ORGANIC LETTERS

2003
Vol. 5, No. 19
3439−3442

One-Pot Three-Component Tandem Metathesis/Diels−Alder Reaction

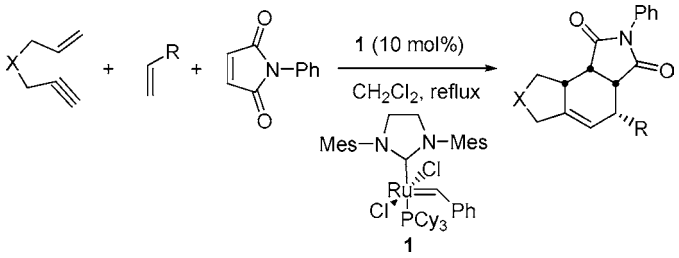
Hee-Yoon Lee,* Hyoun Young Kim, Hyunsup Tae, Byung Gyu Kim, and Jaeyoung Lee

Center for Molecular Design & Synthesis, Department of Chemistry and School of Molecular Science (BK21), Korea Advanced Institute of Science & Technology, Daejon 305-701, Korea

leehy@kaist.ac.kr

Received June 26, 2003

ABSTRACT

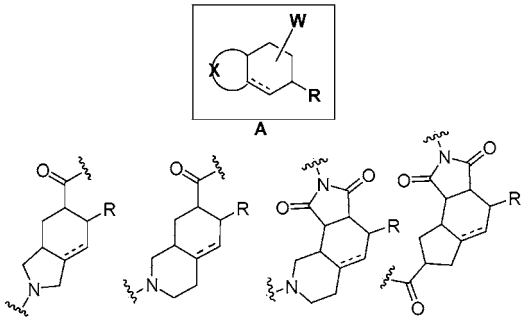


A tandem enyne, diene-ene metathesis reaction followed by Diels−Alder reaction accomplished a stereoselective three-component reaction protocol with four stereocenters.

The development of air-stable and reactive catalysts with general applicability has made olefin metathesis reaction one of the most versatile synthetic transformations in organic synthesis.[1] Consequently, innumerous applications of ring-closing olefin metathesis of dienes (RCM) have been reported.[2] Recently, ruthenium-catalyzed metathesis reaction of enynes[3] has also become popular due to the development of new catalysts and the use of ethylene atmosphere.[4] Since the enyne metathesis reaction produces conjugated dienes, the reaction was soon coupled to the Diels−Alder reaction to form polycyclic compounds.[5]

In the course of developing combinatorial libraries[6] of possible ligands for G-protein-coupled receptors (GPCRs)[7] and peptidomimetics for bioactive peptides, we became interested in bicyclic structure **A** that would provide rigid scaffolds with well-defined arrangements of possible pharmacophores in space (Scheme 1). Compound libraries generated from these scaffolds will make good candidates for receptor ligands and peptidomimetics.[8]

Scheme 1



(1) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141.

(2) For recent reviews on olefin metathesis, see: (a) Furstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3013. (b) Wright, D. L. *Curr. Org. Chem.* **1999**, *3*, 211. (c) Philips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (e) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (f) Furstner, A. *Topics in Organometallics Chemistry*; Springer-Verlag: Berlin, Germany, 1998; Vol. 1.

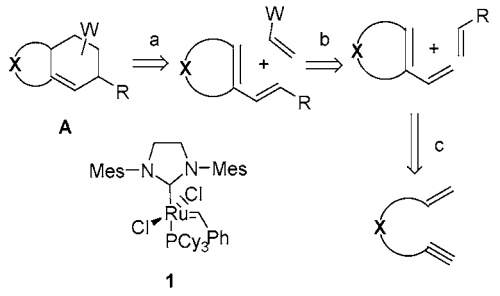
(3) For recent reviews on enyne metathesis, see: (a) Poulsen, C. S.; Madsen, R. *Synthesis* **2003**, 1. (b) Mori, M. *Top. Organomet. Chem.* **1998**, *1*, 133.

(4) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082.

10.1021/ol035194c CCC: $25.00
Published on Web 08/26/2003

Therefore, we were looking for a general and facile way of constructing **A**. Synthetic analysis revealed that the preparation of **A** could ideally be achieved through a one-pot three-component protocol (Scheme 2). Transformations

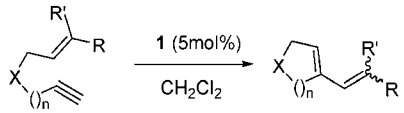
Scheme 2. Retrosynthetic Analysis



b and *c* are both metathesis reactions catalyzed by the same catalyst **1**, and transformation *a* is the Diels−Alder reaction that is known to be compatible with Ru-catalyzed metathesis reaction.

Though the tandem intramolecular enyne metathesis/Diels−Alder reaction has been reported, most of the reported cases were limited to terminal olefins. Enyne metathesis reactions of olefins other than terminal olefins have not been systematically studied.[9] Since the intermolecular diene-ene metathesis reaction has not been reported,[10] success of the tandem reaction might require enynes with an R-group attached to the olefin. The presence of an R-group also brought up the issue of stereoselectivity during the metathesis reaction. Before exploring the three-component reaction, we decided to test the stereoselecitivity of the metathesis reaction of **2** and the feasibility of the tandem enyne/diene-ene metathesis reaction. First, we set out to test the enyne metathesis reaction of internal olefins, and the results are summarized in the Table 1.

Table 1. Enyne Metathesis Reaction[11]



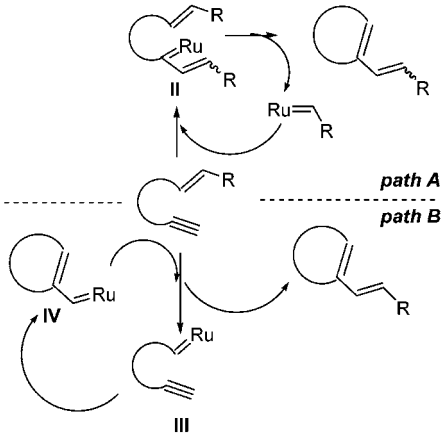
enyne	X	*n*	R	R′	product	yield[a] (*E*/*Z*)[b]
2a	NTs	1	CH_3	H	**3a**	85% (3/1)
2b	NTs	1	CH_2OH	H	**3b**	72% (3/1)
2c	NTs	1	CH_3	CH_3	**3c**	98%
2d	NTs	2	CH_3	H	**3d**	82% (6/1)
2e	NTs	2	CH_2OH	H	**3e**	86% (6/1)
2f	NTs	2	CH_3	CH_3	**3f**	92%
2g	CE_2[c]	1	CH_3	H	**3g**	83% (6/1)
2h	CE_2	1	CH_2OH	H	**3h**	88% (16/1)
2i	CE_2	1	CH_3	CH_3	**3i**	90%
2j	CE_2	2	CH_3	H	**3j**	82% (16/1)
2k	CE_2	2	CH_2OH	H	**3k**	96% (12/1)
2l	CE_2	2	CH_3	CH_3	**3l**	93%

[a] Isolated yield. [b] *E*/*Z* ratio was determined by ^{1}H NMR. [c] *E* = COOEt.

The enyne metathesis reaction proceeded well with internal olefins as anticipated, and the reaction provided good to excellent stereoselectivity, which was quite higher than expected on the basis of the reported cross enyne metathesis reaction.[12] The stereoselectivity was better for six-membered ring compounds than five-membered ring ones, and hetero-atom incorporation in the tether diminished the selectivity.

The reaction could follow two possible catalytic pathways (Scheme 3). In path **A**, the ruthenium carbene complex reacts

Scheme 3. Plausible Mechanistic Pathways



first with the alkyne of the substrate, and thus the product would be expected to show stereoselectivity similar to that of the cross enyne metathesis reaction.[13] On the other hand,

(5) For sequential metathesis/Diels−Alder approach, see: (a) Banti, D.; North, M. *Tetrahedron Lett.* **2002**, *43*, 1561. (b) Guo, H.; Madhushaw, R. J.; Shen, F.-M.; Liu, R.-S. *Tetrahedron* **2002**, *58*, 5627. (c) Schurer, S. C.; Blechert, S. *Chem. Commun.* **1999**, 1203. (d) Hoye, T. R.; Donaldson, S. M.; Vos, T. J. *Org. Lett.* **1999**, *1*, 277. For tandem metathesis/Diels−Alder approach, see: (e) Bentz, D.; Laschat, S. *Synthesis* **2000**, 1766. (f) Moreno-Manas, M.; Pleixats, R.; Santamaria, A. *Synlett* **2001**, 1784.

(6) Nicolaou, K. C.; Hanko, R.; Hartwig, W. *Handbook of Combinatorial Chemistry*; Viley-VCH: Weinhein, 2002; Vol 2.

(7) (a) Kang, K. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Chung, B. Y.; Lee, J. E.; Jung, S. H.; Koh, H. Y.; Lee, H.-Y. *Tetrahedron Lett.* **2001**, *42*, 1057. (b) Cha, M. Y.; Choi, B. C.; Kang, K. H.; Pae, A. N.; Choi, K. I.; Cho, Y. S.; Koh, H. Y.; Lee, H.-Y.; J., D.; Kong, J. Y. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1327. For recent reviews on GPCR ligands, see: (c) Patchett, A. A.; Nargund, R. P. *Annu. Rev. Med. Chem.* **2000**, *35*, 289. (d) Watson, S.; Arkinstall, S. *The G-Protein Linked Receptor*; Academic Press: San Diego, 1994.

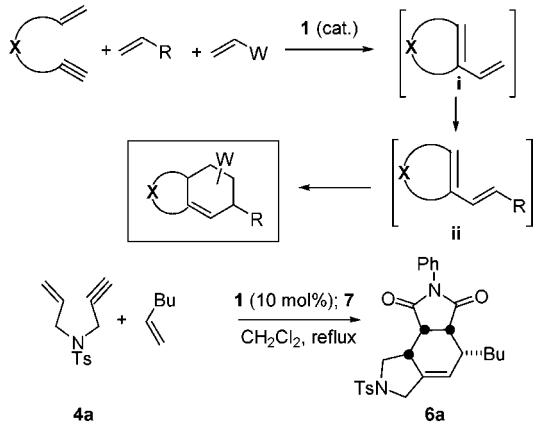
(8) For recent reviews on peptidomimetics, see: (a) Hruby, V. J. *Nature Rev. Drug Discovery* **2002**, *1*, 847. (b) Egushi, M.; Kahn, M. *Mini Rev. Med. Chem.* **2002**, *2*, 447.

(9) (a) Kitamura, T.; Sato, Y.; Mori, M. *Adv. Synth. Catal.* **2002**, *344*, 678. (b) Furstner, A.; Ackermann, L.; Gabor, B.; Goddard, R.; Lehmann, C. W.; Mynott, R.; Stelzer, F.; Thiel, O. R. *Chem.—Eur. J.* **2001**, *7*, 3236.

(10) For the intramolecular diene-ene metathesis, see: (a) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. *Angew. Chem., Int. Ed.* **2000**, *39*, 1664. (b) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171. (c) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (d) Bach, T.; Lemarchand, A. *Synlett* **2002**, 1302. (e) Wagner, J.; Cabrejas, L. M. M.; Grossmith, C. E.; Papageorgiou, C.; Senia, F.; Wagner, D.; France, J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 9255.

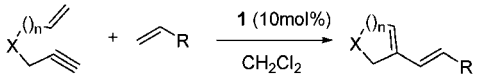
in path **B**, the ruthenium carbene complex **IV** reacts first with the olefin of the substrate and produces the product.

Scheme 4. Multicomponent Tandem Reaction Sequence



The intermediate **IV** was one of the plausible intermediates in the tandem enyne/diene-ene metathesis reaction that led to selective formation of the (*E*)-isomer (Table 2). The isomeric ratio summarized in Table 1 indicated that the reaction followed either path A or both pathways.

Table 2. Tandem Enyne, Diene-ene Metathesis Reaction[15]



enyne	X	*n*	R	product	yield[a,b]
4a	NTs	1	Bu	**5a**	86%
4a	NTs	1	$(CH_2)_2$ac	**5b**	88%
4a	NTs	1	Ph	**5c**	86%
4a	NTs	1	Bn	**5d**	84%
4a	NTs	1	$(CH_2)_2$OBz	**5e**	73%
4a	NTs	1	$(CH_2)_2$Br	**5f**	78%
4a	NTs	1	CH_2TMS	**5g**	93%
4b	NTs	2	Bu	**5h**	85%
4b	NTs	2	$(CH_2)_2$ac	**5i**	74%
4b	NTs	2	Ph	**5j**	68%
4b	NTs	2	Bn	**5k**	86%
4b	NTs	2	$(CH_2)_2$OBz	**5l**	66%
4b	NTs	2	$(CH_2)_2$Br	**5m**	74%
4b	NTs	2	CH_2TMS	**5n**	81%
4c	CE_2	1	Bu	**5o**	85%
4c	CE_2	1	$(CH_2)_2$ac	**5p**	63%
4c	CE_2	1	Ph	**5q**	87%
4c	CE_2	1	Bn	**5r**	86%
4c	CE_2	1	$(CH_2)_2$OBz	**5s**	73%
4c	CE_2	1	$(CH_2)_2$Br	**5t**	82%
4c	CE_2	1	CH_2TMS	**5u**	65%

[a] Isolated yield. [b] *E*/*Z* ratio was determined to be >20:1 by ^{1}H NMR. [c] *E* = COOEt. [d] ac = CH_3CO

Next, we tested the feasibility of the tandem enyne/diene-ene metathesis reaction. The successful execution of this protocol would rely on the cross diene-ene metathesis since cross metathesis reaction between an olefin and a conjugated diene has not been reported.[14] This tandem reaction protocol was first tested with enyne **4a** and 1-hexene. A mixture of **4**, and 1-hexene (5 equiv) with **1** (10 mol %) in dichloromethane was heated to reflux overnight to afford tandem metathesis product **5a** with exclusively (*E*)-stereochemistry in 82% yield (Table 2). The ^{1}H NMR spectrum of the reaction mixture before purification showed no indication of the (*Z*)-isomer. When less than 5 equiv of 1-hexene or a lesser amount of catalyst with up to 10 equiv of 1-hexene was used, a substantial amount of the initially formed intramolecular enyne metathesis product was isolated along with the desired substituted diene **5a**.

Table 2 summarized the result of reaction of various olefins with enynes and showed that the reaction was quite general and stereoselective. Even allylsilane, which is known to rapidly afford a mixture of *E*/*Z* isomers in intermolecular enyne metathesis reaction,[12] produced dienes stereoselectively. The reaction was also tested under an ethylene atmosphere since the addition of ethylene was known to facilitate the enyne metathesis.[4,8] No effect on the efficiency or the selectivity was observed. Presumably, the olefin reagent already played the same role as ethylene.

With the stereoselective execution of the tandem reaction, we next explored the multicomponent reaction.[16] The multicomponent reaction was tested with **4a**, 1-hexene, and *N*-phenylmaleimide (**7**) under the same reaction conditions as for the tandem reaction. Since there were two diene intermediates (**i** and **ii**) in the reaction mixture, the Diels−Alder reaction of **7** could produce two cycloadducts unless the transformation of **i** into **ii** was faster than Diels−Alder reaction. When **4a** and hexene were reacted together with **7**, the reaction became complex and the major product of the reaction was the Diels−Alder adduct of **7** with the initially formed enyne metathesis product **i**, along with the

(11) **General Procedure for the Enyne Metathesis Reaction.** A solution of enyne and Grubbs second-generation catalyst (5 mol %) in CH_2Cl_2 (0.01 M) was stirred at room temperature for 1.0 h, and the solvent was evaporated. Then, the residue was purified by flash column chromatography on silica gel to afford the desired diene product.

(12) Lee, H.-Y.; Kim, B. G.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 1855.

(13) (a) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2518. (b) Rodriguez-Conesa, S.; Candal, P.; Jimenez, C.; Rodriguez, J. *Tetrahedron Lett.* **2001**, *42*, 6699.

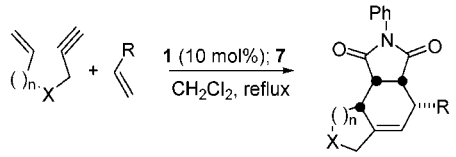
(14) Royer, F.; Vilain, C.; Elkaim, L.; Grimaud, L. *Org. Lett.* **2003**, *5*, 2007.

(15) **General Procedure for the Tandem Enyne/Diene-ene Metathesis Reaction.** Alkyne (1 equiv) and olefin (5 equiv) were dissolved in CH_2Cl_2 (0.05 M) under an Argon atmosphere. Grubbs second-generation catalyst (10 mol %) was added to the reaction mixture at room temperature, and the resulting mixture was heated to reflux for 3−5 h. After the mixture was cooled to room temperature, the solvent was removed under reduced pressure. Then, the residue was purified by flash column chromatography on silica gel to afford the desired diene product.

(16) Hulme, C.; Gore, V. *Curr. Med. Chem.* **2003**, *10*, 51.

(17) **General Procedure for the Three-Component Metathesis/Diels−Alder Reaction.** Alkyne (1 equiv) and olefin (5 equiv) were dissolved in CH_2Cl_2 (0.05 M) under an Argon atmosphere. Grubbs second-generation catalyst (10 mol %) was added to the reaction mixture at room temperature, and the resulting mixture was refluxed for 3−5 h. The solution of *N*-phenyl maleimide (10 equiv) in CH_2Cl_2 was added to the reaction mixture. After the mixture was refluxed for 3−5 days, the reaction mixture was cooled to room temperature and concentrated under reduced pressure. Then, the residue was purified by flash column chromatography on silica gel to afford the desired product.

Table 3. Three-Component Metathesis/Diels−Alder Reaction[17]



4 6

enyne	X	*n*	R	product[a]	yield[b]
4a	NTs	1	Bu	**6a**	83%
4a	NTs	1	Bn	**6b**	75%
4a	NTs	1	$(CH_2)_2Br$	**6c**	71%
4a	NTs	2	Bu	**6d**	78%
4a	NTs	2	Bn	**6e**	78%
4a	NTs	2	$(CH_2)_2Br$	**6f**	71%
4a	CE_2	1	Bu	**6g**	74%
4b	CE_2	1	Bn	**6h**	74%
4b	CE_2	1	$(CH_2)_2Br$	**6i**	77%

[a] Relative stereochemistry of the product was confirmed through NOE experiment. [b] Isolated yield. [c] E = COOEt.

desired product **6a** and unreacted diene intermediates (**i**, **ii**) as minor products. Apparently, the Diels−Alder reaction proceeded before the diene-ene metathesis reaction to afford the Diels−Alder product with enyne metathesis intermediate due to the relatively slow progress of diene-ene metathesis reaction. Thus, the dienophile **7** was added to the reaction mixture after the tandem metathesis reaction became complete. With this modification of the reaction protocol, the three-component reaction adduct **6a** was obtained in 83% yield as a single isomer. Then, the reaction was extended to the other enynes and olefins (Table 3). The reaction proved to be quite general, as variation of the size and the substitution pattern of the tether or olefins produced similar results.

In summary, a stereoselective one-pot three-component reaction using metathesis/Diels−Alder reaction was developed. The current protocol will be useful for the construction of small molecule libraries, as several functional groups could be introduced to the products.

Acknowledgment. This work was supported by the Center for Molecular Design and Synthesis (CMDS-KOSEF) at KAIST. We thank Dr. Barry Levine (Chiron, Emeryville, CA) for helpful discussion and proofreading of the manuscript.

Supporting Information Available: Spectral data of tandem reaction products **5a**−**u**, **6a**−**i**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL035194C