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A new direct synthesis of $\alpha$-methylene- and $\alpha$-alkyldiene-$\beta$-lactams

Marwa Hussein, Assaad Nasr El Dine, Farès Farès, Vincent Dorcet, Ali Hachem and René Grée

$$\text{R}_1^+ \text{Cu}^+ \rightarrow \text{R}_1^+ \text{R}_2^+ \text{R}_3^+ \rightarrow \text{Cu}^+ \rightarrow \text{R}_1^+ \text{R}_2^+ \text{R}_3^+ \rightarrow \text{R}_1^+ \text{R}_2^+ \text{X}^O$$
A new direct synthesis of α-methylene- and α-alkylidene-β-lactams

Marwa Husseina,b, Assaad Nasr El Dinea,b, Farès Farèsa, Vincent Dorcet,b Ali Hachema,a, and René Gréeb

Laboratory for Medicinal Chemistry and Natural Products, Lebanese University, Faculty of Sciences (1) and PRASE-EDST, Hadath, Beirut, Lebanon
Univiersité de Rennes 1, Institut des Sciences Chimiques, CNRS UMR 6226, Avenue du Général Leclerc, 35042 Rennes Cedex, France

Corresponding author. Tel.: +961 3 319 549; fax: +961 5 460 301; e-mail: ahachem@ul.edu.lb
Corresponding author. Tel.: +33 (0)2 23 23 57 15; fax: +33 (0)2 23 23 69 78; e-mail: rene.gree@univ-rennes1.fr

**INFO**

**ABSTRACT**

The Kinugasa reaction applied to alkynes bearing a nucleophile in propargylic position affords directly, and in fair yields, α-methylene- or α-alkylidene-β-lactams.

**Keywords:**
- nitrones
- alkynes
- Kinugasa reaction
- beta-lactams
- propargyl derivatives

**Introduction**

The α-methylene- and α-alkylidene-β-lactams have not been extensively studied, even if some are known as bioactive natural products. For instance, Asparenomycin A and 6-(acetylmethylene)-penicinallic acid, are described as β-lactamase inhibitors. Further, a new class of herbicides, such as the Phyllostictine A, has been discovered recently (Figure 1).

**Scheme 1.** Our working hypothesis towards a new synthesis of α-methylene- and α-alkylidene-β-lactams.

The synthesis of α-alkylidene β-lactams has been performed by a variety of methods, such as the 2+2 cycloaddition of allenes to chlorosulfonylisocyanate. On the other hand, the exomethylene or exoalkylidene double bonds could be introduced starting from already prepared β-lactams. An alternative strategy involved intramolecular cyclisations starting from alkylidene-β-aminoesters. Further, starting from N-allyl amines, the desired α-
alkylidene β-lactams were obtained by intramolecular palladium-catalysed oxidative carbonylations, or by nucleophilic substitutions. Propiolamides were also useful starting materials allowing various α-methylene-β-lactams through PPh3-catalyzed cyclizations. Finally, the cross-metathesis of α-methylene-β-lactams, as well as the ring closing metathesis reactions, were also used successfully to prepare the corresponding α-alkylidene derivatives. Thus, the synthesis of this class of molecules generally involves multistep sequences with costly and/or sensitive reagents, therefore it appeared interesting to develop a new, and more direct, approach.

The Kinugasa reaction has already proved to be of much use in the synthesis of β-lactams. However, to the best of our knowledge, there is only one reported example of such a reaction affording an α-methylene-β-lactam and this was done by using proline as a catalyst. For the Kinugasa reaction a first mechanism, through oxaziridinyl intermediates, has been proposed by Ding and Irving while a second, via ketenes, was proposed by Tang et al. Our strategy towards the title target molecules is based on this second mechanism and our working hypothesis is indicated in Scheme 1: if we perform a Kinugasa reaction with an alkyne bearing a nucleofugue in propargylic position, at the ketene open intermediate stage, the classical ring closure to the β-lactam could be in competition with the simultaneous loss of this X (atom or leaving group) to afford directly the corresponding α-methylene- and α-alkylidene-β-lactams. The results obtained recently in our groups for Kinugasa reactions applied to gem-difluoro propargylic systems give some support to this working hypothesis.

The goal of this publication is to demonstrate that such a process is indeed working well with various types of substrates, offering a very simple and direct entry into this class of molecules.

Results and discussion

The reaction was explored first with the C,N-diphenyl nitrone and alkynes chosen as models, and the results are indicated in Scheme 2 and Table 1.

Scheme 2. Kinugasa reaction from nitrone 1 with alkynes 2.

We selected the previously found optimized conditions with reactions performed at room temperature in a 3:1 mixture of acetonitrile and water for 15 h. No reaction was observed with the propargylic alcohol 2a neither at room temperature nor at 50°C (Table 1, entry 1), while the Kinugasa reaction was indeed observed with the acetate 2b (Table 1, entry 2). A 31:69 mixture of the desired alkylidene-β-lactams was obtained, however in low yield (22%). A similar result was obtained starting from correspondent benzoate 2c (Table 1, entry 3). A significant improvement was observed by using carbonate 2d as starting material. In that case, the desired target molecules 3 were obtained in 40% overall yield (Table 1, entry 4). When the reaction was performed at 50°C, a 74% overall yield was obtained with a 28:72 mixture of the Z and E isomers (Table 1, entry 5). However, no further improvement was obtained by a reaction at reflux (Table 1, entry 6). Finally, the use of fluoride as nucleofugue proved to be also a possible good choice since 2e gave the target molecules in 58% overall yield (Table 1, entry 7). Compounds 3E and 3Z have been isolated by chromatography and their structure established by physical and analytical data. Particularly relevant for the stereochemistry of the double bond are the NOESY data (Figure 2). In the case of 3E, correlations were found between the methylene protons and the β-lactam proton and also with the ortho aromatic proton. In the case of 3Z correlations were observed between the vinlylic proton and the β-lactam proton. Further, it has been checked that the reaction was under kinetic control. No interconversion between 3E and 3Z was observed by heating each of them alone at 50°C. The same result was obtained by heating either 3E or 3Z under the Kinugasa reaction conditions.

Figure 2. Relevant NOESY data on compounds 3E and 3Z.

Table 1. Alkylidene-β-lactams 3 produced via Scheme 2.

<table>
<thead>
<tr>
<th>Entry</th>
<th>X</th>
<th>T</th>
<th>Yield %</th>
<th>Z/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-OH</td>
<td>50°C</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>-OCOMe</td>
<td>rt</td>
<td>22</td>
<td>31/69</td>
</tr>
<tr>
<td>3</td>
<td>-OCOPh</td>
<td>rt</td>
<td>24</td>
<td>29/71</td>
</tr>
<tr>
<td>4</td>
<td>-OCOEt</td>
<td>rt</td>
<td>40</td>
<td>38/62</td>
</tr>
<tr>
<td>5</td>
<td>-OCOOEt</td>
<td>50°C</td>
<td>74</td>
<td>28/72</td>
</tr>
<tr>
<td>6</td>
<td>-OCOOEt</td>
<td>reflux</td>
<td>65</td>
<td>42/58</td>
</tr>
<tr>
<td>7</td>
<td>-F</td>
<td>50°C</td>
<td>58</td>
<td>36/64</td>
</tr>
</tbody>
</table>

The reaction was conducted during 3 hours.

In a next step, the Kinugasa reaction was extended to the simple model alkynes 4, by using the same reaction conditions. The corresponding results are reported in Scheme 3. In that case, the reaction is working already with the propargylic alcohol 4a, affording the known α-methylene-β-lactam 5 in 37% yield. A similar result was obtained with acetate 4b (38% yield), while some improvement was observed with benzoate 4c (47% yield). Here again the carbonate 4d was found to give the best result with a 52% yield. The corresponding tosylate 4e gave a 40% yield while the bromo- and chloro- derivatives 4f and 4g gave lower yields, respectively 22% and 24%. The structure of 5 was established by comparison of its spectral data with literature.

Scheme 3. Kinugasa reaction between nitrone 1 and alkynes 4.
The nitrone in 68% yield and as a 1:2 mixture of the alkylidene-

Then the reaction was extended to other alkynes and a few other

b The cyclic nitrone 9 was used for this reaction. NR: no reaction.

Then the reaction was extended to other alkynes and a few other

Under the previously optimized reaction conditions, the

H2O (3 mL) was first degassed by bubbling nitrogen. Cul (0.225 g, 1.1 equiv) was added to previous water and then MeCN (5 mL). This solution was stirred for a few minutes under nitrogen at room temperature (Solution X). In another flask, Et3N (0.18 mL, 1.2 equiv) was added dropwise at 0 °C under nitrogen to a solution of carbonate 2d (0.25 g, 1 equiv) in MeCN (5 mL). The mixture was stirred for 30 min (Solution Y). Solution Y was added dropwise to the solution X at room temperature. After which a solution of the nitrone 1 (0.255 g, 1.2 equiv) in MeCN (5 mL) was added slowly over a period of 10 min. The reaction mixture was stirred upon heating at 50°C for 16 hr. Then the reaction mixture was diluted with H2O (12 mL) and filtered through celite. The celite was washed with EtAc (20 mL). The combined filtrate was extracted with EtAc (3 x 10 mL). The organic layer was washed with NH4Cl, H2O and brine, dried over MgSO4 and evaporated. After purification by column chromatography on silica gel, using hexane/EtAc as eluant (90/10), the two isomers of exoalkylidene-β-lactams 3E and 3Z were isolated in 50% (3E) and 24% (3Z) respectively.

(E) 1, 4-Diphenyl-3-(3-phenyl-propylidene)-azetidin-2-one (3E)

White solid, mp= 57°C, Rf = 0.33 (hexane/ethyl acetate 9/1). 1H NMR (CDCl3, 400 MHz), (ppm): 7.36 (m, 5H); 7.15 (m, 7H); 6.92 (m, 3H); 6.25 (td, 1H, J= 7.8 Hz, J= 1.6 Hz); 5.14 (dd, 1H, J= 1.6 Hz); 2.42 (m, 2H, J= 7.8 Hz); 2.16 (m, 2H). 13C NMR (CDCl3, 100 MHz), (ppm): 161.40 (1C), 142.64 (1C); 140.48 (1C); 137.72 (1C); 136.76 (1C); 129.07 (2C); 129.00 (2C); 21.

Scheme 4. Kinugasa reaction between nitrones 1, 6-9 and alkynes 10-12, and 4.

Table 2. Alkylidene-β-lactams 13-21 (Scheme 4)

<table>
<thead>
<tr>
<th>N°</th>
<th>R1</th>
<th>R2</th>
<th>R3</th>
<th>Yield %</th>
<th>E/Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>-Ph</td>
<td>-Ph</td>
<td>-C6H11</td>
<td>61</td>
<td>34:66</td>
</tr>
<tr>
<td>14</td>
<td>-Ph</td>
<td>-Ph</td>
<td>-C6H19</td>
<td>68</td>
<td>36:64</td>
</tr>
<tr>
<td>15</td>
<td>-Ph</td>
<td>-Ph</td>
<td>-(CH3)2OBn</td>
<td>71</td>
<td>42:58</td>
</tr>
<tr>
<td>16</td>
<td>-Ph</td>
<td>-Bu</td>
<td>-CH2CH2Ph</td>
<td>a</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>-Ph</td>
<td>-Bn</td>
<td>-CH2CH2Ph</td>
<td>62</td>
<td>40:60</td>
</tr>
<tr>
<td>18</td>
<td>-Ph</td>
<td>-Bn</td>
<td>-H</td>
<td>54</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>-CO2Bn</td>
<td>Bn</td>
<td>-CH2CH2Ph</td>
<td>60</td>
<td>47:53</td>
</tr>
<tr>
<td>20</td>
<td>-CO2Bn</td>
<td>Bn</td>
<td>-H</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>21</td>
<td>b</td>
<td>b</td>
<td>-CH2CH2Ph</td>
<td>NR</td>
<td>-</td>
</tr>
<tr>
<td>22</td>
<td>b</td>
<td>b</td>
<td>-H</td>
<td>NR</td>
<td>-</td>
</tr>
</tbody>
</table>

a The, slow, reaction gave a complex mixture mostly decomposition products.

b The cyclic nitrone 9 was used for this reaction. NR: no reaction.
128.74 (1C), 128.39 (2C); 128.34 (2C); 127.26 (1C); 127.06 (2C); 126.12 (1C); 126.70 (1C); 116.82 (2C); 62.75 (1C); 34.54 (1C); 29.83 (1C). Exact mass calculated for \( \text{C}_{24}\text{H}_{21}\text{NONa} \): \([M+Na]^+\): m/z 362.1520. Found: m/z 362.1516 (1 ppm).

(Z) 1, 4-Diphenyl-3-(3-phenyl-propylidene)-azetidin-2-one (1Z)

White solid, mp = 96°C, \( R_m = 0.40 \) (hexane/ethyl acetate 9/1). \(^1\)H NMR (CDCl\(_3\), 400 MHz), (ppm): 7.23 (m, 9H); 7.11 (m, 5H); 4.02 (s, 1H); 3.99 (d, 1H, J\(_{1H,2H}\) = 7.9 Hz, J\(_{1H,2H}\) = 1.5 Hz); 2.80 (m, 4H). \(^13\)C NMR (CDCl\(_3\), 100 MHz), (ppm): 161.55 (1C); 141.98 (1C); 140.63 (1C); 137.88 (1C); 137.14 (1C); 131.12 (1C); 129.03 (2C); 128.95 (2C); 128.51 (2C); 128.48 (2C); 128.36 (2C); 126.62 (1C); 126.01 (1C); 123.72 (1C); 116.83 (2C); 62.67 (1C); 35.35 (1C); 30.03 (1C). Exact mass calculated for \( \text{C}_{24}\text{H}_{21}\text{NONa} \): \([M+Na]^+\): m/z 362.1517 (1 ppm).

Acknowledgments

We thank CNRS and the Ministère de l’Enseignement Supérieur et de la Recherche (France) and the Research Grant Program at the Lebanese University for financial support. We thank Mr. O. Tasseau for his help regarding 2D NMR experiments and all members of the two teams (Beirut and Rennes) for fruitful discussions. We thank CRMPO (Rennes) for the mass spectral analysis.

Supplementary Material

Experimental procedures and copies of the 1D and 2D NMR spectra for all compounds plus X-Ray data for compound 14Z.

References and notes

16. CCDC 1455725 contain the supplementary crystallographic data for compound 14Z. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
Highlights

- New simple (1 step) method for the preparation of these challenging molecules.
- Method using cheap and easily available reagents.
- These methylene and alkylidene beta lactames have interesting potential in bioorganic and medicinal chemistry.