ORGANIC LETTERS

2012
Vol. 14, No. 12
3134–3137

A New Approach to 1,4-Oxazines and 1,4-Oxazepines via Base-Promoted Exo Mode Cyclization of Alkynyl Alcohols: Mechanism and DFT Studies

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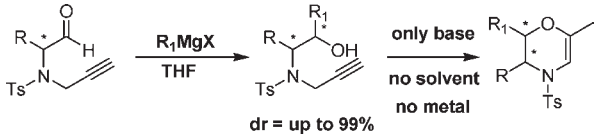
Received May 4, 2012

ABSTRACT



A new approach was developed to synthesize 1,4-oxazine and 1,4-oxazepine derivatives without solvent and metal. Regioselective cyclization occurred to afford exclusively the *exo-dig* product, and stereochemistry was studied by circular dichroism and specific optical rotation techniques. The Grignard reaction is a key synthetic step to produce high diastereomeric compounds via Cram's rule and was well supported by DFT calculations. A hydroalkoxylation mechanism was proposed and supported by DFT calculations.

The design and synthesis of appropriately desired, quick, and tolerable methods to attain the architectural complex molecules from simple starting materials is challenging work in modern synthetic and medicinal chemistry. The method for the synthesis of compounds containing nitrogen and oxygen in a cyclic ring is of growing importance by virtue of such molecules being present in numerous biologically important compounds.[1] In particular, much work has been dedicated to design the most effective routes to cyclic compounds. The addition of various O−H nucleophiles to carbon−carbon (C−C) multiple bonds represents one of the great methods for preparing such oxygen-containing heterocycles.[2−4] However, due to so many factors including

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(1) (a) Shimizu, Y. *Marine Natural Products*; Academic Press: New York, 1978; Vol. 1. (b) Moore, R. E. *Marine Natural Products: Chemical and Biological Perspectives*; Scheuer, P. J., Ed.; Academic Press: New York, 1978; Vol. 2. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1986**, *3*, 1. (d) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897. (e) Faulkner, D. J. *Nat. Prod. Rep.* **1996**, *13*, 75.

(2) (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–735. (b) Fukudome, Y.; Naito, H.; Hata, T.; Ura, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821. (c) Broggini, G.; Beccalli, E. M.; Borsini, E.; Fasana, A.; Zecchi, G. *Synlett* **2011**, *2*, 227–230. (d) Wang, Z.; Lin, X.; Luck, R. L.; Gibbons, G.; Fang, S. *Tetrahedron* **2009**, *65*, 2643–2648. (e) Pauff, S. M.; Miller, S. C. *Org. Lett.* **2011**, *13*, 6196–6199. (f) Zhao, W.; Carreira, E. M. *Org. Lett.* **2011**, *13*, 5084–5087.

(3) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395–3442.

(4) (a) Suzuki, S.; Tokunaga, E.; Reddy, D. S.; Matsumoto, T.; Shiro, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4131–4135. (b) Ohno, H.; Hamaguchi, H.; Ohata, M.; Kosaka, S.; Tanaka, T. *J. Am. Chem. Soc.* **2004**, *126*, 8744–8754. (c) Sordo, T.; Campomanes, P.; Diéguez, A.; Rodrıguez, F.; Fananas, F. J. *J. Am. Chem. Soc.* **2005**, *127*, 944–952. (d) Chaudhuri, G.; Kundu, N. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 775–779. (e) Abbiati, G.; Canevari, V.; Caimi, S.; Rossi, E. *Tetrahedron Lett.* **2005**, *46*, 7117–7120. (f) Yue, D.; Della Cà, N.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1581–1584. (g) Patil, N. T.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 5139–5142. (h) Asao, N.; Nogami, T.; Takahashi, K.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 764–765. (i) Barluenga, J.; Vazquez-Villa, H.; Ballesteros, A.; González, J. M. *J. Am. Chem. Soc.* **2003**, *125*, 9028–9029. (j) Park, J. H.; Bhilare, S. V.; Youn, S. W. *Org. Lett.* **2011**, *13*, 2228–2231. (k) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, *8*, 947–950. (l) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385–3387. (m) Mukai, C.; Kobayashi, M.; Kubota, S.; Takahashi, Y.; Kitagaki, S. *J. Org. Chem.* **2004**, *69*, 2128–2136. (n) Ohno, H.; Kadoh, Y.; Fujii, N.; Tanaka, T. *Org. Lett.* **2006**, *8*, 947–950. (o) Kitagaki, S.; Teramoto, S.; Mukai, C. *Org. Lett.* **2007**, *9*, 2549–2552. (p) Mukai, C.; Ukon, R.; Kuroda, N. *Tetrahedron Lett.* **2003**, *44*, 1583–1586. (q) Mukai, C.; Kuroda, N.; Ukon, R.; Itoh, R. *J. Org. Chem.* **2005**, *70*, 6282–6290. (r) Kitagaki, S.; Shibata, D.; Mukai, C. *Tetrahedron Lett.* **2007**, *48*, 1735–1738. (s) Kitagaki, S.; Teramoto, S.; Ohta, Y.; Kobayashi, H.; Takabe, M.; Mukai, C. *Tetrahedron* **2010**, *66*, 3687–3694.

10.1021/ol301219c
Published on Web 06/04/2012

the relatively high bond enthalpies of most O−H σ-bonds and the modest reactivity of electron-rich olefins with nucleophiles, an efficient intramolecular hydrofunctionalization reaction remains a challenge. For intramolecular alkynyl alcohol hydroalkoxylations, their exist two possible compounds elucidated by the *exo* and *endo*-enol ethers, as shown in Figure 1, where either *exo-dig* or *endo-dig* cyclization affords six- or seven-membered rings according to the Baldwin rules.[2a] Metal catalysis represents a new frontier in this regard, and there exists plenty of methods to achieve such conversions. Yamamoto and co-workers reported the coinage metal-assisted synthesis of heterocycles from various substrates via C−O bond formation.[3] However, unlike addition of other nucleophiles, analogue addition of OH functionality across C−C triple bonds is supposed to be difficult due to their poor nucleophilicity of the hydroxyl group. Unfortunately, the formation of seven-membered rings by metal catalysts is not common compared to five- and six-membered rings. In addition, very expensive catalysts are known to catalyze such processes. Considering these aspects, we sought to develop a new method which overcomes these issues. Herein, we report a metal as well as a solvent-free protocol for the hydroalkoxylation of alkynyl alcohols with NaH under very mild conditions.

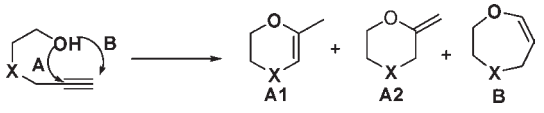
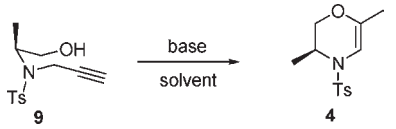


Figure 1. Three possible cyclized intermediates.

Earlier reports explored the synthesis of exocylic as well as endocyclic ring formation from various starting materials in the presence of metal or Lewis acids or bases,[6] whereas in most cases, the exo mode cyclization has given the A2 compound from alkynyl alcohols with lanthanide catalysts,[5] W,[6] Au,[7] Ag,[8] Cu,[9] and base.[10] In a similar way, the exo mode cyclization with compound A1 from alkynyl alcohols with metals such as Au,[11] Ru,[12] Pd,[13] Ga,[14] Pt,[15] and base[16,17] such as sodium amide was reported; the reaction involves more steps to convert into the exocylic product with high temperature and prolonged reaction times, and the reaction was not explored well with various substrates, even though we performed our reaction with sodium amide. Unfortunately, the reaction was not controlled at that temperature, and it was decomposed. Endo mode cyclization with alkynyl alcohols was reported with metals such as Os,[18] W,[19] Ru,[20] Rh,[21] Mo,[22] and others.

We designed our route starting from amino acids to synthesize the oxazine and oxazepine derivatives. To the best of our knowledge, such a route has not been documented, and to date, NaH has not been exploited as a

Table 1. Optimization Reaction Conditions for Cyclization[a]



SN	base	solvent	time	temp (°C)	yield (%)
1	K_2CO_3	DMF	4 h	130	32
2	Na_2CO_3	DMF	12 h	130	traces
3	Cs_2CO_3	DMF	6 h	130	26
4	*t*-BuOK	DMF	4 h	130	traces
5	NaH	DMF	4 h	110	41
6	DBU		4 h	80	0
7	DABCO		4 h	80	0
8	NaH	THF	4 h	reflux	traces
9	NaH	toluene	4 h	reflux	34
10	NaH	CH_3CN	4 h	reflux	37
11[b]	NaH	DMF	4 h	110	55
12	NaH		1 h	110	75
13[b]	NaH		1 h	110	76
14	NaH		30 min	110	57
15	NaH		40 min	70	94
16	$NaNH_2$		4 h	70	41

[a] Reactions were performed with 1 equiv of base unless otherwise noted. [b] Reactions were performed with 2 equiv of base.

(5) (a) Yu, X.; Seo, S. Y.; Marks, T. J. *J. Am. Chem. Soc.* **2007**, *129*, 7244–7245. (b) Dzudza, A.; Marks, T. J. *Chem.—Eur. J.* **2010**, *16*, 3403–3422. (c) Seo, S.; Yu, X.; Marks, T. J. *J. Am. Chem. Soc.* **2009**, *131*, 263–276.

(6) Barluenga, J.; Dieguez, A.; Rodriguez, F.; Fananas, F. J.; Sordo, T.; Campomanes, P. *Chem.—Eur. J.* **2005**, *11*, 5735–5741.

(7) Ruettinger, R.; Leutzow, J.; Wilsdorf, M.; Wilckens, K.; Czekelius, C. *Org. Lett.* **2011**, *13*, 224–227.

(8) Pale, P.; Chuche, J. *Eur. J. Org. Chem.* **2000**, *6*, 1019–1026.

(9) Praveen, C.; Iyyappan, C.; Perumal, P. T. *Tetrahedron Lett.* **2010**, *51*, 4767–4771.

(10) Davies, S. G.; Roberts, P. M.; Stephenson, P. T.; Thomson, J. E. *Tetrahedron Lett.* **2009**, *50*, 3509–3512.

(11) Hashmi, A. S. K.; Haufe, P.; Schmid, C.; Nass, A. R.; Frey, W. *Chem.—Eur. J.* **2006**, *12*, 5376–5382.

(12) Cadierno, V.; Diez, J.; Gimeno, J.; Nebra, N. *J. Org. Chem.* **2008**, *73*, 5852–5858.

(13) (a) Riediker, M.; Schwartz, J. *J. Am. Chem. Soc.* **1982**, *104*, 5842–5844. (b) Ramana, C. V.; Induvadana, B.; Srinivas, B.; Yadagiri, K.; Deshmukh, M. N.; Gonnade, R. G. *Tetrahedron* **2009**, *65*, 9819–9832.

(14) Li, H. J.; Guillot, R.; Gandon, V. *J. Org. Chem.* **2010**, *75*, 8435–8449.

(15) (a) Barluenga, J.; Fernandez, A.; Satrustegui, A.; Dieguez, A.; Rodriguez, F.; Fananas, F. *Chem.—Eur. J.* **2008**, *14*, 4153–4156. (b) Wang, J. Z.; Lin, X.; Luck, R. L.; Gibbons, G.; Fang, S. *Tetrahedron* **2009**, *65*, 2643–2648.

(16) Lysek, R.; Furman, B.; Kaluza, Z.; Frelek, J.; Suwinska, K.; Urbanczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3131–3150.

(17) Pettigrew, J. D.; Wilson, P. D. *Org. Lett.* **2006**, *8*, 1427–1429.

(18) Fernandez, A. V.; Yebra, C. G.; Varela, J. A.; Esteruelas, M. A.; Saa, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 4278–4281.

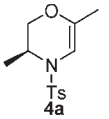
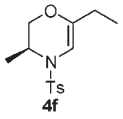
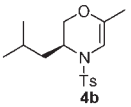
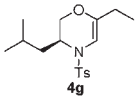
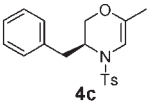
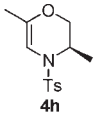
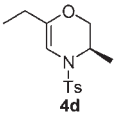
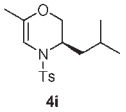
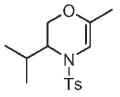
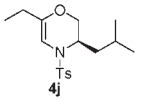
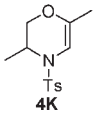
(19) (a) Alcazar, E.; Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 3877–3880. (b) McDonald, F.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653–3655.

(20) Liu, F. N.; Su, F. H.; Wen, T. B.; Sung, H.-Y.; Williams, I. D.; Jia, G. *Chem.—Eur. J.* **2010**, *16*, 7889–7897.

(21) Trost, B. M.; Rhee, Y. H. *J. Am. Chem. Soc.* **2003**, *125*, 7482–7483.

(22) McDonald, F. E.; Gleason, M. M. *J. Am. Chem. Soc.* **1996**, *118*, 6648–6659.

Table 2. One Chiral Center of 1,4-Oxazines

entry	compd **4**	yield (%)	entry	compd **4**	yield (%)
1	 **4a**	94[a]	6	 **4f**	62[a]
2	 **4b**	78[a]	7	 **4g**	59[a]
3	 **4c**	85[a]	8	 **4h**	91[c]
4	 **4d**	61[c]	9	 **4i**	86[c]
5	 **4e**	72[b]	10	 **4j**	64[c]
			11.	 **4K**	82[b]

[a] The L form. [b] Racemic. [c] The D form.

reagent without solvent for the synthesis of 1,4-oxazine and 1,4-oxazepine derivatives[2b−f] with high regioselectivity at moderate temperature with less reaction time from *N*-tosyl amide derivatives.

Herein, we report the stereospecific synthesis of oxazines with one chiral center (Table 2) as well as with two chiral carbon centers (Figure 3). The investigation of this reaction started with amino acid derivative *N*-(2 hydroxy-1-methylethyl)-4-methylbenzenesulfonamide **9** to obtain compound **4**. The reaction was optimized with various bases, whereas the best condition was observed in the presence of NaH without solvent at 70 °C for 40 min as it produced the desired compound with excellent 94% yield (Table 1, entry 15). With this optimized condition in hand, we explored the scope of the reaction with different amino acid derivatives. In Table 2 with various substituents, the cyclization was successful with high yields. The D and L forms of alanine derivatives were afforded in excellent yields, 94 and 91% (entries 1 and 8). An isobutyl chain on an adjacent carbon of nitrogen resulted in high yields, 78 and 86%, with D and L forms (entries 2 and 9). By replacing the isobutyl with isopropyl, entry 5 produced a satisfactory yield of 72%. The benzyl group also produced the desired compound in a high yield of 85% (entry 3), and substituted alkynes gave moderate yields, 59−64% (entries 4, 6, 7, and 10). All of the reactions were well tolerated to afford the desired compound **4** in moderate to excellent yields.

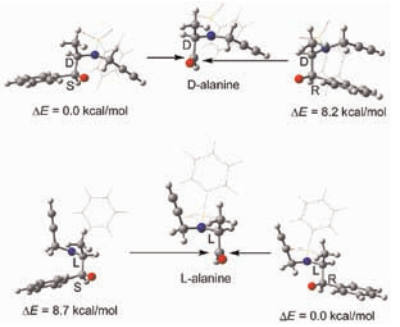


Figure 2. Grignard reagent attack on carbonyl group of D and L forms of alanine derivatives. For clarity, the tosyl group substituent is represented in wireframe.

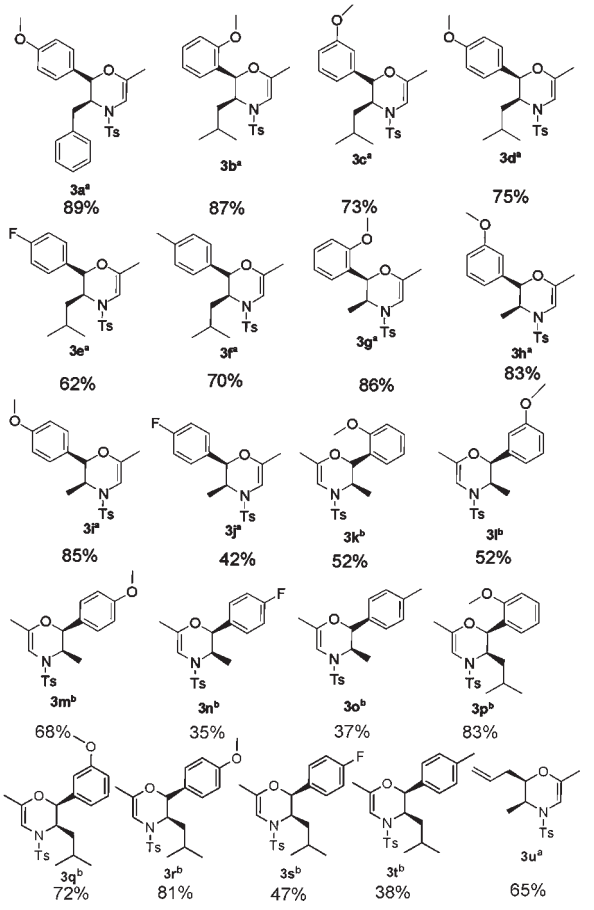


Figure 3. Two chiral centered 1,4-oxazines. [a]L form. [b]D form.

The desired diastereomeric alcohols were obtained from the aldehydes via the Grignard reaction (see the Supporting Information). Here the stereoselectivity was induced by the adjacent carbon stereochemistry which was studied in detail by the Cram's rule[23] application (see the Supporting Information), and density functional theory (DFT) calculations[24] (Figure 2) were employed to rationalize the

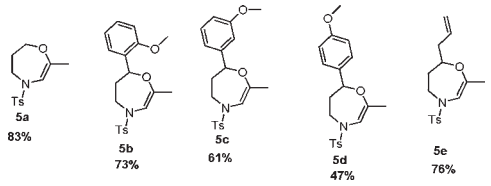


Figure 4. 1,4-Oxazepines.

chiral properties of the products. To examine the origin of the observed stereospecificity, we calculate the D and L form amino acid derivatives attacked by the nucleophile. The DFT results show that if the starting amino acid derivative is in the D form, the resultant (*R*,*S*) intermediate will be more stable than the (*R*,*R*) by ca. 8 kcal/mol, and vice versa (Figure 2), consistent with the experimental observation. Inspection of the optimized structures clearly reveals that the stereospecificity arises from the steric hindrance given by the alkyne group adjacent to the nitrogen atom.

With various functional groups, the two chiral centered molecules were also afforded in moderate to high yields (Figure 3) with the same reaction conditions, whereas with fluoro and methyl groups, the yields were low compared to the other functional groups (compounds **3j**, **3n**, **3o**, **3s**, and **3t**). The stereochemistry of compounds with one chiral center and two chiral center molecules was studied by circular dichroism and specfic optical rotation (see the Supporting Information).

The 7-*exo-dig* cyclization also proceeded smoothly to give 1,4-oxazepine derivatives with the same method (Table 1, entry 15) from β-amino acid derivatives. Moderate to high yields were obtained with various substituents (Figure 4). 1,4-Oxazine and 1,4-oxazepine derivatives were screened against various cancer cell lines, and promising results were observed with compound **4c** against MCF-7 cell lines (see the Supporting Information).

The *exo-dig* cyclization was proposed in two possible pathways, which are sketched in Figure 5: route A proceeds via the formation of the allene intermediate, **1Db**, followed by nucleophilic attack, whereas in route B, direct attack of nucleophile takes place on the acetylene intermediate, **1Dd**. On the basis of DFT calculations (Figure 5), the allene intermediate was found to be 0.9 kcal/mol lower than the acetylene intermediate, indicating that the equilibrium is shifted in the former. The DFT results further point out that the cyclization reaction along path A is an exergonic process (−12.0 kcal/mol) with a barrier of

(23) (a) Chen, X.; Hortelano, E. R.; Eliel, E. L. *J . Am. Chem. Soc.* **1990**, *112*, 6130–6131. (b) Chen, X.; Hortelano, E. R.; Eliel, E. L.; Frye, S. V. *J. Am. Chem. Soc.* **1992**, *114*, 1778–1784.

(24) Density functional theory of M06-2X/6-31+G* level was used for geometry optimizations and frequency analyses in this work. The free energy corrections were made at the condition of 1 atm, and all calculations were performed using Gaussian 09 package.

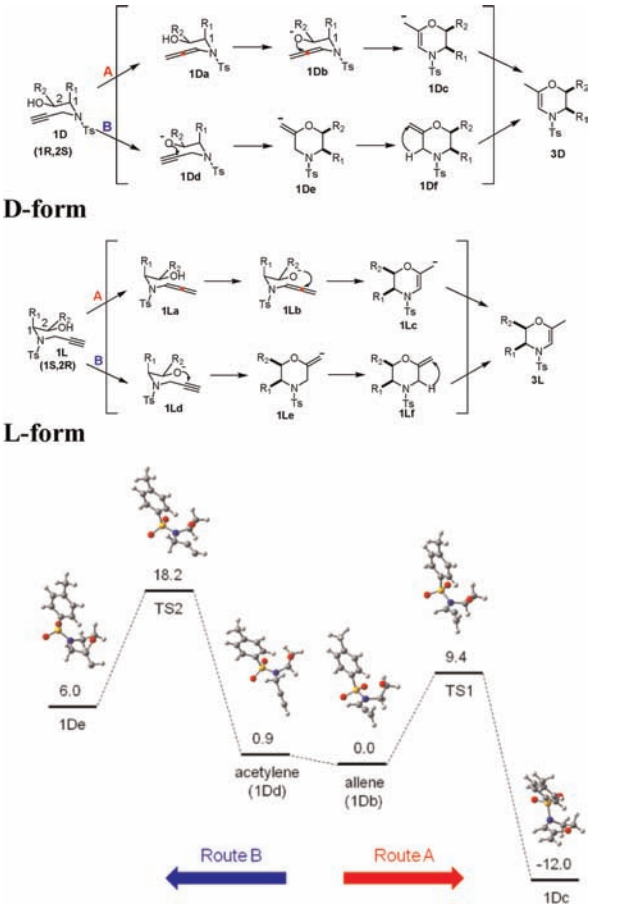


Figure 5. Mechanism and M06-2X/6-31+G* free energy profile.

9.4 kcal/mol, while the analogous process along path B is endergonic (6.0 kcal/mol) with a relatively high energetic barrier of 18.2 kcal/mol. All these computational results, in terms of both thermodynamic and kinetic points of view, support mechanism A as the dominant reaction pathway.

In summary, we have developed a highly efficient and convenient method to synthesize the regio- and stereoselective 1,4-oxazine and 1,4-oxazepine derivatives without metal and solvent and *exo-dig* cyclization supported by DFT calculations.

Acknowledgment. We thank the National Science Council of the Republic of China for financial support. This work was also supported by a grant from the Kaohsiung Medical University Research Foundation.

Supporting Information Available. Experimental procedures and characterization data for all new compounds and biological data provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.