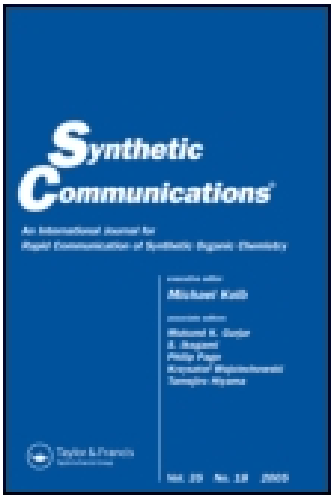


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

$Yb(OTf)_3$-Catalyzed Intermolecular Imino Diels-Alder Reaction of 2-Azetidinone-Tethered Aryl Imines as Azadienes

E. Ramesh [a], E. Elamparuthi [a] & R. Raghunathan [a]
[a] Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai, India
Published online: 16 Aug 2006.

To cite this article: E. Ramesh, E. Elamparuthi & R. Raghunathan (2006) $Yb(OTf)_3$-Catalyzed Intermolecular Imino Diels-Alder Reaction of 2-Azetidinone-Tethered Aryl Imines as Azadienes, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:10, 1431-1436

To link to this article: http://dx.doi.org/10.1080/00397910500522157

Synthetic Communications®, 36: 1431–1436, 2006

ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500522157

$Yb(OTf)_3$-Catalyzed Intermolecular Imino Diels–Alder Reaction of 2-Azetidinone-Tethered Aryl Imines as Azadienes

E. Ramesh, E. Elamparuthi, and R. Raghunathan
Department of Organic Chemistry, University of Madras,
Guindy Campus, Chennai, India

Abstract: $Yb(OTf)_3$ is an efficient catalyst for the intermolecular imino Diels–Alder reaction of aldimines derived from 2-azetidinone-tethered aryl imines and electron-rich dienophiles to afford the quinoline-β-lactams.

Keywords: Ytterbium triflate, β-lactam, imino Diels-Alder

INTRODUCTION

The 2-azetidinone nucleus has been recognized as the central motif of the so-called β-lactam antibiotics, the most widely employed family of antimicrobial agents to date.[1] Furthermore, the recent discoveries of some azetidinones that display a broad range of enzyme-inhibitory activity justify a renewed interest in these compounds. Beside their significance as bioactive agents, they are important as synthetic intermediates.

Imino Diels–Alder reactions involving aza-dienes are widely used in the construction of nitrogen-containing compound.[2] The Lewis acid–catalyzed aza-Diels–Alder reaction of N-arylimines with dienophiles has shown to be a very powerful tool for the synthesis of tetrahydroquinoline derivatives. The inter- and intramolecular imino Diels–Alder reaction of imines with

Received in India October 10, 2005
Address correspondence to R. Raghunathan, Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600025, India. E-mail: ragharaghunathan@yahoo.com

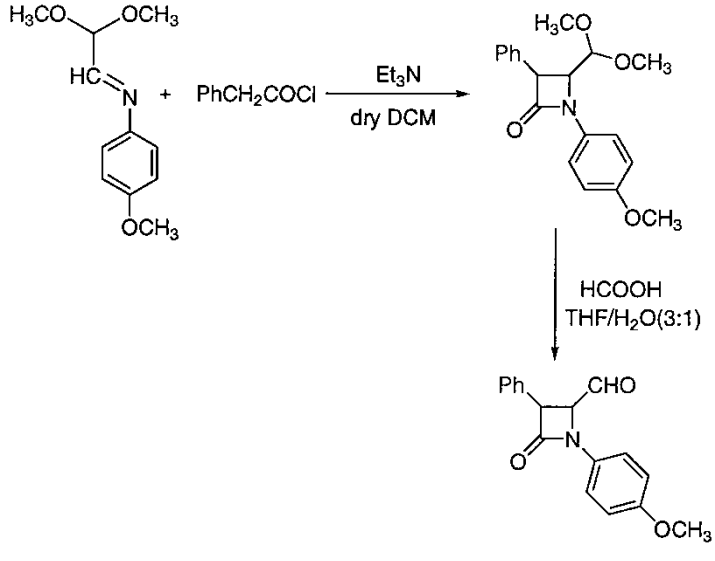
electron-rich dienophiles has been catalyzed by Lewis acids such as $BF_3 \cdot Et_2O$,[3,4] transition-metal carbonyls,[5] $InCl_3$[6], and so forth.

Herein we describe the catalytic activity of $Yb(OTf)_3$ in the synthesis of quinoline-β-lactams from β-lactam imines and various electron-rich dienophiles via intermolecular imino Diels–Alder reaction in acetonitrile at room temperature in a short time with excellent yields. Synthesis of β-lactam imine from glyoxal dimethylacetal imine leads to 4-dimethylacetal β-lactams, which, on acid hydrolysis, give 4-formyl-β-lactams (Scheme 1).

In the presence of 20 mol% $Yb(OTf)_3$, β-lactams imines derived from anisidine and various dienophiles in acetonitrile at room temperature give quinoline-β-lactam in 87–98% yield as a mixture of diastereoisozners **3** and **4**. In all cases, the products were obtained as a mixture of diastereoisomers, which can be separated by column chromatography on silica gel. Several other β-lactam imines underwent smooth cycloaddition to give the corresponding quinoline-β-lactams in good yields (Table 1). The (+)**3a–c** and (+)**4a–c** stereochemistry of the products was assigned on the basis of coupling constants of the protons in the ^{1}H NMR spectra (Scheme 2).

CONCLUSION

We found that the intermolecular imino Diels reaction can be carried out very conveniently starting from the various electron-rich dienophiles and β-lactams imines. This would be a highly desirable method for the preparation

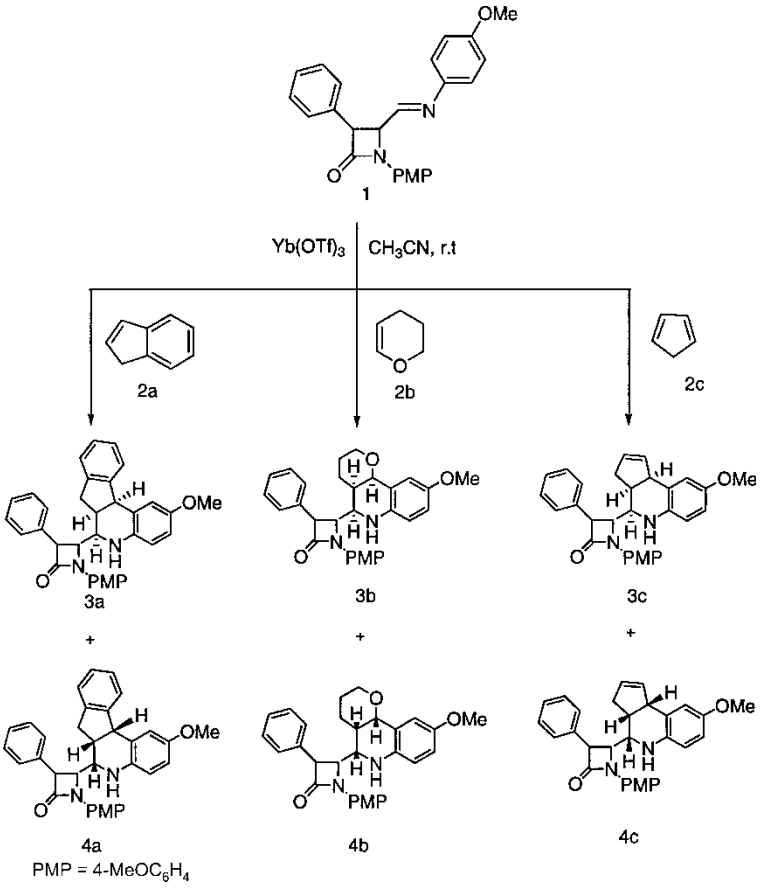


Scheme 1.

Table 1. Synthesis of tricyclic quinoline β-lactams[a]

3a	**4a**	Overall yield, % (**3a** + **4a**)[b]	**3b**	**4b**	Overall yield, % (**3b** + **4b**)[b]	**3c**	**4c**	Overall yield, % (**3c** + **4c**)[b]	Time, min
36%	51%	87	46%	49%	95	47%	51%	97	20

[a]All the products were characterized by IR, ^{1}H and ^{13}C NMR.
[b]Yield refers to the mixture of diastereoisomers of products **3a** pure forms by column chromatography.



Scheme 2.

of heteropolycyclic systems. We conclude that $Yb(OTf)_3$ is an efficient catalyst for cyclization of β-lactams imines with various electron-rich dienophiles derivatives.

EXPERIMENTAL

General Procedure for the Preparation of Imine

A solution of p-anisidine (1.50 mmol) in dichloromethane (10 mL) was added dropwise to a stirred suspension of 4-oxoazetidine-2- carbaldehyde 1 (1.0 mmol) and anhydrous sodium sulfate (1.50 mmol) in dichloromethane (100 mL) at room temperature. After stirring for 12 h at room temperature, the mixture was filtered, and the solvent was removed under reduced

pressure. The residue was recrystallized with chloroform to yield the analytically pure compound (mp 124°C).

General Procedure for the Synthesis of Derivatives 3 and 4

A solution of the corresponding imine (1 mmol) in acetonitrile (5 mL) was added dropwise to a stirred suspension of $Yb(OTf)_3$ (0.2 mmol) in acetonitrile (13 mL) at room temperature for 5 min, and then electron-rich dienophile (1.20 mmol) was introduced. The reaction was decomposed with saturated aqueous $NaHCO_3$ (10 mL), and the mixture was extracted with chloroform (3×20 mL). The combined organic extract was washed with brine, dried ($MgSO_4$), and concentrated on silica gel under reduced pressure. Chromatography of the residue eluting with ethyl acetate/hexanes mixture (3 : 7) gives **3** and **4**.

Data

Cycloadduct (3c): white solid; mp 168°C, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 6.80$ and 7.20 (m, each 2H), 6.43 (m, 3H), 5.70 (m, 1H), 5.56 (m, 1H), 4.68 (d, $J = 5.3$ Hz, 1H), 4.17 (dd, $J = 9.0$, 5.3 Hz, 1H), 3.71 (m, 4H), 3.63 (m, 7H), 2.54 (m, 2H), 2.11 ppm (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 165.6$, 157.7, 153.2, 138.4, 133.9, 130.1, 129.4, 127.1, 122.4, 117.3, 114.4, 113.9, 112.5, 83.2, 59.8, 59.3, 56.0, 55.7, 55.5, 46.1, 40.6, 31.4 ppm; IR ($CHCl_3$): 3345, 1743 cm^{-1}; MS: m/z: 452$(M)^+$. Elemental analysis calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19; found: C, 77.26; H, 6.41; N, 5.88.

Cycloadduct (4c): white solid; mp 172°C, ^{1}H NMR (300 MHZ, $CDCl_3$): $\delta = 6.94$ and 7.51 (m, each 2H), 6.57 (d, $J = 2.8$ Hz, 1H), 6.46 (ddd, $J = 8.6$, 2.9, 0.5 Hz, 1H), 6.21 (d, $J = 8.6$ Hz, 1H), 5.86 (m, 1H), 5.75 (m, 1H), 4.68 (d, $J = 5.5$ Hz, 1H), 4.34 (dd, $J = 9.8$, 5.5 Hz, 1H), 3.98 (m, 1H), 3.83 (m, 4H), 3.67 and 3.71 (s, each 3H), 3.06 (qd, $J = 10.8$, 2.9 Hz, 1H), 2.81 (m, 1H), 2.38 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.0$, 157.1, 153.3, 138.1, 134.3, 130.9, 130.1, 127.1, 120.2, 117.3, 114.6, 113.9, 112.3, 82.8, 60.5, 59.8, 59.7, 56.1, 55.7, 55.6, 46.2, 39.1, 31.6 ppm; IR (KBr): 3342, 1744 cm^{-1}; MS: m/z (%): 452(M^+). Elemental analysis calcd. for $C_{29}H_{28}N_2O_3$: C, 76.97; H, 6.24; N, 6.19; found: C, 77.16; H, 6.38; N, 596.

Cycloadduct (3b): pale yellow solid; mp 180°C, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.48$ (m, 2H), 7.25 (m, 2H), 6.97 (m, 3H), 6.74 (m, 3H), 6.56 (ddd, $J = 8.7$, 2.9, 0.5 Hz, 1H), 6.18 (d, $J = 8.7$ Hz, 1H), 5.00 and 5.37 (d, $J = 5.4$ Hz, each 1H), 4.63 (dd, $J = 9.8$, 5.4 Hz, 1H), 3.92 (m, 1H), 1.46 (m, 4H), 3.67 and 3.77 (s, each 3H), 3.51 (m, 2H), 2.40 ppm (m, 1H);

^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 164.2$, 157.5, 157.0, 153.2, 137.9, 130.4, 129.6, 122.6, 121.5, 120.1, 116.4, 115.8, 114.9, 114.3, 111.6, 79.5, 71.5, 60.9, 57.8, 56.6, 55.6, 55.4, 33.0, 24.9, 18.8 ppm; IR (KBr): 3418, 1751 cm^{-1}; MS (CI): m/z (%): 470 (M^+). Elemental analysis calcd. for $C_{29}H_{30}N_2O_4$ (%): C, 74.02; H, 6.43; N, 5.95; found: C, 74.27; H, 6.64; N, 5.65.

Cycloadduct (4b): pale yellow solid; mp 177°C, ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.18$ (m, 6H), 6.84 (m, 3H), 6.65 (dd, $J = 8.7$, 2.9 Hz, 1H), 6.37 (d, $J = 8.7$ Hz, 1H), 4.93 and 5.46 (d, $J = 5.2$ Hz, each 1H), 4.51 (dd, $J = 9.4$, 5.2 Hz, 1H), 4.07 (m, 1H), 3.68 and 3.77 (s, each 3H), 3:41 (m, 3H); 1.57 ppm (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 163.6$, 157.6, 157.0, 153.3, 137.9, 129.7, 129.6, 129.1, 122.8, 121.7, 116.3, 115.7, 115.1, 114.4, 111.4, 80.4, 71.7, 60.6, 57.2, 56.7, 55.6, 55.4, 33.7, 24.9, 18.6 ppm; IR (KBr): 3422, 1750 cm^{-1}; MS: m/z: 470 (M^+). Elemental analysis calcd. for $C_{29}H_{30}N_2O_4$: C, 74.02; H, 6.43; N, 5.95; found: C, 74.28; H, 6.60; N, 5.74.

ACKNOWLEDGMENTS

E. Ramesh thanks CSIR, New Delhi, for the fellowship. R. Raghunathan thanks Council of Scientific and Industrial Research (CSIR), New Delhi, for the financial support.

REFERENCES

1. For reviews see (a) Ojima, I. *Adv. Asym. Synth.* **1995**, *1*, 95; (b) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377.
2. For reviews see (a) Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099; (b) Jorgensen, K. A. *Angew. Chem.* **2000**, *112*, 3702; *Angew. Chem., Int. Ed.* **2000**, *39*, 3558; (c) Behforouz, M.; Ahmmadian, M. *Tetrahedron* **2000**, *56*, 5259; (d) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (e) Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131; (f) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *190*, 1; (g) Waldmann, H. *Synlett* **1995**, 133.
3. (a) Katritzky, A. R.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070, and references cited therein; (b) Yamada, N.; Kadowaki, S.; Takahashi, K.; Umezu, K. *Biochem. Pharmacol.* **1992**, *44*, 1211–1213; (c) Johnson, J. V.; Rauckman, S.; Baccanari, P. D.; Roth, B. *J. Med. Chem.* **1989**, *32*, 1942–1949.
4. Bager, D. L. *Tetrahedron* **1983**, *39*, 2869–2939.
5. Joh, T.; Hagihara, N. *Nippon Kagaku Zashi* **1970**, *91*, 378–383; *Chem. Abstr.* **1970**, 73, 45294x.
6. Elamparuthi, E.; Perumal, P. T. *ARKIVOC* **2004**, *2005*, 6–16.