatography (silica gel, ethyl acetate/hexane=10/90) to afford pure α,β-unsaturated ketones. All the products are known compounds as referred in Table I and characterized from physical and spectral (IR, ¹H NMR and MS) data.

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