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Ytterbium(III) triflate-catalyzed electrophilic cyclization of glyoxalate-derived unsaturated imines

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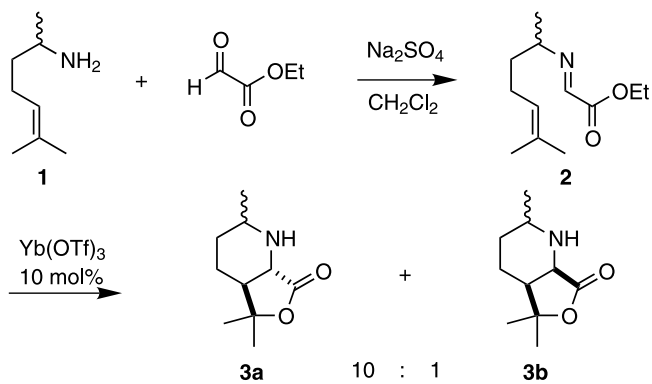
Abstract—Ytterbium(III) triflate was found to catalyze the electrophilic cyclization of some glyoxalate-derived unsaturated imines. The cyclization reactions gave exclusively fused amino γ-lactone products with good stereoselectivity. Moreover, a solid-phase version of the lanthanide-catalyzed reaction featured a lactonization with simultaneous cleavage of the product from the solid support.

Lanthanide triflates are unique versatile Lewis acids that are currently of considerable research interest. They have been used to catalyze a variety of C–C bond-forming reactions both in organic solvents and aqueous media.[1–7] Due to their high activating ability towards imines,[8] lanthanide triflates are particularly useful catalysts for the synthesis of nitrogen-containing compounds. As part of a research program to investigate the use of lanthanide triflates for organic transformations,[9] we recently studied ytterbium triflate-catalyzed imino-ene reactions.[10] Interestingly, other than the expected ene products, some α-ketoester-derived unsaturated imines underwent electrophilic cyclization producing exclusively γ-lactone compounds.

In an initial experiment, (±) 2-amino-6-methyl-5-heptene **1** was reacted with 1.0 equiv. of ethyl glyoxalate in the presence of anhydrous sodium sulfate to give the corresponding imine **2**. The resulting mixture was then treated with $Yb(OTf)_3$ (10 mol%). After 12 h, surprisingly, no imino-ene product was isolated. Instead, α-amino lactones **3a** and **3b** were isolated in a combined yield of 72% and a ratio of 10:1 (Scheme 1). The structures of **3a** and **3b** were fully elucidated by 1D, 2D and NOE NMR experiments, which indicated the piperidine ring fused forming a *trans* and *cis* γ-lactone ring, respectively.

Presumably, the formation of the lactone was initiated by electrophilic attack of the $Yb(OTf)_3$-activated imine carbon by the C=C bond. The tertiary carbocation formed interacted intramolecularly with the carbonyl to afford the lactone product. Tietze et al. observed similar lactone formations accompanied by ene-type products[11] when working with imines derived from malonates in the presence of stoichiometric quantities of TMS–OTf and varying types of Lewis acids. Imines obtained from glyoxalates, however, did not give lactone products under the same conditions.[12] Interestingly, our study demonstrated that in the presence of $Yb(OTf)_3$ γ-lactones were the only products isolated from the reaction of the glyoxalate-derived imine **2**. The reaction proceeded stereoselectively, producing the *trans* isomer **3a** as the primary product. This could be explained by a transition state where the ester moiety prefers an equatorial position (Scheme 2). We observed that benzyl glyoxalate afforded even higher stereoselec-



Scheme 1.

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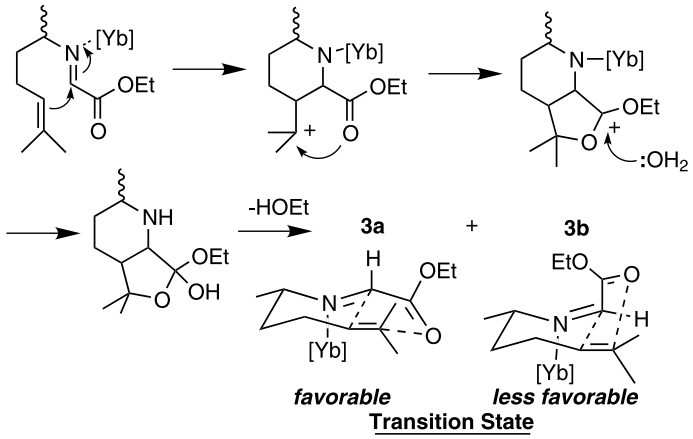
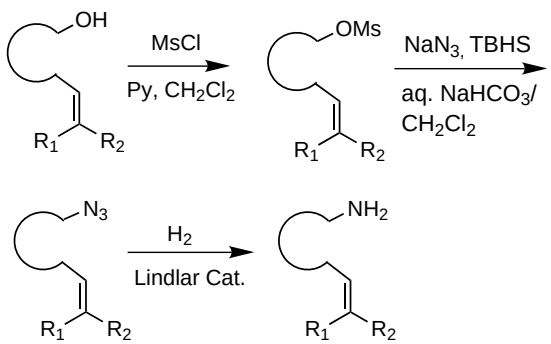


Scheme 2.

tivity (**3a**/**3b**: 13/1), serving as further evidence for the proposed transition state. In addition, the chelation of both the imine and ester groups to ytterbium might also be involved in the favorable transition state, affording high *trans* selectivity. It should also be noted that for the reaction to be catalytic, hydrated $Yb(OTf)_3$ must be used. In fact, when the reaction was performed under strictly dry conditions, 1 equiv. of the lanthanide was required for complete conversion. Apparently, the hydrated salt served as the source of water involved in the reaction mechanism. It was found that higher catalyst-loading yielded comparable results compared with the 10 mol% loading. However, experiments using less than 10 mol% of the catalyst generally gave lower yields.

Several other unsaturated amines were prepared according to the general procedure shown in Scheme 3.[13] They were treated with ethyl glyoxalate, giving rise to the corresponding imines, which were then tested for the $Yb(OTf)_3$-catalyzed cyclization.[14] In addition, we replaced ethyl glyoxalate by ethyl/phenyl pyruvate and ketomalonate shown in Table 1. Ketomalonate worked very well, however, the cyclization did not occur with ethyl/phenyl pyruvate under the typical experiment condition.[14]



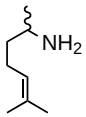
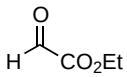
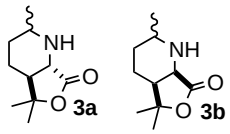
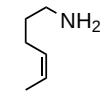
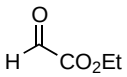
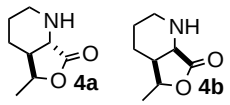
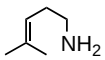
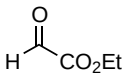
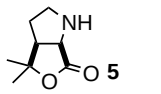
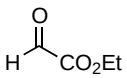
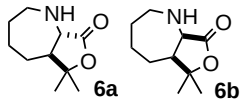
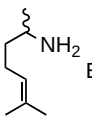
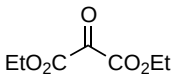
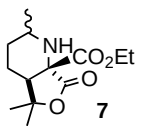
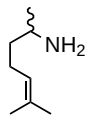
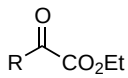
Scheme 3.

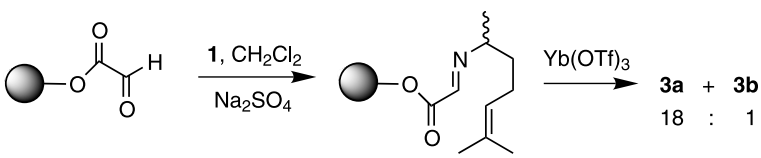
As indicated in Table 1, 1-amino-4-hexene produced fused piperidine γ-lactones **4a** and **4b** with similar selectivity as seen in **2**, but in considerably lower yields. This in part was due to decreased nucleophilicity of the double bond as well as decreased stability of the carbocation. This observation further supports the proposed mechanism. From 1-amino-6-methyl-5-heptene, amino lactones **6a** and **6b** were produced in 51% yield, and a ratio of 1:3, favoring the *cis* isomer, which was thermodynamically more stable conformation. When 1-amino-4-methyl-3-pentene was employed, *cis*-fused pyrolidine lactone **5** was isolated as the only product. Apparently in this case *trans*-fused lactone was too sterically strained to form. In the case of symmetric of ketomalonate, only **7** was formed since both transition states gave rise to the same product (Scheme 2).

Since the original ester linkage of the glyoxalate is cleaved during the lactonization, we envisioned an application of the cyclization in solid-phase synthesis. In this case, the formation of the lactone would be accompanied by simultaneously cleavage of the product from the resin. One advantage of this solid-phase reaction is that only the desired products will be cleaved into solution and any by-products derived from other pathways would stay on the solid support. To verify the idea, a resin-bound imine was synthesized and then treated with catalytic amounts of $Yb(OTf)_3$. As expected, ^1H NMR analysis of the resulting solution indicated **3a** and **3b** in 42% yield, with essentially no impurities and higher stereoselectivity (**3a**/**3b**: 18/1) (Scheme 4).

In summary, we have demonstrated that α-ketoester-derived unsaturated imines undergo stereoselective electrophilic cyclization in the presence of catalytic amount of $Yb(OTf)_3$. The ytterbium triflate-catalyzed reactions provide an easy access to fused amino γ-lactones and could be applied to solid-phase synthesis.

Table 1. $Yb(OTf)_3$-catalyzed cyclization of imines derived from keto-ester and unsaturated amines

Amine	Keto-ester	Product	Yield (%)	Selectivity (**a**:**b**)
			72	10:1
			23	7:1
			64	/
			51	1:3
			69	/
	 R = Me, Ph	—		



Scheme 4.

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References

1. For recent reviews in lanthanide triflate-catalyzed organic reactions, see: (a) Kobayashi, S. *Synlett* **1994**, 689; (b) Marshman, R. *Aldrichimica Acta* **1995**, *28*, 77; (c) Xie, W.-H.; Jin, Y. F.; Wang, P. G. *Chemtech* **1999**, February, 23.
2. Suga, H.; Kakehi, A.; Ito, S.; Inoue, K.; Ishida, H.; Ibata, T. *Org. Lett.* **2000**, *2*, 3145.
3. Barrett, A. G. M.; Braddock, D. C.; Ducray, R.; McKinnell, R. M.; Waller, F. J. *Synlett* **2000**, 57.
4. Ma, Y.; Qian, C.; Wang, L.; Yang, M. *J. Org. Chem.* **2000**, *65*, 3864.
5. Graven, A.; Grotli, M.; Meldal, M. *J. Chem. Soc., Perkin 1* **2000**, 955.
6. Lu, R.-J.; Liu, D.-P.; Giese, R. W. *Tetrahedron Lett.* **2000**, *41*, 2817.
7. Dudot, B.; Royer, J.; Sevrin, M.; George, P. *Tetrahedron Lett.* **2000**, *41*, 4367–4371.
8. Kobayashi, S.; Nagayama, S. *J. Am. Chem. Soc.* **1997**, *119*, 10049.
9. (a) Zhang, W.; Wang, P. G. *J. Org. Chem.* **2000**, *65*, 4732; (b) Xie, W.-H.; Fang, J.-W.; Li, J.; Wang, P. G. *Tetrahedron* **1999**, *55*, 12929; (c) Zhang, W.; Xie, W.-H.; Fang, J.-W.; Wang, P. G. *Tetrahedron Lett.* **1999**, *40*, 7929; (d) Xie, W.-H.; Bloomfield, K. M.; Jin, Y.-F.; Dolney, N. Y.; Wang, P. G. *Synlett* **1999**, 498.
10. Yamanaka, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 159.
11. Tietze, L. F.; Bratz, M. *Chem. Ber.* **1989**, *122*, 997.
12. Tietze, L. F.; Bratz, M. *Synthesis* **1989**, 439.
13. Among several methods, hydrogenation using Lindlar catalyst was found to be the best for the reduction of the unsaturated azides in terms of both yield and separation: Corey, E. J.; Nicolaou, K. C.; Balanson, R. D.; Machida, Y. *Synthesis* **1975**, 590.

14. In a typical experiment, a mixture of 2-amino-6-methyl-5-heptene **1** (0.254 g, 2 mmol) and ethyl glyoxalate (0.474 g, 43% toluene solution, 2 mmol, Fluka) in CH_2Cl_2 (15 ml) was stirred at room temperature in the presence of anhydrous Na_2SO_4 (4 g) for 2.5 h. ^{1}H NMR indicated quantitative formation of the corresponding imine. $Yb(OTf)_3$–hydrate (0.150 g) was added to the resulting mixture and stirred further for approximately 12 h. Once complete the reaction mixture was filtered and the filtrate washed with saturated aqueous NaCl solution. The organic phase was then concentrated under reduced pressure and crude mixture was subjected to isolation by silica gel column chromatography (EtOAc/MeOH/ Et_3N: 6/1/0.1) to afford 0.240 g of **3a** and 0.024 g of **3b**. **3a**: ^{1}H NMR, δ 1.18 (3H, d, $J=6.5$ Hz), 1.23 (1H, dtd, $J=13.2$, 12.2, 3.6 Hz), 1.32 (3H, s), 1.38 (1H, qd, $J=12.3$, 3.7 Hz), 1.45 (3H, s), 1.82 (1H, dtd, $J=13.4$, 3.7, 2.7 Hz), 1.86 (1H, dtd, $J=12.3$, 3.7, 2.5 Hz), 1.98 (1H, ddd, $J=12.8$, 12.0, 3.2 Hz), 2.80 (1H, dpd, $J=12.0$, 6.5, 3.5 Hz), 3.29 (1H, br), 3.38 (1H, d, $J=12.8$ Hz) ppm, ^{13}C NMR, δ 22.1, 22.6, 25.4, 28.4, 34.0, 51.8, 53.9, 60.9, 86.3, 174.6 ppm. **3b**: ^{1}H NMR, δ 1.05 (1H, dtd, $J=13.0$, 10.5, 3.0 Hz), 1.07 (1H, d, $J=6.0$ Hz), 1.27 (1H, qd, $J=12.6$, 3.2 Hz), 1.37 (3H, s), 1.42 (3H, s), 1.62 (1H, dtd, $J=13.2$, 3.6, 2.0 Hz), 1.83 (1H, dtd, $J=12.5$, 3.2, 2.2 Hz), 1.89 (1H, br), 2.17 (1H, ddd, $J=12.5$, 6.5, 3.2 Hz), 2.62 (1H, dqd, $J=10.8$, 6.0, 3.6 Hz), 4.09 (1H, d, $J=6.5$ Hz) ppm, ^{13}C NMR, δ 23.4, 23.8, 24.5, 27.2, 32.3, 42.2, 48.4, 58.2, 83.9, 177.1 ppm.