Tetrahedron Letters 50 (2009) 1020–1022

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Cross-metathesis of α-methylene-β-lactams: the first tetrasubstituted alkenes by CM

Yanke Liang, Ravinder Raju, Tri Le, Christopher D. Taylor, Amy R. Howell *

Department of Chemistry, University of Connecticut, Storrs, CT 06269-3060, United States

ARTICLE INFO

Article history:
Received 6 December 2008
Accepted 11 December 2008
Available online 24 December 2008

ABSTRACT

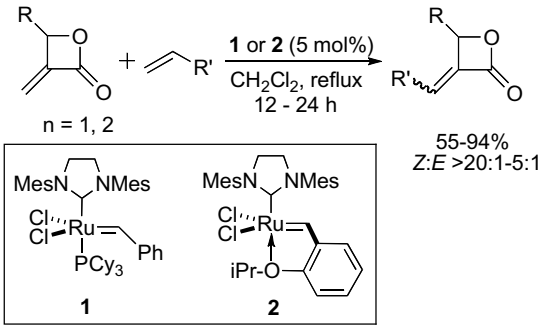
α-Alkylidene-β-lactams have been prepared in good to excellent yields by olefin cross-metathesis. Electron-poor α-methylene-β-lactams undergo cross-metathesis more rapidly and efficiently than more electron-rich analogs. Significantly, tetrasubstituted alkenes have for the first time been accessed by CM reactions.

α-Alkylidene-β-lactams are structural units found in several potent β-lactamase inhibitors.[1] Moreover, they serve as building blocks for the preparation of β-lactam antibiotics,[2] as well as β-amino alcohols and acids.[3] A recent investigation in our group demonstrated that cross-metathesis (CM)[4] is an efficient and powerful tool to introduce various functional groups to α-methylene-β-lactones (Scheme 1).[5] It was anticipated that α-methylene-β-lactams would exhibit similar reactivity. We herein describe our CM results with α-methylene-β-lactams, examining specifically the effect of substitution on the amide nitrogen. In addition, CM to give tetrasubstituted alkenes is reported for the first time.

Preliminary studies involved reactions between α-methylene-β-lactam **3** and terminal olefins **a**–**c** (2 equiv) in the presence of Grubbs second generation catalyst **1** or the Grubbs-Hoveyda catalyst **2** (Table 1, entries 1, 7, 8, 14, and 15). Coupling of **3** with 1-pentene (**a**) was complete within 1 h using 2 mol % of **1** (entry 1). Coupling with **b**, however, was only marginally promoted by **1**, while portion-wise additions of catalyst **2** gave a remarkable increase in yield (entries 7 and 8). Catalyst **1** did not promote the coupling of **3** with **c**; however, catalyst **2** did (entries 14 and 15). Overall, with less reactive cross-partners (**b** and **c**), **2** appeared to be more effective, and optimal yields were realized with portion-wise additions.

In order to determine whether the conclusions with **3** could be extrapolated to other α-methylene-β-lactams, we examined the series **3**–**7**. The reactivity of electron-poor lactam **3** was compared to more electron-rich lactams **4**–**7**. All lactams coupled efficiently with **a** (Table 1, entries 1–6), and the most electron-deficient lactam **3** required the least amount of catalyst. Lactam **4** coupled with **a** in a lower yield (61%) when catalyst **1** was employed (entry 2); however, catalyst **2** furnished **4a** in 89% yield (entry 3).

The influence of the substituent on the amide nitrogen was evident when less reactive cross-partners, **b** and **c**, were used (Table 1, entries 7–20). The lactams (entries 8–12) were subjected to identical reaction conditions, and the yields for lactams **3b** and **4b** were the same. However, a notable decrease in yield was observed for more electron-rich lactams, **5**–**7**. The yield of **7b** could be improved from 57% (entry 12) to 72% with increased catalyst loading (entry 13).



Scheme 1. CM reactions of α-methylene-β-lactones.

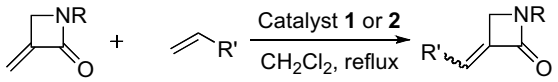
For cross-partners, **a** and **b**, the initial charge of catalyst **2** usually led to the greatest conversion, but this barely promoted CM reactions between allyl chloride (**c**) and lactams **3**–**7**. In all cases, the addition of a 5 mol % portion of **2** with heating for 12 h led to considerable conversions, and an additional 1 mol % of **2** with continued heating for 1 h provided lactams **3c**, **5c**, **6c,** and **7c** in reasonable yields (Table 1, entries 15, and 18–20). Although only 25% yield of **4c** was obtained by using the same protocol (entry 16), portion-wise addition of **2** over the course of 3 h resulted in the formation of **4c** in an improved 60% yield (entry 17). However, reactions with **c** were incomplete in all cases, and increasing the catalyst loading did not improve the yields.

Both electron-rich and electron-poor styrenes coupled efficiently with **3** (entries 21 and 22). Notably, the *E*-selectivity was higher, which may be a result of increased branching at the

* Corresponding author. Tel.: +1 860 486 3460; fax: +1 860 486 2981.
E-mail address: amy.howell@uconn.edu (A.R. Howell).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.12.060

Table 1
CM reactions of lactams **3**–**7**



3: R = Boc
4: R = H
5: R = Bn
6: R = Ph
7: R = *p*-MeOPh

a: R' = $(CH_2)_2CH_3$
b: R' = $(CH_2)_2OAc$
c: R' = CH_2Cl
d: R' = *p*-MeOPh
e: R' = *p*-FPh
f: R' = CH_2OH

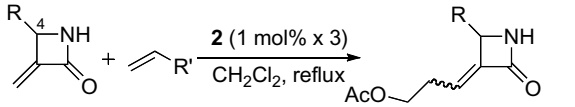
Entry	Reactants	Product	Catalyst (loading)	Yield (%)	*E*:*Z*[a]
1	**3**, **a**	**3a**	**1** (2 mol %)	84	2.5:1
2	**4**, **a**	**4a**	**1** (2 mol % × 3)	61	2:1
3	**4**, **a**	**4a**	**2** (1 mol % × 3)	89	2:1
4	**5**, **a**	**5a**	**1** (2 mol % × 2)	89	2:1
5	**6**, **a**	**6a**	**1** (2 mol % × 2)	82	3:1
6	**7**, **a**	**7a**	**1** (2 mol % × 2)	80	2.5:1
7	**3**, **b**	**3b**	**1** (2 mol % × 5)	57	2:1
8	**3**, **b**	**3b**	**2** (1 mol % × 3)	90	2:1
9	**4**, **b**	**4b**	**2** (1 mol % × 3)	90	2:1
10	**5**, **b**	**5b**	**2** (1 mol % × 3)	77	1.5:1
11	**6**, **b**	**6b**	**2** (1 mol % × 3)	76	2:1
12	**7**, **b**	**7b**	**2** (1 mol % × 3)	57	1.5:1
13	**7**, **b**	**7b**	**2** (2 mol % × 5)	72	1.5:1
14	**3**, **c**	**3c**	**1** (2 mol % × 3)	NR	—
15	**3**, **c**	**3c**	**2** (5 mol %; 1 mol %)	78	1.2:1
16	**4**, **c**	**4c**	**2** (5 mol %; 1 mol %)	25	1.1:1
17	**4**, **c**	**4c**	**2** (3 mol % × 3)	60	1.1:1
18	**5**, **c**	**5c**	**2** (5 mol %; 1 mol %)	58	1.1:1
19	**6**, **c**	**6c**	**2** (5 mol %; 1 mol %)	54	1.1:1
20	**7**, **c**	**7c**	**2** (5 mol %; 1 mol %)	48	1.1:1
21	**3**, **d**	**3d**	**2** (1 mol % × 3)	87	5:1
22	**3**, **e**	**3e**	**2** (1 mol % × 3)	90	3:1
23	**3**, **f**	**3f**	**2** (2 mol % × 5)	77	2:1

[a] Determined by ^{1}H NMR.

α-carbon of the alkene. Additionally, CM of **3** with unprotected allyl alcohol, which did not undergo CM with α-methylene-β-lactones,[5] gave a good yield of **3f**, although increased catalyst loading was required (entry 23).

The stereoselectivity of CM reactions can be quite varied, but generally, *E*-isomers predominate.[4,6] However, our initial investigations[5] involving CM of exocyclic enones evaluated an α-methylene-β-lactone with a bulky substituent at C-4, which led to CM adducts with high *Z*-selectivity (Scheme 1). In comparison, CM reactions with α-methylene-β-lactams **3**–**7**, which have no substituent at C-4, gave rise to cross-products that were slightly *E*-selective.[7] To assess the steric influence that C-4 substitution imposes on the *E*:*Z* ratio, α-methylene-β-lactam **8** was examined (Scheme 2). When **8** was reacted with **b** under the conditions developed for **4** (Table 1, entry 9), α-alkylidene-β-lactam **8b** was isolated in 81% with an *E*/*Z* ratio of 1:3. Thus, a group as small as methyl significantly impacted the *E*/*Z* selectivity.

Unlike the successful construction of tetrasubstituted cycloalkenes via ring-closing metathesis (RCM),[8] CM reactions to give tetrasubstituted alkenes have not yet been reported to our knowledge. The facility with which α-methylene-β-lactones



4: R = H
8: R = CH_3

4b: R = H, 90%, *E*/*Z* = 2:1
8b: R = CH_3, 81%, *E*/*Z* = 1:3

Scheme 2. The impact of C-4 branching on CM reactions.

underwent CM to give trisubstituted alkenes (see Scheme 1) prompted us at that time to attempt the preparation of tetrasubstituted alkenes. This was unsuccessful. However, in contrast to our α-methylene-β-lactones that had relatively large substitutents at C-4, most of our α-methylene-β-lactams were unsubstituted at that position. Consequently, we decided to examine CM between the most reactive α-methylene-β-lactam **3** and terminal disubstituted alkenes. The results are shown in Table 2.

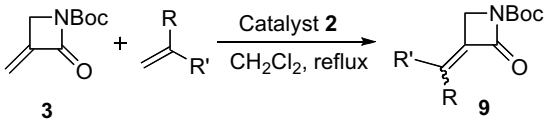
CM reactions between **3** and various disubstituted alkenes (Table 2, entries 1–8) proceeded in moderate to excellent yields and with little to no stereoselectivity. Comparing the conditions and results of entries 1–3 with the preparations of trisubstituted alkenes **3a**–**c** (Table 1, entries 1, 8, and 15), the CM reactions to give tetrasubstituted alkenes generally required more catalyst. Compatible functional groups included ester,[9] phenyl, trimethylsilyl, and unprotected alcohol groups (Table 2, entries 4–7). 3-Methyl vinyl acetate, however, did not undergo CM reaction with **3** (entry 8), presumably due to the electronic nature of the vinyl acetate. In most cases, 10 mol % loading of catalyst **2** was required to reach a reasonable conversion.

The substituents of the cross-partners could be extended (from Me to Et) without diminishing the reactivity of CM (Table 2, entry 9). However, any α-branching on the allylic position[10] appeared to shut down the CM reaction completely (Table 2, entries 10 and 11). On the other hand, CM reaction of **3** with 2-methyl-1-penten-3-ol, which bears an allylic alcohol, proceeded in moderate yield with an *E*:*Z* ratio of 1:2.5 (entry 12). The yield was further improved to 69% by using increased catalyst loading and extended refluxing (entry 13).

To further clarify the role that steric factors play in CM reactions, the reactivity of **10**, which contains a methyl group on C-4 of the lactam, with 2-methyl-1-pentene was examined (Table 3, entry 1). No cross-product was observed. On the other hand, the CM reactions to form tetrasubstituted alkenes could take place when an electron-rich α-methylene-β-lactam **5** was employed (entry 2), which may suggest that the electronic effects are not as important as steric effects in these reactions.

Additional support for a prominent role for steric effects is seen in the contrast in CM reactivity of enoates **12** and **13**. α-Methyl-substituted enoate **12** was reported to undergo CM with a simple, terminal alkene in the presence of catalyst **1** in excellent yield with

Table 2
CM reactions of α-methylene-β-lactam **3** with 1,1-disubstituted alkenes

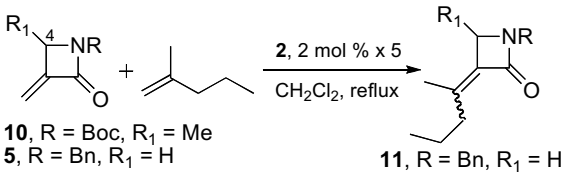


3 **9**

Entry	R	R′	Catalyst loading	Yield (%)	*E*:*Z*[a]
1	Me	$CH_2CH_2CH_3$	2 mol % × 3	85	1:1
2	Me	CH_2CH_2OAc	2 mol % × 3	64	1:1.5
3	Me	CH_2Cl	2 mol % × 5	58	1:1.6
4	Me	CH_2COOEt	2 mol % × 5	41	1:1.5
5	Me	CH_2Ph	2 mol % × 5	81	1:1.5
6	Me	CH_2SiMe_3	2 mol % × 5	73	1:1.7
7	Me	CH_2OH	2 mol % × 5	86	1:1.7
8	Me	OAc	2 mol % × 3	NR	—
9	Et	Et	2 mol % × 5	65	—
10	Me	$CH(CH_3)_2$	2 mol % × 3	NR	—
11	Me	Ph	2 mol % × 3	NR	—
12	Me	$CH(OH)C_2H_5$	2 mol % × 5[b]	40	1:2.5
13	Me	$CH(OH)C_2H_5$	5 mol % × 3[c]	69	1:2.5

[a] Determined by ^{1}H NMR.
[b] The reaction was refluxed for 12 h after the last addition of the catalyst.
[c] The reaction was refluxed for 12 h after each addition of the catalyst.

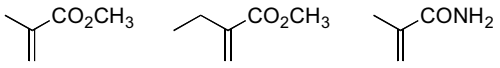
Table 3
Investigation of steric and electronic effects



Entry	R	R_1	Catalyst loading	Yield (%)	*E*:*Z*[a]
1	Boc	Me	2 mol % × 3	NR	—
2	Bn	H	2 mol % × 5	74	1:1.2

[a] Determined by ^{1}H NMR.

high *E*-selectivity.[6b] However, we found that, under similar conditions and with 1-pentene as a cross-partner, enone **13** did not react at all. The result was the same with extended reaction times and higher catalyst loading with either **1** or **2**. Sensitivity to steric effects is further illustrated by the failure of amide **14** to undergo CM with disubstituted terminal olefin 3-methylbut-3-enyl acetate (see alkene for entry 2, Table 2) in the presence of either catalyst **1** or **2**, even with high catalyst loading and extended reaction time. The broad CM reactivity of α-methylene-β-lactones and -lactams in contrast to the limited reactivity of 1,1-disubstituted enoates and enamides suggests that these strained heterocycles could find utility as masked enoates and enamides.



12 **13** **14**

In conclusion, it has been shown that α-methylene-β-lactams undergo efficient CM reactions. Notably, for the first time, the application of CM to the formation of tetrasubstituted alkenes has been demonstrated. The observation that electron-poor lactams exhibit superior reactivity to electron-rich lactams is consistent with the CM reactivity profile of monosubstituted α,β-unsaturated amides.[11] Interestingly, C-4 unsubstituted lactams **3**-**7** do not undergo CM with substantial *E*-selectivity. However, substitution at C-4 (substrate **8**) led to *Z*-selectivity without diminished reactivity for the α-methylene-β-lactam, which is consistent with the CM of α-methylene-β-lactones. The impact of allylic branching on CM reactivity has also been illustrated. Overall, α-methylene-β-lactones and -lactams are excellent substrates for CM reactions, and they can be viewed as masked 1,1-disubstituted enoates and enamides, which have very limited or nonexistent CM reactivity. Our results also suggest that steric factors play a dominant role in both stereoselectivity and feasibility of CM reactions.

Acknowledgments

We thank Krystle T. Clarke (Houston-Tillotson University) and Laura Allen (Ohio Northern University) for conducting preliminary experiments. Helpful discussions with Bob Grubbs and Martha Morton are also acknowledged.

Supplementary data

The supplementary data include detailed experimental procedures, characterization data, and ^{1}H and ^{13}C spectra for previously unreported compounds. Supplementary data associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.060.

References and notes

1. For recent reviews, see: (a) Sandanayaka, V. P.; Prashad, A. S. *Curr. Med. Chem.* **2002**, *9*, 1145; (b) Buynak, J. D. *Curr. Med. Chem.* **2004**, *11*, 1951 and references therein.
2. (a) Buynak, J. D.; Rao, M. N.; Pajouhesh, H.; Chandrasekaran, R. Y.; Finn, K.; de Meester, P.; Chu, S. C. *J. Org. Chem.* **1985**, *50*, 4245; (b) Brickner, S. J.; Gaikema, J. J.; Greenfield, L. J.; Zurenko, G. E.; Manninen, P. R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 2241; (c) Di Giacomo, B.; Tarzia, G.; Bedini, A.; Gatti, G.; Bartoccini, F.; Balsamini, C.; Tontini, A.; Baffone, W.; Di Modugno, E.; Felici, A. *Farmaco* **2002**, *57*, 273.
3. (a) Saalfrank, R. W.; Paul, W.; Liebenow, H. *Angew. Chem.* **1980**, *92*, 740; (b) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755; (c) Adam, W.; Groer, P.; Humpf, H.-U.; Saha-Moller, C. R. *J. Org. Chem.* **2000**, *65*, 4919; (d) Hitchcock, P. B.; Papadopoulos, K.; Young, D. W. *Org. Biomol. Chem.* **2003**, *1*, 2670; (e) Basak, A.; Ghosh, S. C. *Synlett* **2004**, 1637; (f) De Vitis, L.; Troisi, L.; Granito, C.; Pindinelli, E.; Ronzini, L. *Eur. J. Org. Chem.* **2007**, *2*, 356.
4. For recent reviews on cross metathesis, see: (a) Connor, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900; (b) Chatterjee, A. K.; Choi, T.-L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360; (c) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117; (d) Netscher, T. *J. Organomet. Chem.* **2006**, *691*, 5155.
5. Raju, R.; Howell, A. R. *Org. Lett.* **2006**, *8*, 2139.
6. (a) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751; (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783; (c) Engelhardt, F. C.; Schmitt, M. J.; Taylor, R. E. *Org. Lett.* **2001**, *3*, 2209.
7. *E*/*Z* isomeric ratio was determined by ^{1}H NMR. Resonances for the exocyclic alkene proton, for all β-lactam cross products, were consistent with our NOE based *E*/*Z* assignments of α-alkylidene-β-lactones.
8. (a) Yao, Q.; Zhang, Y. *J. Am. Chem. Soc.* **2004**, *126*, 74; (b) Michrowska, A.; Bujok, R.; Harutyunyan, S.; Sashuk, V.; Grela, K. *J. Am. Chem. Soc.* **2004**, *126*, 9318; (c) Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912; (d) Nosse, B.; Schall, A.; Jeong, W. B.; Reiser, O. *Adv. Synth. Catal.* **2005**, *347*, 1869; (e) Berlin, J. M.; Campbell, K.; Ritter, T.; Funk, T. W.; Chlenov, A.; Grubbs, R. H. *Org. Lett.* **2007**, *9*, 1339; (f) Stewart, I. C.; Ung, T.; Pletnev, A. A.; Berlin, J. M.; Grubbs, R. H.; Schrodi, Y. *Org. Lett.* **2007**, *9*, 1589.
9. Interestingly, during the silica gel chromatographic purification of entry 4 (Table 2), there was significant isomerization of the exocyclic alkenes to the corresponding α,β-unsaturated esters (see Supplementary data).
10. (a) Courchay, F. C.; Baughman, T. W.; Wagener, K. B. *J. Organomet. Chem.* **2006**, *691*, 585; (b) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. *Org. Lett.* **2008**, *10*, 441.
11. Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277.