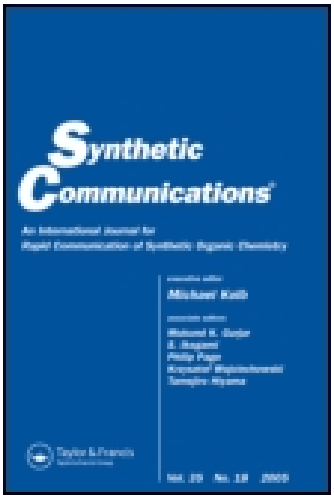


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient One-Pot Synthesis of Substituted Lactams via Three-Component Solvent-Free Reaction Catalyzed by Ytterbium Triflate

Arasampattu S. Nagarajan [a] & Boreddy S. R. Reddy [a]

[a] Industrial Chemistry Laboratory , Central Leather Research Institute, Adyar , Chennai , India

Accepted author version posted online: 08 May 2012.Published online: 21 Feb 2013.

To cite this article: Arasampattu S. Nagarajan & Boreddy S. R. Reddy (2013) Efficient One-Pot Synthesis of Substituted Lactams via Three-Component Solvent-Free Reaction Catalyzed by Ytterbium Triflate, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 43:9, 1229-1236, DOI: 10.1080/00397911.2011.628774

To link to this article: http://dx.doi.org/10.1080/00397911.2011.628774

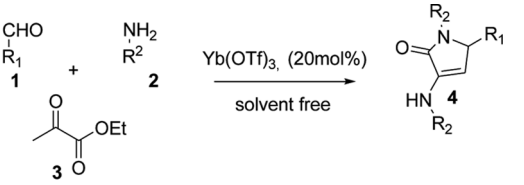
Synthetic Communications®, 43: 1229–1236, 2013

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397911.2011.628774

EFFICIENT ONE-POT SYNTHESIS OF SUBSTITUTED LACTAMS VIA THREE-COMPONENT SOLVENT-FREE REACTION CATALYZED BY YTTERBIUM TRIFLATE

Arasampattu S. Nagarajan and Boreddy S. R. Reddy
Industrial Chemistry Laboratory, Central Leather Research Institute, Adyar, Chennai, India

GRAPHICAL ABSTRACT



R_1= Aromatic and aliphatic aldehyde
R_2= Aromatic and aliphatic amine

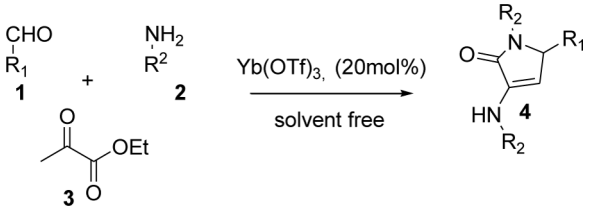
Abstract *Three-component synthesis of 1,5-dihydro-2*H*-pyrrol-2-one derivatives from pyruvate, aldehyde, and aniline was described. The reaction proceeds successfully under solvent-free conditions using ytterbium as a catalyst. The structures of the synthesized compounds are assigned on the basis of elemental analysis, infrared,* ^{1}H *NMR,* ^{13}C *NMR, and mass spectral data.*

Keywords Ethyl pyruvate; pyrrol-2-ones; solvent-free condition; substituted lactams; ytterbium triflate

INTRODUCTION

Multicomponent reactions (MCRs)[1] have received great attention from the chemical community because they permit the building of architecturally complex molecules from relatively simple starting materials. Although significant progress has been made in the area of MCRs, there is still a high demand for new processes aimed at the rapid assembly of heterocyclic molecules. 1,5-Dihydro-2*H*-pyrrol-2-ones, heterocyclic compounds that are found in many natural products and exhibit promising biological properties,[2–4] have been subjected to extensive study in the past years. Accordingly, synthetic efforts have been made toward the construction of this class of molecules. In general, 3-aminopyrrol-2-ones were obtained by the

Received August 25, 2011.
Address correspondence to Boreddy S. R. Reddy, Industrial Chemistry Laboratory, Central Leather Research Institute, Adyar, Chennai 600 020, India. E-mail: nagarajan12003@gmail.com



Scheme 1. Synthesis of 1,5-dihydro-2*H*-pyrrol-2-ones.

two-component condensation of anilines with pyrrolidine-2,3-diones[3c] or β,γ-unsaturated α-oxo esters.[4a] Pyrrolidinediones and β,γ-unsaturated α-oxo esters were normally prepared from the corresponding aldehydes and pyruvate derivatives. A one-pot, three-component coupling of aniline, aldehyde, and pyruvate would be an ideal process for the synthesis of these targeted lactams. In this regard, a single example of such a three-component coupling reaction in the presence of sulfuric acid has been reported.[4b] An asymmetric, catalytic, one-pot, three-component coupling of aniline, aldehyde, and pyruvate has been reported.[5] Recently, a simple and effective approach to the synthesis of 1,5-dihydro-2*H*-pyrrol-2-one derivatives via three-component reactions by hydrogen bonding catalyst has also been reported by Cheng et al.[6] However, both (asymmetric and hydrogen bonding catalyst) of these reactions require cumbersome workup and purification steps. Most of these procedures were time-consuming and produce lots of waste products.

Recently, ytterbium triflate chemistry has attracted much attention as $Yb(OTf)_3$ has emerged as an alternative, safe, economical, air- and moisture-tolerant Lewis acid that has been used in various organic transformations.[7] Therefore, we have investigated ytterbium triflate catalyst in a one-pot, simple, mild, and efficient procedure for the rapid construction of 1,5-dihydro-2*H*-pyrrol-2-ones via a three-component reaction of substituted cyclic or acyclic aldehydes **1**, amines **2**, and ethyl pyruvate **3** (Scheme 1).

To the best of our knowledge, there is no report on the one-pot synthesis of 1,5-dihydro-2*H*-pyrrol-2-ones in the literature using ytterbium triflate as a catalyst.

Table 1. One-pot, three-component synthesis of lactam **4.5** using different Lewis acids[a]

Entry	Lewis acid	Time (h)	Yield (%)[b]
1	$AlCl_3$	8	18
2	$ZnCl_2$	5	07
3	$TiCl_4$	6	11
4	BF_3-OEt_3	11	02
5	$SnCl_2$	10	09
6	$Yb(OTf)_3$	2	84
7	$ZrCl_4$	9	13
8	SiO_2	10	17

[a]Reaction conditions: o-chlorobenzaldehyde (0.1 mmol), 2,4,6-trimethylaniliine (0.2 mmol), ethyl pyruvate (0.3 mmol), catalyst (20 mol%), rt.
[b]Yield of isolated and purified products.

Table 2. Effect of catalyst loading on one-pot, three-component reaction[a]

Entry	$Yb(OTf)_3$ (mol%)	Time (h)	Yield (%)
1	5	2	56
2	10	2	71
3	15	2	74
4	20	2	81

[a]o-Chlorobenzaldehyde (0.1 mmol), 2,4,6-trimethylaniline (0.2 mmol), ethyl pyruvate (0.3 mmol), and ytterbium triflate (5–20 mol%), rt.

Initially, a one-pot, three-component reaction of o-chlorobenzaldehyde **1** (0.1 mmol), 2,4,6-trimethyl aniline **2** (0.2 mmol), and ethyl pyruvate **3** (0.3 mmol) was planned (Scheme 1). Several Lewis acids were screened in our model reaction (Table 1).

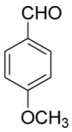
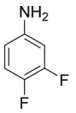
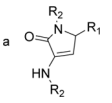
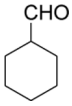
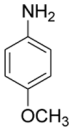
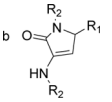
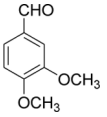
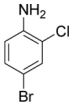
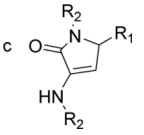
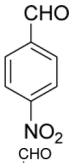
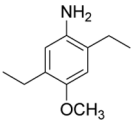
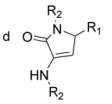
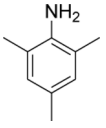
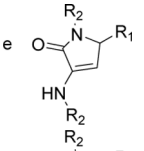
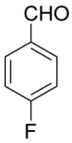
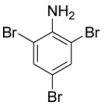
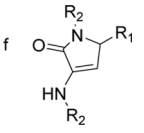
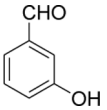
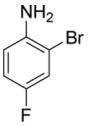
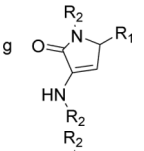
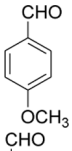
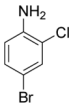
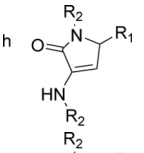
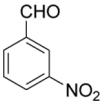
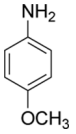
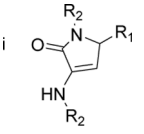
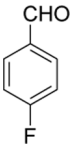
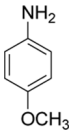
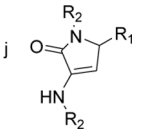
RESULTS AND DISCUSSION

Interestingly, the use of other Lewis acids such as $AlCl_3$, $SnCl_4$, $ZnCl_2$, and BF_3-OEt_2 were found to have lower catalytic activity and resulted in a small or trace amount of the desired product. Only $AlCl_3$ gave a minor amount of 1,5-dihydro-2*H*-pyrrol-2-one **4** along with other side products. $Yb(OTf)_3$ gave a high yield of **4** within a short time. Therefore, $Yb(OTf)_3$ alone was the most effective Lewis acid catalyst for the one-pot, three-component synthesis of **4**. Various solvents such as EtOH, MeCN, CH_2Cl_2, tetrahydrofuran (THF), Et_2O, and PhMe were also screened for this reaction. The best results were observed under solvent-free conditions. In a further investigation, a sequential one-pot reaction of aldehyde **1** (0.1 mmol), amine (0.2), and ethyl pyruvate **3** (0.3 mmol) in the presence of ytterbium triflate (5–20 mol%) was performed, leading to the synthesis of 1,5-dihydro-2*H*-pyrrol-2-one **4**. The progress of the reaction was monitored by thin-layer chromatography (TLC). After the complete consumption of aldehyde with ethyl pyruvate, amine (2 mmol) was added to the same flask. Product **4** was obtained in 57–84% yield within 1–2 h. Encouraged by this initial result, a one-pot, three-component reaction was performed by mixing aldehyde, amine, and ethyl pyruvate. The catalyst loading was optimized using different molar concentrations of ytterbium triflate under solvent-free conditions at room temperature (Table 2). A good yield of product 4 was obtained using 20 mol% of catalyst. Prolonging the reaction time and increasing the amount of $Yb(OTf)_3$ catalyst to 40 mol% did not improve the yield.

On increasing the concentration of $Yb(OTf)_3$ and not that of ethyl pyruvate, many other side products were obtained. From these results, it was evident that the catalyst concentration plays a crucial role in optimizing the reaction.

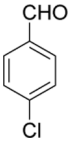
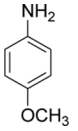
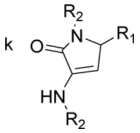
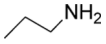
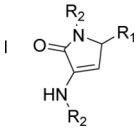
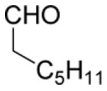
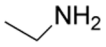
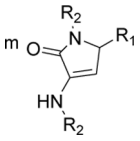
To explore the generality and scope of this method, a wide variety of substituted aromatic aldehydes and amines were reacted with ethyl pyruvate under the same experimental conditions to afford the corresponding **4**. $Yb(OTf)_3$ was found to be compatible with various substituents (electron withdrawing as well as donating substituents) such as OMe, OH, NO_2, Cl, and Me. The presence of an electron-releasing group such as methoxy in the *para* position to the aldehyde and

Table 3. One-pot, three-component synthesis of **4**

Entry	1	2	Product	Yield (%)
4.1				65
4.2				71
4.3				64
4.4				62
4.5				84
4.6				57
4.7				74
4.8				68
4.9				70
4.10				73

(*Continued*)

Table 3. Continued

Entry	1	2	Product	Yield (%)
4.11				69
4.12				71
4.13				62

Notes. Reaction time 2 h, Yb $(OTf)_3$, 20 mol%.

the *para* position to amine enhances the product formation as indicated by greater yield (Table 3, entries 4.1 and 4. 2). Similarly, the presence of electron-withdrawing group (halogen/nitro) in the *para* position to the aldehyde and *ortho* and *para* groups to the amine reduces the product formation as indicated by lower yield (Table 3, entries 4.3 and 4.4). For a strong electron-withdrawing group such as nitro or fluro in the *para* position to the aldehyde group and bromo in *ortho and para* to amine requires longer reaction time and lower yield (Table 3, entries 4.6). An aliphatic group reaction proceeds smoothly to gives greater yield (Table 3, entries 4.12 and 4.13). The resultant products were obtained in good to excellent yields in short reaction times (Table 3). All the products obtained were fully characterized by spectroscopic methods including IR, ^{1}H NMR, ^{13}C NMR, and mass spectroscopy. The spectral data were also compared with the reported values.

CONCLUSION

In summary, this method provides an efficient multicomponent approach for the synthesis of 1,5-dihydro-2*H*-pyrrol-2-ones. The reaction is versatile and also offers several advantages such as good yields, shorter reaction times, cleaner reaction profiles, and simple experimental and workup procedures.

EXPERIMENTAL

Ethyl pyruvate 3 (0.3 mmol) and ytterbium triflate (20 mol%) were added successively to a stirred mixture of aldehyde **1** (0.1 mmol) and amine **2** (0.2 mmol) at

room temperature with vigorous stirring for 1–2 h. The precipitated solid was filtered and washed with a mixture of ethyl acetate/hexane (20:80 v/v). The product obtained was pure as found by TLC and ^{1}H and ^{13}C NMR spectroscopy. However, the products were further purified by recrystallization from ethyl acetate and ethanol (70:30 v/v).

1-(3,4-Diflurophenyl)-5-(4-methoxyphenyl)-3-[(3,4-diflurophenyl) amino]-4H-pyrrol-2(5H)one, 4a

IR (KBr): 3357 (N–H), 1677 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.75$ (s, 3H), 5.72 (d, $J = 2.74$ Hz, 1 H), 6.04 (d, $J = 2.74$ Hz, 1 H), 6.72 (s, 1 H), 6.94 (d, $J = 9.06$ Hz, 2 H), 7.17–7.19 (m, 2 H), 7.25–7.30 (m, 2H), 7.35–7.39 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 54.7$, 64.13, 108.5, 113.4, 118.5, 118.8, 122.5, 126.6, 128.9, 129.5, 131.7, 131.6, 132.4, 136.1, 136.8, 140.9, 54.1, 156.6, 158.1, 159.3, 166.99 ppm; LCQ–MS (ESI) m/z 428.1. Anal. calcd. for $C_{23}H_{16}F_4N_2O_2$: C, 64.49; H, 3.76; N, 6.54. Found C, 64.41; H, 3.69; N, 6.48.

1-(4-Methoxyphenyl)-5-(cyclohexyl)-3-[(4-methoxy phenyl)amino]-4H-pyrrol-2(5H)-one, 4b

IR (KBr): ν max = 3327 (s, N–H enamine), 1674 (s, C=O amide) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.97$–2.24 (m, 10H), 3.74 (s, 3 H), 3.77 (s, 3 H), 5.96 (d, $J = 2.74$ Hz, 1 H), 6.07 (d, $J = 2.47$ Hz, 1 H), 6.33 (s, 1 H), 6.44 (t, $J = 2.47$ Hz, 2 H,), 6.81–6.86 (m, 2H), 7.03 (d, $J = 9.33$ Hz, 2 H), 7.48 (d, $J = 9.33$ Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 15.7$, 19.3, 21.9, 25.7, 26.6, 27.5, 55.9, 64.2, 98.5, 104.7, 106.8, 117.9, 118.2, 122.2, 127.4, 135.7, 154.1, 159.1, 166.7 ppm; MS (EI+): LCQ–MS (ESI) m/z 392.2. Anal. calcd. for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found C, 73.37; H, 7.23; N, 7.21.

ACKNOWLEDGMENT

A. S. Nagarajan thanks the Council of Scientific and Industrial Research, New Delhi, for financial assistance.

REFERENCES

1. (1) For a recent review see (a) Ugi, I.; Werner, B.; Domling, A. Synthesis and biological activity of fluoroquinolones. *Targets Heterocycl. Syst.* **2000**, *4*, 1–7; (b) Ugi, I. Recent progress in the chemistry of multicomponent reactions. *Pure Appl. Chem.* **2001**, *73*, 187–191; (c) Nair, V.; Rajesh, C.; Vinod, A. U.; Bindu, S.; Streekenth, A. R.; Mathen, J. S.; Balagopal, L. Strategies for heterocyclic construction via novel multicomponent reactions based on isocyanides and nucleophilic carbenes. *Acc. Chem. Res.* **2003**, *36*, 899–907; (d) Ramon, D. J.; Yus, M. Asymmetric multicomponent reactions (AMCRs): The new frontier. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 1602–1634; (e) Domling, A. Recent developments in isocyanide-based multicomponent reactions in applied chemistry. *Chem. Rev.* **2006**, *106*, 17–89.

2. (a) Gein, V. L.; Popov, A. V.; Kolla, V. E.; Popova, N. A.; Potemkin, K. D. Synthesis and biological activity of 1,5-diaryl-3-arylamino-4-carboxymethyl-2,5-dihydro-2-pyrrolones and 1,5-diaryl-4-carboxymethyltetrahydropyrrole-2, 3-diones. *Pharm. Chem. J.* **1993**, *27*, 343; (b) Gein, V. L.; Popov, A. V.; Kolla, V. E.; Popova, N. A. Synthesis and biological activity of 5-diaryl-3-alkylamino-4-carboxymethyl-2,5-dihydropyrrol-2-ones and 1,5-diaryl-4-carboxymethyltetrahydropyrrol-2,3-diones. *Pharmazie* **1993**, *48*, 107–109.
3. (a) Vaughan, W. R.; Tripp, R. C. 1,5-Diaryl-2,3-pyrrolidinediones, XII: Enamines and the pseudo-pyrrolidinediones. *J. Am. Chem. Soc.* **1960**, *82*, 4370–4376.
4. (a) Wu, Y. C.; Liu, L.; Wang, D.; Chen, Y. J. Efficient synthesis of 3-arylaminopyrroline-2-ones by the tandem reaction of anilines and β,γ-unsaturated α-ketoesters. *J. Heterocycl. Chem.* **2006**, *43*, 949–955; (b) Palacios, F.; Vicario, J.; Aparicio, D. An efficient synthesis of achiral and chiral cyclic dehydro-α-amino acid derivatives through nucleophilic addition of amines to β,γ-unsaturated α-keto esters. *Eur. J. Org. Chem.* **2006**, *12*, 2843–2850.
5. (a) Luo, S. Z.; Xu, H.; Chen, L. J.; Cheng, J. P. Asymmetric direct aldol reactions of pyruvic derivatives. *Org. Lett.* **2008**, *10*, 1775–1778; (b) Luo, S. Z.; Xu, H.; Zhang, L.; Li, J. Y.; Cheng, J. P. Highly enantioselective direct *syn*- and *anti*-aldol reactions of dihydroxyacetones catalyzed by chiral primary amine catalysts. *Org. Lett.* **2008**, *10*, 653–656; (c) Luo, S. Z.; Xu, H.; Li, J.; Zhang, Y. L.; Cheng, J. P. A simple primary–tertiary diamine–Brønsted acid catalyst for asymmetric direct aldol reactions of linear aliphatic ketones. *J. Am. Chem. Soc.* **2007**, *129*, 3074.
6. Xin, L.; Hui, D.; Sanzhong, L.; Cheng, J. P. Organocatalytic three-component reactions of pyruvate, aldehyde, and aniline by hydrogen-bonding catalysts. *Eur. J. Org. Chem.* **2008**, 4350–4356.
7. (a) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. Ytterbium triflate–promoted synthesis of 1,5-benzodiazepine derivatives. *Tetrahedron Lett.* **2001**, *42*, 3193–3195; (b) Curini, M.; Epifano, F.; Marcotullio, M. C.; Rosati, O. A facile and convenient synthesis of 1,2,3,6-tetrahydropyridazines using azodicarboxylates under lanthanum triflate catalysis. *Heterocycles.* **2001**, *55*, 1599–1604; (c) Curini, F.; Epifano, M; Marcotullio C.; Rosati, O. The synthesis of solvent-free glycidic esters from diazoesters and carbonyl compounds catalysed by lanthanide triflates. *Eur. J. Org. Chem.* **2002**, 1562–1565; (d) Curini, M.; Epifano, O. F.; Maltese, F.; Rosati, O. Carbamate synthesis from amines and dimethyl carbonate under ytterbium triflate catalysis. *Tetrahedron Lett.* **2002**, *43*, 4895–4897; (e) Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. Ytterbium triflate–promoted coupling reaction between aryl alkynes and aldehydes. *Synlett.* **2003**, 552–554; (f) Curini, M.; Epifano, F.; Marcotullio, M.; Maltese, C. Aldol-grob reaction: Regioselective synthesis of (E)-alkenes from aldehydes and ketones under ytterbium triflate catalysis. *Eur. J. Org. Chem.* **2003**, 1631–1634; (g) Curini, F.; Epifano, F.; Montanari, F.; Rosati, O.; Taccone, S. Ytterbium triflate promoted synthesis of benzimidazole derivatives. *Synlett* **2004**, 1832–1834; (h) Curini, M.; Epifano, F.; Geno, S. Preparation of triaryl- and triheteroarylmethanes under ytterbium triflate catalysis and solvent-free conditions. *Eur. J. Org. Chem.* **2009**, 1132–1135; (i) Marcotullio, M. C.; Rosati, O. Ytterbium triflate-promoted tandem one-pot oxidation–cannizzaro reaction of aryl methyl ketones. *Org. Lett.* **2005**, *7*, 1331–1333; (j) Curini, M.; Epifano, F.; Genovese, S. Ytterbium triflate–catalyzed synthesis of β-keto enol ethers. *Tetrahedron Lett.* **2006**, *47*, 4697–4700; (k) Curini, M.; Epifano, F.; Genovese, S. Ytterbium triflate catalyzed synthesis of β-naminones. *Tetrahedron Lett.* **2007**, *48*, 2717–2720; (l) Zhang, X.; Teng, W.; Teo, P.; Hong Chan, W. Ytterbium(III) triflate–catalyzed tandem friedel–Crafts alkylation/hydroarylation of propargylic alcohols with phenols as an expedient route to indenols. *Org. Lett.* **2009**, *11*, 4990–4993; (m) Yamanaka, M.; Nishida, A.; Nakagawa, M. Ytterbium(III) triflate/TMSCl: Efficient catalyst for imino ene reaction. *Org. Lett.* **2000**, *2*, 159–161; (n) Kumareswaran, R.; Shahi, P. S; Rani, S.; Gupta, A.; Madhusudananb, K. P.; Vankar, Y. D. Ytterbium triflate– (and trimethylsilyl triflate–)-catalyzed isomerization of glycidic esters to

α-hydroxy-β,γ-unsaturated esters and their conversion into cyclopentanoids using Johnson–Claisen rearrangement. *Arkivoc* **2002**, *7*, 126–135; (o) Lee, S. G.; Park, J. H. Ytterbium(III) triflate–catalyzed one-pot Mannich-type reaction in ionic liquid. *Bull. Korean Chem. Soc.* **2002**, *23*, 1367–1368; (p) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; William, W.; Lam, L. Rare-earth metal triflates in organic synthesis. *Chem. Rev.* **2002**, *102*, 2227–2302; (q) Huang, Y.; Yang, F.; Zhu, C. Highly enantioseletive Biginelli reaction using a new chiral ytterbium catalyst: Asymmetric synthesis of dihydropyrimidines. *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387; (r) Lundgren, S.; Lutsenko, S.; Johnsson, C.; Moberg, C. Polymer-supported pyridine-bis(oxazoline): Application to ytterbium-catalyzed silylcyanation of benzaldehyde. *Org. Lett.* **2003**, *5*, 3663–3665; (s) Yamanaka, M.; Nishida, Atsushi.; Nakagawa, M. Ytterbium(III) triflate/TMSCl: Efficient catalyst for imino ene reaction. *Org. Lett.* **2000**, *2*, 159–161; (t) Curini, M.; Epifano, F.; Genovese, S.; Marcotullio, M. C.; Rosati, O. Ytterbium triflate–Promoted tandem one-pot oxidation–Cannizzaro reaction of aryl methyl ketones. *Org. Lett.* **2005**. *7*, 1331–1333.