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Tetrahedron Letters 44 (2003) 7953–7956

TETRAHEDRON
LETTERS

A new methodology of intramolecular hetero Diels–Alder reaction with β-alkoxy-substituted conjugated nitroalkenes as heterodienes: stereoselective one-pot synthesis of *trans*-fused bicyclic γ-lactones

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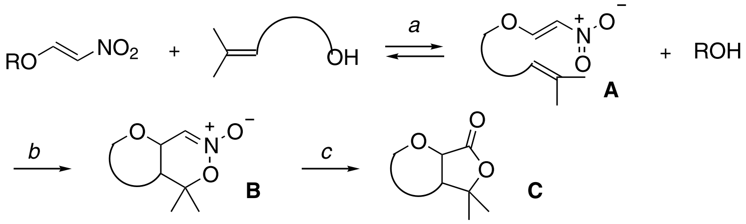
Received 18 July 2003; revised 29 August 2003; accepted 29 August 2003

Abstract—Tandem reaction of (*E*)-1-ethoxy-2-nitroethylene with δ,ε-unsaturated alcohols leading to stereoselective *trans*-fused bicyclic γ-lactones has been developed using a catalytic amount of a Lewis acid such as $Yb(OTf)_3$ and $Ni(ClO_4)_2{\cdot}6H_2O$. This process involves the stereoselective tandem transetherification–intramolecular hetero Diels–Alder reaction leading to bicyclic nitronates, and sequential transformation of the nitronate moiety to a lactone functional group under similar reaction conditions in good yields.

Tandem reactions have emerged as a powerful method for efficient and stereoselective construction of polyheterocyclic and polycarbocyclic skeletons.[1] One most remarkable example is the tandem Knoevenagel-intramolecular hetero Diels–Alder (HDA) reaction, which is useful for the construction of polyheterocycles. Recently, we have developed a new type of tandem reaction by the use of β-alkoxy-substituted α,β-unsaturated carbonyl compounds and δ,ε-unsaturated alcohols as electrophilic heterodienes and nucleophilic dienophiles, respectively. These tandem transetherification–intramolecular HDA reactions proceed stereoselectively to afford functionalized *trans*-fused hydropyranopyran derivatives.[2] On the other hand, the synthetic utility of nitroalkenes as heterodiene components in inverse electron demand HDA reaction has been extensively studied by Denmark.[1d,3]

As part of our research program aimed at the development of an effective synthetic route in stereoselective preparation of polyheterocycles, our attention has been directed to investigation of the applicability of β-alkoxy-substituted nitroalkenes as heterodiene components in tandem reaction with unsaturated alcohols mentioned above. It was found that this tandem reaction proceeds in one flask as follows: (1) first, conjugate



Scheme 1. (a) Transetherification; (b) intramolecular hetero Diels–Alder reaction; (c) lactonization.

Keywords: nitroalkene; intramolecular hetero Diels–Alder reaction; Lewis acid; tandem reaction; transetherification; δ,ε-unsaturated alcohols; molecular sieves.

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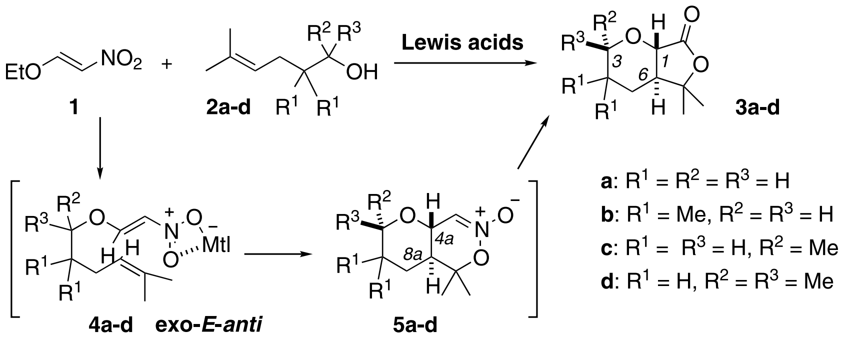
doi:10.1016/j.tetlet.2003.08.106



Scheme 2.

addition of unsaturated alcohols to β-alkoxy-substituted nitroalkenes; (2) reversible elimination of alcohols; (3) intramolecular HDA reaction of the resulting transetherified compounds **A** leading to bicyclic nitronates **B**; (4) further transformation of **B** to bicyclic γ-lactones **C** as outlined in Scheme 1.

In this communication, we present the preliminary results of Lewis acid-promoted stereoselective one-pot synthesis of *trans*-fused bicyclic γ-lactones **3** by way of the expected tandem transetherification–intramolecular HDA reaction and followed in tandem by transformation of a functional group using (*E*)-1-ethoxy-2-nitroethylene **1**[4] and *prim*-, *sec*-, and *tert*-δ,ε-unsaturated alcohols **2**[5] having two methyl substituents at the terminal position (Scheme 2).[6]

The tandem reaction was investigated with nitroalkene **1**[4] and 5-methyl-4-hexen-1-ol **2a** as a model reaction. The results are summarized in Scheme 2 and Tables 1–3. First, thermal reactivity was examined at 130°C for 70 h in *o*-dichlorobenzene to afford the corresponding transetherified nitrodiene **4a** ($R^1=R^2=R^3=H$) as the only *trans*-isomer in a poor 28% yield, which was inert to thermal cycloaddition (entry 1 in Table 1). Thus, suitable Lewis acid catalysts and reaction conditions were sought to activate the nitroalkene function as heterodiene. When $TiCl_4$ (10 mol%) as a typical Lewis acid was used in CH_2Cl_2, the reaction could not be observed to proceed even after 17 h at room temperature (entry 2). On the other hand, it was found that use of ytterbium triflate as a water- and alcohol-compatible Lewis acid was very effective.[7] The reaction with equimolecular amounts of **1** and **2a** proceeded smoothly in CH_2Cl_2 at room temperature for 17 h in the presence of $Yb(OTf)_3$ (10 mol%) to afford the corresponding *trans*-fused bicyclic γ-lactone **3a** instead of the expected bicyclic nitronate **5a** as a single isomer in a moderate 47% yield (entry 3).[6a] The use of 1.5 equiv. alcohol **2a** was not effective to increase the yield of **3a** (45%) (entry 4). When the amount of nitroalkene **1** was increased to 1.5 and 2.0 equivalents, the yield of γ-lactone **3a** increased to 74 and 68%, respectively (entries 5 and 6). It was also found that trifluoromethanesulfonic acid (10 mol%) catalyzed the sequential transformation to **3a** in lower yield (13%) along with transetherified nitrodiene **4a** (28%) (entry 8). The assignment of structure for **3a**[6a] rests on the characteristic IR stretch (1770 cm^{-1}) and ^{13}C NMR resonance (171.59 ppm) for γ-lactone. The stereochemistry at the junction of **3a** was estimated to be *trans* based on the large vicinal coupling constant for J_{1-6} (12.2 Hz) by ^1H NMR spectrum analysis. Further, the stereostructure of **3a** has been established by X-ray diffraction analysis (Fig. 1).[8]

Next, the influence of the solvent on both reactivity and chemical yield of **3a** was investigated with 1.5 equiv. of nitroalkene **1** in the presence of $Yb(OTf)_3$ (10 mol%) as a catalyst. When CH_2Cl_2 was the solvent better results were obtained than in 1,2-dichloroethane, MeCN,

Table 1. The tandem reaction of nitroalkene **1** with 5-methyl-4-hexen-1-ol **2a** leading to *trans*-fused γ-lactone **3a**[a]

Entry	Catalyst	Equiv. of **1**	Yield (%) of **3a**[b]
1[c]	–	1	(28)[d]
2	$TiCl_4$	1	–[e]
3	$Yb(OTf)_3$	1	47
4	$Yb(OTf)_3$	0.7	45
5	$Yb(OTf)_3$	1.5	74
6	$Yb(OTf)_3$	2	68
7	CF_3CO_2H	1	(28)[d]
8	CF_3SO_3H	1	13 (28)[d]

[a] Unless otherwise noted, all reactions were performed in CH_2Cl_2 for 17 h at rt in the presence of 10 mol% of catalyst.

[b] Yield of isolated products.

[c] The reaction was carried out at 130°C for 10 h in *o*-dichlorobenzene.

[d] Yield of transetherified nitrodiene **4a** is shown in parentheses.

[e] The progress of the reaction was not observed.

Table 2. Solvent effect in the tandem reaction of **1** with **2a** leading to **3a**[a]

Entry	Solvent	Time	Yield (%) of **3a**[b]
1	$ClCH_2CH_2Cl$	20	61
2	MeCN	26	44
3	EtOH	26	30
4	*t*-BuOMe	60	30
5	THF	60	34

[a] All reactions were performed using 1.5 equiv. of **1** in the solvent shown at rt in the presence of 10 mol% of $Yb(OTf)_3$.

[b] Yield of isolated product.

Table 3. The tandem reaction of **1** and **2a** leading to **3a** with several Lewis acids[a]

Entry	Lewis acid	Time (h)	Yield (%) of **3a**[b]
1	$Sc(OTf)_3$	30	52
2	$Hf(OTf)_4$	17	35
3	$Cu(OTf)_2$	38	47
4	$Yb(OTf)_3{\cdot}nH_2O$	17	62
5	$Cu(ClO_4)_2{\cdot}6H_2O$	30	26
6	$Zn(ClO_4)_2{\cdot}6H_2O$	30	54
7	$Ni(ClO_4)_2{\cdot}6H_2O$	30	72

[a] All reactions were performed by use of 1.5 equiv. of **1** in CH_2Cl_2 at rt in the presence of 10 mol% of Lewis acid.

[b] Yield of isolated product.

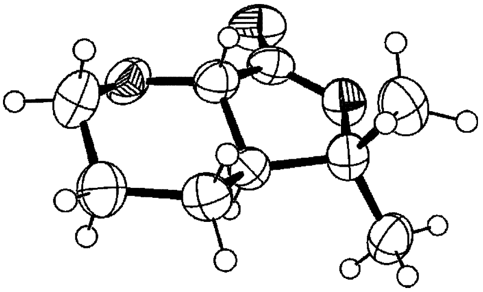


Figure 1. The stereo ORTEP drawing of **3a**.

EtOH, *tert*-butyl methyl ether, or THF (entry 5 in Table 1 versus entries 1∼5 in Table 2). In addition, several metal triflates and metal salt hydrates were tested as Lewis acid catalysts (each 10 mol%) in CH_2Cl_2 and were found to be effective promoters of the tandem reaction leading to **3a**. They include $Sc(OTf)_3$, $Hf(OTf)_4$, $Cu(OTf)_2$, $Yb(OTf)_3{\cdot}nH_2O$, $Cu(ClO_4)_2{\cdot}6H_2O$, $Zn(ClO_4)_2{\cdot}6H_2O$, and $Ni(ClO_4)_2{\cdot}6H_2O$. The results, collected in Table 3 show that $Ni(ClO_4)_2{\cdot}6H_2O$ catalyst gave **3a** (72%) in the best yield (entry 7), which is comparable to that with $Yb(OTf)_3$ (74%) as catalyst (entry 5 in Table 1).

Then, the generality of the present one-pot formation of bicyclic δ-lactone was investigated by using several alcohols **2b–d** as nucleophilic dienophiles under the most suitable conditions at room temperature in the presence of 10 mol% of the Lewis acid catalyst. The results are summarized in Table 4. The reaction with primary alcohol **2b** having additional dimethyl substituents at the tether proceeded smoothly at room temperature in the presence of $Yb(OTf)_3$ to afford the corresponding *trans*-fused γ-lactone **3b** ($J_{1\text{–}6} = 12.8$ Hz)[9] as a single stereoisomer in 55% yield (entry 1). The reaction with secondary alcohol **2c** in the presence of both $Yb(OTf)_3$ and $Ni(ClO_4)_2{\cdot}6H_2O$ as catalyst also proceeded to afford the corresponding γ-lactone **3c**[9] as a single stereoisomer in 65% and 68% yields, respectively (entries 2 and 3). The stereostructure of **3c** was determined on the basis of the ^{1}H NMR spectrum: based on the large vicinal couplings for $J_{1\text{–}6}$ (12.3 Hz) as well as notable NOEs between H-1/H-3, the stereoisomer was confirmed to be the 1,3-*cis*-1,6-*trans* structure. Additionally, the large vicinal coupling for $J_{3\text{–}4}$ (12.3 Hz) indicates the axial position of H-3. The reaction with the bulky tertiary alcohol **2d** also took place to afford *trans*-fused **3d** (for $J_{1\text{–}6} = 12.8$ Hz) and better yield was obtained with $Ni(ClO_4)_2{\cdot}6H_2O$ (53%) than with $Yb(OTf)_3$ (38%) as a catalyst (entries 4 and 5).

Table 4. The tandem reaction of **1** and **2b–d** leading to **3b–d**[a]

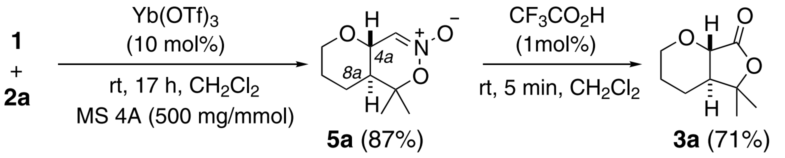
Entry	Alcohol	Lewis acid	Time (h)	Yield (%) of **3**[b]
1	**2b**	$Yb(OTf)_3$	17	**3b** 55
2	**2c**	$Yb(OTf)_3$	40	**3c** 65
3	**2c**	$Ni(ClO_4)_2{\cdot}6H_2O$	30	**3c** 68
4	**2d**	$Yb(OTf)_3$	43	**3d** 38
5	**2d**	$Ni(ClO_4)_2{\cdot}6H_2O$	30	**3d** 51

[a] All reactions were performed by use of 1.5 equiv. of **1** in CH_2Cl_2 at rt in the presence of 10 mol% of Lewis acid.

[b] Yield of isolated product.

In the course of our investigation, the reaction pathway for the formation of stereoselective bicyclic γ-lactones **3** still remained as an unsolved problem. It can be easily predicted that γ-lactones **3** could be obtained from bicyclic nitronates **5** via the hydrolytic process by the action of a strong acid generated from the Lewis acids with a small amount of water existing in both nitoroalkene **1**[4] and the Lewis acid.[10] Therefore, molecular sieves (MS) 4 Å was used as a dehydration agent to remove this small amount of water existing in the reaction mixture in order to prevent the acid-induced transformation.[11] This anticipation indeed proved to be correct. When the reaction of nitroalkene **1** with alcohol **2a** was allowed to react in CH_2Cl_2 at room temperature for 17 h in the presence of $Yb(OTf)_3$ (10 mol%) and MS 4 Å (500 mg/mmol), the corresponding *trans*-fused bicyclic nitronate **5a** was obtained as a single stereoisomer in 87% yield. The structure of **5a** was established by extensive spectroscopic analysis.[6b] The stereochemistry at the junction of **5a** was estimated to be *trans* based on the large vicinal coupling constant for $J_{4a\text{–}8a}$ (10.4 Hz) by ^{1}H NMR spectrum analysis. The *trans* structure arises from the *exo*-*E*-*anti* transition state of the transetherified intermediate **4a** (Scheme 1), which is well-documented.[1,12b] Transformation of cyclic nitronate **5a** to γ-lactone **3a** with retention of *trans*-stereochemistry at the junction was achieved successfully in 71% yield by treatment with 1 mol% of trifluoroacetic acid in CH_2Cl_2 at room temperature within 5 min (Scheme 3).[3b,12] These results indicate that a strong acid moiety plays an important role in transformation of six-membered nitronates to γ-lactones, while details of the mechanism are still unclear.

In summary, we have developed a Lewis acid-promoted stereoselective one-pot synthesis of bicyclic γ-lactones by using (*E*)-2-ethoxy-1-nitroethene and δ,ε-unsaturated alcohols. This new methodology of tandem reac-



Scheme 3.

tion also involves a new type of intramolecular HDA reaction of nitroalkenes as heterodienes, which provides stereochemically defined bicyclic nitronates. Furthermore, it is noteworthy that a catalytic amount of the metal triflates is enough to complete the cycloaddition reactions with nitroalkenes, because it has been well-known that more than stoichiometric amounts of Lewis acids are needed in similar reactions.[3] Currently, efforts are under way to probe the scope and limitations of this new stereoselective sequential transformation reaction.

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6. Characterization of the new compounds discussed in this work was based on the spectral and analytical data. Some typical spectral data are shown as follows: (a) *trans*-fused γ-lactone **3a** (1,6-*trans*-7,7-dimethyl-2,8-dioxabicyclo-[4,3,0]nonan-9-one): colorless solid (hexane–Et$_2$O); mp 93–94°C; IR (KBr): 1770, 1275, 1200, 1130, 1075, and 910 cm^{-1}; ^{1}H NMR (CDCl$_3$) $\delta=1.34$ and 1.47 (each 3H, each s, 2×7-Me), 1.51–1.55 (1H, m), 1.63–1.74 (2H, m), 1.96–2.03 (2H, m), 3.53 (1H, dt, $J_{gem}=J_{3ax\text{–}4ax}=11.7$ and $J_{3ax\text{–}4eq}=3.9$ Hz, H-3ax), 3.80 (1H, d, $J_{1\text{–}6}=12.2$ Hz, H-1), and 4.18 (1H, br. dd, $J_{gem}=11.7$ and $J_{3eq\text{–}4eq}=4.6$ Hz, H-3eq). ^{13}C NMR (CDCl$_3$) $\delta=21.55$ (7-Me), 24.21 (7-Me), 25.07 (C-5), 27.89 (C-4), 50.00 (C-6), 69.56 (C-3), 76.26 (C-1), 84.63 (C-7), and 171.59 (C-9); FAB-MS *m*/*z* 171 [M+1]$^+$ (calcd 170.1). Anal. calcd for C$_9$H$_{14}$O$_3$: C, 63.51; H, 8.29%. Found: C, 63.45; H, 8.31. (b) Bicyclic nitronate **5a** (1,1-dimethyl-4a,7,8,8a-tetrahydro-1*H*,6*H*-pyrano[2,3-*d*][1,2]oxazine *N*-oxide): white solids (hexane–Et$_2$O); mp 118–119°C; IR (KBr): 1622, 1267, 1247, 1228, and 908 cm^{-1}; ^{1}H NMR (C$_6$D$_6$) $\delta=0.51$ (1H, dq, $J_{8ax\text{–}7ax}=3.9$ and $J_{gem}=J_{8ax\text{–}8a}=J_{8ax\text{–}7ax}=12.3$ Hz, H-8ax), 0.83 and 0.92 (each 3H, each s, 2×1-Me), 1.02–1.08 (1H, m), 1.15–1.20 (1H, m), 1.21–1.30 (1H, m), 1.37–1.43 (1H, m), 2.95 (1H, dt, $J_{6ax\text{–}7eq}=2.4$ and $J_{6ax\text{–}7ax}=J_{gem}=11.6$ Hz, H-6ax), 3.27 (1H, dd, $J_{4a\text{–}4}=2.2$ and $J_{4a\text{–}8a}=10.4$ Hz, H-4a), 3.66 (1H, dd, $J_{6eq\text{–}7eq}=4.6$ and $J_{gem}=11.6$ Hz, H-6eq), and 6.17 (1H, d, $J_{4\text{–}4a}=2.2$ Hz, H-4). ^{13}C NMR (C$_6$D$_6$) $\delta=19.17$ (1-Me), 23.86 (1-Me), 25.31 (C-8), 25.98 (C-7), 43.09 (C-8a), 68.03 (C-6), 72.71 (C-4a), 84.15 (C-1), and 109.72 (C-4). MS (70 eV) (relative intensity, %) *m*/*z* 185 (M$^+$, 7), 167 (30), 149 (89), 111 (17), 97 (base peak), 95 (16), 84 (25), 83 (19), 81 (28), 69 (36), and 58 (50). HRMS (70 eV) calcd for C$_9$H$_{15}$NO$_3$: *m*/*z* 185.1052 (M$^+$). Found: *m*/*z* 185.1049.
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8. A single crystal of **3a** was monoclinic having a space group $P2_1/n$, $a=7.3242(9)$ Å, $b=13.945(1)$ Å, $c=8.9584(8)$ Å, $\beta=99.817(4)°$, $Z=4$. The final *R* factor was 0.064 for 3554 measured reflection.
9. The products **3b**∼**3d** show characteristic spectra data of IR stretch (cm^{-1}) and ^{13}C NMR resonance (ppm) for γ-lactones as follows: **3b** (1786 cm^{-1} and 171.36 ppm); **3c** (1776 cm^{-1} and 171.75 ppm); **3d** (1778 cm^{-1} and 172.67 ppm).
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