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A new direct synthesis of α -methylene- and α -alkylidene- β -lactams

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INFO

ABSTRACT

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

Keywords:

Keyword_1: nitrones

Keyword_2: alkynes

Keyword_3: Kinugasa reaction

Keyword_4: beta-lactams

Keyword_5: 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 A¹ and 6-(acetylmethylene)-penicinallic acid,² are described as β -lactamase inhibitors. Further, a new class of herbicides, such as the Phyllostictine A, has been discovered recently (Figure 1).³

Figure 1. Representative examples of bioactive α -alkylidene- β -lactams

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.² On the other hand, the exomethylene or exoalkylidene double bonds could be introduced starting from already prepared β -lactams.⁴ An alternative strategy involved intramolecular cyclisations starting from alkylidene- β -amino esters.⁵ Further, starting from *N*-allyl amines, the desired α -

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alkylidene β -lactams were obtained by intramolecular palladium-catalysed oxidative carbonylations,⁶ or by nucleophilic substitutions.⁷ Propiolamides were also useful starting materials affording various α -methylene- β -lactams through PPh_3 -catalyzed cyclizations.⁸ Finally, the cross-metathesis of α -methylene- β -lactams,⁹ as well as the ring closing metathesis reactions,³ 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.^{10, 11} 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.¹² For the Kinugasa reaction a first mechanism, through oxaziridinum intermediates, has been proposed by Ding and Irwing¹³ while a second, *via* ketenes, was proposed by Tang *et al.*¹⁴ 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 nucleofuge 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.¹⁵

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 nitron 1 and alkynes 2 chosen as models, and the results are indicated in Scheme 2 and Table 1.

Scheme 2. Kinugasa reaction from nitron 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 15h.¹⁵ 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 α -alkylidene- β -lactams was obtained, however in low yield (22%). A similar result was obtained starting from corresponding 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

nucleofuge 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 vinylic 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

Entry	X	T	Yield %	Z/E
1	-OH	50°C	-	-
2	-OCOMe	rt	22	31/69
3	-OCOPh	rt	24	29/71
4	-OCO ₂ Et	rt	40	38/62
5	-OCO ₂ Et	50°C	74	28/72
6	-OCO ₂ Et	Reflux ^a	65	42/58
7	-F	50°C	58	36/64

^aThe 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.¹²

Scheme 3. Kinugasa reaction between nitron 1 and alkynes 4.

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

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

N ^o	R ¹	R ²	R ³	Yield %	E/Z
13	-Ph	-Ph	- $n\text{C}_5\text{H}_{11}$	61	34/66
14	-Ph	-Ph	- $n\text{C}_9\text{H}_{19}$	68	36/64
15	-Ph	-Ph	-(CH_2) ₃ OBn	71	42/58
16	-Ph	- $t\text{Bu}$	- $\text{CH}_2\text{CH}_2\text{Ph}$	^a	-
17	-Ph	-Bn	- $\text{CH}_2\text{CH}_2\text{Ph}$	62	40/60
18	-Ph	-Bn	-H	54	-
19	-CO ₂ Bn	Bn	- $\text{CH}_2\text{CH}_2\text{Ph}$	60	47/53
20	-CO ₂ Bn	Bn	-H	NR	-
21	^b	^b	- $\text{CH}_2\text{CH}_2\text{Ph}$	NR	-
22	^b	^b	-H	NR	-

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

^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 nitrones, as indicated in Scheme 4 and Table 2.

Under the previously optimized reaction conditions, the nitrone **1** reacted with propargylic derivative **10** to give the α -alkylidene- β -lactams **13** in 61% yield, and in a 1:2 *E/Z* ratio (Table 2). In the same way, nitrone **1** reacted with **11** to give **14** in 68 % yield and as a 1:2 mixture of the *E* and *Z* isomers. The structure of **14Z** with the *Z* double bond was confirmed by X-Ray crystallography analysis.¹⁶ The nitrone **1** reacted also smoothly with the alkyne **12** bearing a protected alcohol function to afford in 71% overall yield a 42:58 mixture of **15E** and **15Z**. However, the *C*-Phenyl-*N*-*t*Bu nitrone **6** reacted very slowly with alkyne **2** affording very little, if any, of the desired alkylidene- β -lactams **16** and mostly decomposition products. On the contrary, the *C*-Phenyl-*N*-Benzyl nitrone **7** reacted with **2** to give the target molecules **17** in 62% yield and as a 40/60 mixture of the *E* and *Z* isomers. This nitrone **7** also reacted well with alkyne **4** to give the corresponding methylene β -lactam **18** in 54% yield. On the other hand, the functionalized nitrone **8** reacted smoothly with alkyne **2** to give the target derivatives **19** in 60% yield and as a

Figure 3. ORTEP Diagram of alkylidene- β -lactam **14Z**.

47:53 mixture of *E* and *Z* isomers. However surprisingly, this nitrone **8** did not react with alkyne **4**. Finally, compound **9** selected as a model for a cyclic nitrone, did not react with both alkynes **2** and **4**, thus failing to afford the targets **21E** and **21Z**. These last results indicate that the reaction is presently limited to acyclic nitrones. For all new alkylidene- β -lactams, the *E* and *Z* isomers were separated by chromatography and their stereochemistry was established by 2D NMR experiments as for **3E** and **3Z**.

In conclusion, application of the Kinugasa reaction to alkynes bearing a nucleofuge in propargylic position gives a very direct entry to α -methylene- and α -alkylidene- β -lactams. The process is very simple and uses only cheap and easily available reagents. Thus it expands the scope of the use of the Kinugasa reaction to derivatives which have been less studied previously but become now easily available.

Experimental section

All compounds have been prepared in racemic form.

Representative procedure for the preparation of **3E** and **3Z**.

H₂O (3 mL) was first degassed by bubbling nitrogen. CuI (0.225g, 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** (0.255g, 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 eluent (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, *R*_f = 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, ³*J* = 7.8 Hz, ⁴*J* = 1.6 Hz); 5.14 (dd, 1H, ⁴*J* = 1.6 Hz); 2.42 (m, 2H, ³*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);

128.74 (1C), 128.39 (2C); 128.34 (2C); 127.26 (1C); 127.06 (2C); 126.12 (1C); 123.70 (1C); 116.82 (2C); 62.75 (1C); 34.54 (1C); 29.83 (1C). Exact mass calculated for $C_{24}H_{21}NONa$: $[M + Na]^+$: m/z 362.1520. Found: m/z . 362.1516 (1 ppm).

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

White solid, mp= 96°C, R_f = 0.40 (hexane/ethyl acetate 9/1). 1H NMR ($CDCl_3$, 400 MHz), (ppm): 7.23 (m, 9H); 7.11 (m, 5H); 6.93 (m, 1H); 5.51 (td, 1H, $^3J = 7.9$ Hz, $^4J = 1.5$ Hz); 5.20 (s, 1H); 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 $C_{24}H_{21}NONa$: $[M + Na]^+$: m/z 362.1520. Found: m/z . 362.1517 (1 ppm).

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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

1. a) Tanaka, K.; Shoji, J.; Terui, Y.; Kondo, E.; Mayama, M.; Kawamura, Y.; Hattori, T.; Matsumoto, K.; Yoshida T. *J. Antibiot.* **1981**, *34*, 909-911; b) Arisawa, M.; Then, R. L. *J. Antibiot.* **1982**, *35*, 1578-1583.
2. Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. Y.; Finn K. *J. Org. Chem.* **1985**, *50*, 4245-4252.
3. Coe, S.; Pereira, N.; Geden, J. V.; Clarkson, G. J.; Fox, D. J.; Napier, R. M.; Neve, P.; Shipman, M. *Org. Biomol. Chem.* **2015**, *13*, 7655-7663.
4. a) Anklam, S.; Liebscher, J. *Tetrahedron* **1998**, *54*, 6369-6384; b) Torchiarolo, G. C.; D'Onofrio, F.; Margarita, R.; Parlanti, L.; Piancatelli, G.; Bella, M. *Tetrahedron* **1998**, *54*, 15657-15666; c) Bari, S. S.; Arora, R.; Bhalla, A.; Venugopalan, P. *Tetrahedron Lett.* **2010**, *51*, 1719-1722.
5. a) Adam, W.; Groer, P.; Humpf, H-U.; Saha-Möller, C. H. *J. Org. Chem.* **2000**, *65*, 4949-4922; b) Lee, S. I.; Moon, S. Y.; Hwang, G-S.; Ryu, D. H. *Org. Lett.* **2010**, *12*, 3234-3237.
6. a) Crisp, G. T.; Meyer, A. G. *Tetrahedron* **1995**, *51*, 5585-5596; b) Bukovec, C.; Kazmaier, U. *Org. Biomol. Chem.* **2011**, *9*, 2743-2750; c) Li, W.; Liu, C.; Zhang, H.; Ye, K.; Zhang, G.; Zhang, W.; Duan, Z.; You, S.; Lei, A. *Angew. Chem. Int. Ed.* **2014**, *53*, 2443-2446.
7. a) Wang, X.; Meng, F.; Wang, Y.; Han, Z.; Chen, Y-J.; Liu, L.; Wang, Z.; Ding, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 9276-9285; b) Li, Z.; Sharma, U. K.; Liu, Z.; Sharma, N.; Harvey, J. N.; Van der Eycken, E. V. *Eur. J. Org. Chem.* **2015**, 3957-3962.
8. Zhu, L.; Xiong, Y.; Li, C. *J. Org. Chem.* **2015**, *80*, 628-633.
9. Liang, Y.; Raju, R.; Le, T.; Taylor, C. D.; Howell, A. R. *Tetrahedron Lett.* **2009**, *50*, 1020-1022.
10. Kinugasa, M.; Hashimoto S. *J. Chem. Soc. Chem. Commun.* **1972**, 466-467.
11. For recent comprehensive reviews on the Kinugasa reaction, see: a) Marco-Contelles, J. *Ang. Chem. Int. Ed.* **2004**, *43*, 2198-2200; b) Pal, R.; Ghosh, S. C.; Chandra, K.; Basak, A. *Synlett* **2007**, *15*, 2321-2330; Khangarot, R. K.; Kaliappan K. P. *Eur. J. Org. Chem.* **2013**, *34*, 7664-7677; c) Stecko, S.; Furman, B.; Chmielewski M. *Tetrahedron* **2014**, *70*, 7817-7844; d) Chigrinova, M.; MacKenzie, D. A.; Sherratt, A. R.; Cheung, L.L. W.; Pezacki J. P. *Molecules* **2015**, *20*, 6959-6969.
12. Basak, A.; Ghosh C. *Synlett* **2004**, *9*, 1637-1639.
13. Ding, L. K.; Irwing, W. J. *J. Chem. Soc. Perkin Trans 1* **1976**, 2382-2386.
14. a) Ye, M.-C.; Zhou, J.; Whang, Z-Z.; Tang Y. *Chem. Commun.* **2003**, 2554-2555; b) Ye, M.-C.; Zhou, J.; Tang Y. *J. Org. Chem.* **2006**, *71*, 3576-3582; see also: c) Anh, C.; Kennington Jr. J. W., De Shong P. *J. Org. Chem.* **1994**, *59*, 6282-6286; d) Santoro, S.; Liao, R.-Z.; Marcelli, T.; Hammar, P.; Himo, F. *J. Org. Chem.* **2015**, *80*, 2649-2660.
15. Nasr el Dine, A.; Grée, D.; Roisnel, T.; Caytan, E.; Hachem, A.; Grée, R. *Eur. J. Org. Chem.* **2016**, 556-561.
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.