Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron Letters 47 (2006) 2803–2806
Tetrahedron Letters

Stereoselective synthesis of 3,4-*trans*-disubstituted pyrrolidines and cyclopentanes via intramolecular radical cyclizations mediated by CAN

Vijay Nair,[a,*] Kishor Mohanan,[a] T. D. Suja[a] and Eringathodi Suresh[b]

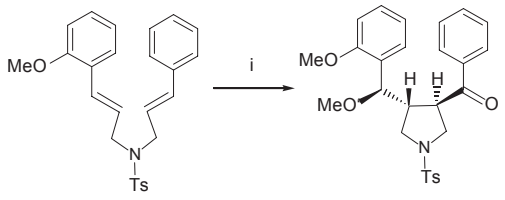
[a]*Organic Chemistry Division, Regional Research Laboratory (CSIR), Trivandrum, India*
[b]*Central Salt and Marine Chemicals Research Institute (CSIR), Bhavnagar 364 002, India*

Received 23 December 2005; revised 1 February 2006; accepted 9 February 2006

Abstract—The stereoselective intramolecular cyclizations of bis(cinnamyl)tosylamides and dimethyl bis(cinnamyl)malonates mediated by cerium(IV) ammonium nitrate leading to the synthesis of 3,4-*trans*-disubstituted pyrrolidines and cyclopentanes are described.

In recent years, cerium(IV) ammonium nitrate (CAN) has emerged as an important reagent for the construction of carbon–carbon and carbon–heteroatom bonds via radical intermediates.[1–7] Most of this chemistry, however, has involved intermolecular reactions; intramolecular reactions have received only limited attention.[8–11] In the course of our investigations in this area, it was observed that CAN is an excellent reagent for the stereoselective synthesis of functionalized tetrahydrofurans, tetrahydropyrans, and piperidines.[12] The efficiency and stereoselectivity observed in these reactions prompted us to examine the scope of the CAN mediated cyclization in the synthesis of pyrrolidine ring systems. It is noteworthy that pyrrolidine frameworks constitute important structural units of a number of natural and unnatural biologically active compounds and thus the stereoselective synthesis of functionalized pyrrolidines has been a topic of current interest.[13] The preliminary results of our investigations are presented in this *Letter*.

The substrate chosen for our initial experiments was *N*-cinnamyl-*N*-tosyl-2-methoxycinnamyl amine **1**. Treatment of **1** with CAN in methanol resulted in the selective formation of 3,4-*trans*-disubstituted pyrrolidine **2a** in moderate yield (Scheme 1).[14]



1 **2a**

Scheme 1. Reagents and conditions: (i) CAN (2.5 equiv), MeOH, O_2, 2 h, 43%.

In the IR spectrum of **2a**, a strong absorption at 1683 cm^{-1} indicated the presence of a benzoyl group, which was established by a signal at δ 198.6 in its ^{13}C NMR spectrum. In the ^{1}H NMR spectrum, the benzylic proton resonated as a doublet at δ 4.52 ($J = 7.8$ Hz). The final confirmation of the structure and stereochemistry of **2a** was obtained from single crystal X-ray analysis (Fig. 1).

To explore the generality of the reaction, experiments were conducted with various substituted bis(cinnamyl)amines and the results of these investigations are presented in Table 1.

A proposed mechanistic pathway for the formation of the pyrrolidine derivatives is given in Scheme 2. On exposure to Ce(IV), the methoxystyrenyl moiety undergoes single electron oxidation giving a transient radical

* Corresponding author. Tel.: +91 471 2490406; fax: +91 471 2491712; e-mail: vijaynair_2001@yahoo.com

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2006.02.051

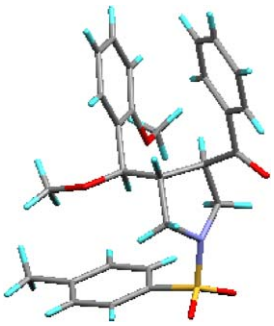
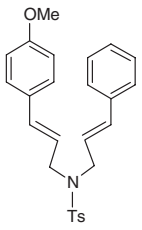
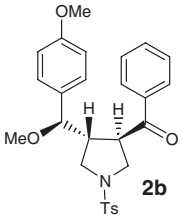
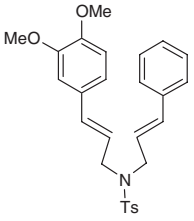
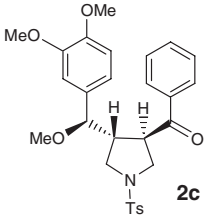
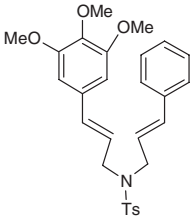
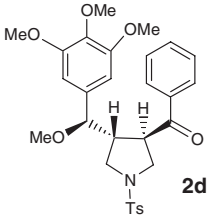
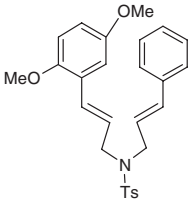
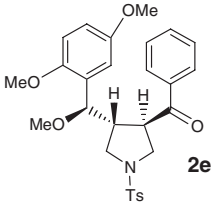


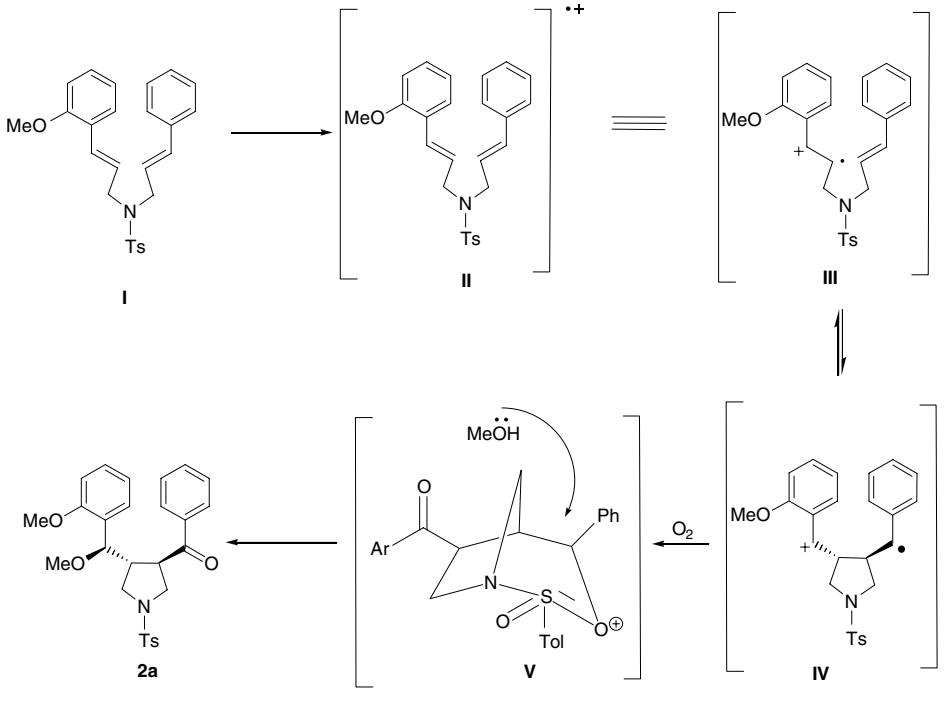
Figure 1. Single crystal X-ray structure of compound **2a**.

cation **III**. Conceivably it exists in equilibrium with its cyclic version **IV**. The radical and cationic centers of the latter intermediate are quenched by oxygen and methanol, respectively, to provide the pyrrolidine derivative. It is noteworthy that methanol attacks the cation from one face selectively providing a single diastereoisomer. This stereochemical outcome cannot be easily explained. One possibility is that the cationic center is being stabilized by the sulfonyl oxygen to afford the transient intermediate **V**, thus predisposing the methanol attack from a single face to deliver the observed product.

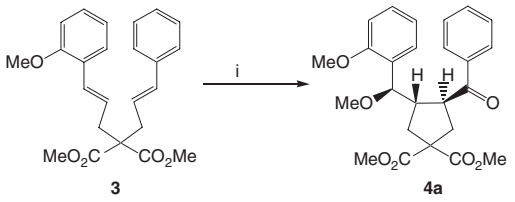
Encouraged by the successful stereoselective synthesis of 3,4-*trans*-disubstituted pyrrolidines, we turned our attention to the synthesis of cyclopentanes. In view of their presence in a number of biologically important compounds, there has been considerable interest in devising new strategies for the stereoselective synthesis of cyclopentanes.[15] The cyclization-substrate selected

Table 1.

Entry	Substrate	Product	Yield (%)
1		 **2b**	58
2		 **2c**	51
3		 **2d**	41
4		 **2e**	46



Scheme 2.



Scheme 3. Reagents and conditions: (i) CAN (2.5 equiv), MeOH, O_2, 2 h, 35%.

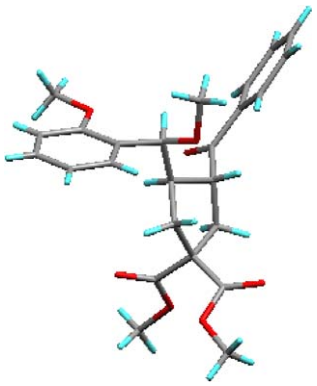
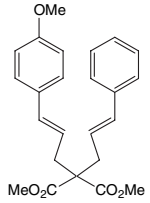
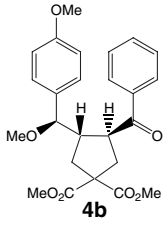
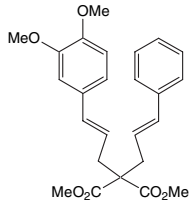
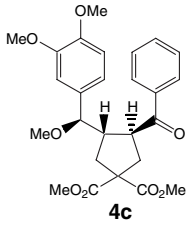
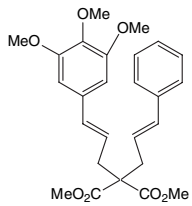
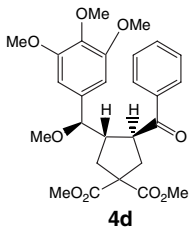
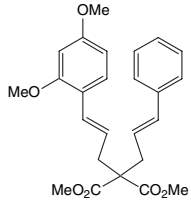
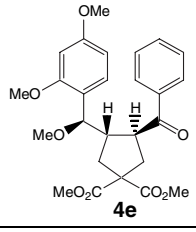


Figure 2. Single crystal X-ray structure of compound **4a**.

Table 2.

Entry	Substrate	Product	Yield (%)
1			55
2			55
3			48
4			46

for the initial study was dimethyl α-cinnamyl-α-(2-methoxycinnamyl)-malonate **3**. This, on exposure to a methanolic solution of CAN, resulted in the stereoselective formation of the cyclopentane derivative **4a** in moderate yield (Scheme 3).[16]

The structure of the product was elucidated from its spectroscopic data. In the IR spectrum, the ester and benzoyl groups showed strong absorptions at 1735 and 1680 cm^{-1}, respectively. In the ^{13}C NMR spectrum, the resonances due to the benzoyl and ester carbonyl groups were observed at δ 197.3 and 163.9, respectively. In its ^{1}H NMR spectrum, the benzylic proton resonated as a doublet at δ 4.49 ($J = 5.7$ Hz). Final proof for the structure assigned for **4a** was derived from single crystal X-ray analysis (Fig. 2).

The reaction was studied with four other substrates and the results are given in Table 2.

In conclusion, CAN has been successfully employed in intramolecular cyclization reactions leading to the synthesis of pyrrolidines and cyclopentanes in moderate yields.

Acknowledgments

The authors thank the Council of Scientific and Industrial Research (CSIR), New Delhi, for research fellowships. The authors also thank Ms. Soumini Mathew and Ms. S. Viji for NMR and high resolution mass spectra.

References and notes

1. Reviews: (a) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, *26*, 127–132; (b) Nair, V.; Panicker, S. B.; Nair, L. G.; George, T. G.; Augustine, A. *Synlett* **2003**, 156–165; (c) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21–30.
2. (a) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187–188; (b) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1881–1882; (c) Nair, V.; Mathew, J.; Kanakamma, P. P.; Panicker, S. B.; Sheeba, V.; Zeena, S.; Eigendorf, G. K. *Tetrahedron Lett.* **1997**, *38*, 2191–2194; (d) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 1575–1577.
3. (a) Baciocchi, E.; Ruzziconi, R. *J. Org. Chem.* **1986**, *51*, 1645–1649; (b) Baciocchi, E.; Civatarese, G.; Ruzziconi, R. *Tetrahedron Lett.* **1987**, *28*, 5357–5360; (c) Baciocchi, E.; Ruzziconi, R. *Synth. Commun.* **1988**, *18*, 1841–1846.
4. (a) Narasaka, K.; Okauchi, T.; Tanaka, K.; Murakami, M. *Chem. Lett.* **1992**, 2099–2102; (b) Narasaka, K.; Arai, N.; Okauchi, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 2995–3003; (c) Narasaka, K.; Kohno, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 3456–3463.
5. (a) Mandal, P. K.; Maiti, G.; Roy, S. C. *J. Org. Chem.* **1998**, *63*, 2829–2834; (b) Roy, S. C.; Guin, C.; Rana, K. K.; Maiti, G. *Synlett* **2001**, 226–227.
6. Linker, T.; Sommermann, T.; Kahlenberg, F. *J. Am. Chem. Soc.* **1997**, *119*, 9377–9384.
7. (a) Zhang, Y.; Flowers, R. A. *J. Org. Chem.* **2003**, *68*, 4560–4562; (b) Raines, A. J.; Flowers, R. A. *Org. Lett.*

2003, *5*, 2363; (c) Zhang, Y.; Raines, A. J.; Flowers, R. A. *J. Org. Chem.* **2004**, *69*, 6267–6272.
8. (a) Snider, B. B.; Kwon, T. *J. Org. Chem.* **1990**, *55*, 4786–4788; (b) Snider, B. B.; Shi, B.; Quickley, C. A. *Tetrahedron* **2000**, *56*, 10127–10136; (c) Baciocchi, E.; Paolobelli, A. B.; Ruzziconi, R. *Tetrahedron* **1992**, *48*, 4617–4622.
9. Wang, L.; Seiders, J. R.; Floreancig, P. E. *J. Am. Chem. Soc.* **2004**, *126*, 12596–12603.
10. (a) Durand, A.-C.; Dumez, E.; Rodriguez, J.; Dulcere, J.-P. *Chem. Commun.* **1999**, 2437–2438; (b) Durand, A.-C.; Rodriguez, J.; Dulcere, J.-P. *Synlett* **2000**, 731–733.
11. (a) Takemoto, Y.; Ibuka, T. *Tetrahedron Lett.* **1998**, *39*, 7545–7548; (b) Takemoto, Y.; Furuse, S. I.; Hayase, H.; Echigo, T.; Iwata, C.; Tanaka, T.; Ibuka, T. *Chem. Commun.* **1999**, 2515–2516.
12. (a) Nair, V.; Balagopal, L.; Sheeba, V.; Panicker, S. B.; Rath, N. P. *Chem. Commun.* **2001**, 1682–1683; (b) Nair, V.; Balagopal, L.; Rajan, R.; Deepthi, A.; Mohanan, K.; Rath, N. P. *Tetrahedron Lett.* **2004**, *45*, 2413–2416; (c) Nair, V.; Mohanan, K.; Suja, T. D.; Suresh, E. *Tetrahedron Lett.* **2006**, *47*, 127.
13. (a) Enyedy, I. J.; Zaman, W. A.; Sakamuri, S.; Kozikowski, A. P.; Johnson, K. M.; Wang, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1113–1118; (b) Debuffet, T.; Muller, O.; Simonet, S. S.; Descombes, J.; Laubie, M.; Verbeuren, T. J.; Lavielle, G. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 349–352, and references cited therein.
14. Experimental procedure and spectral data for representative examples: A solution of CAN (437 mg, 0.866 mmol) in methanol was added dropwise to a stirred solution of **1** (150 mg, 0.346 mmol) in methanol under oxygen. The stirring was continued until the consumption of **1** was complete as confirmed by TLC (2 h). The solvent was distilled off in vacuo and the residue diluted with water then extracted with dichloromethane (3×10 mL). The combined organic extracts were washed with water, brine and dried over anhydrous sodium sulfate. After removal of the solvent, column chromatographic separation (SiO_2) using 30:70 ethyl acetate–hexane mixture gave the pyrrolidine derivative **2a** (71 mg, 43%) as a colorless crystalline solid; mp 135–136 °C. IR (KBr) ν_{max}: 3067, 2943, 2835, 1683, 1599, 1491, 1460, 1347, 1238, 1161,1099 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.71 (d, $J = 8.2$ Hz, 2 H), 7.51–7.15 (m, 9H), 6.94 (t, $J = 7.4$ Hz, 1H), 6.64 (d, $J = 8.2$ Hz, 1H), 4.52 (d, $J = 7.8$ Hz, 1H), 3.90–3.80 (m, 1H), 3.76–3.61 (m, 5H), 3.28–3.10 (m, 5H), 2.86–2.76 (m, 1H), 2.46 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 198.6, 143.2, 133.1, 129.6, 128.9, 128.2, 127.8, 124.3, 121.0, 110.3, 104.6, 103.7, 77.4, 77.0, 73.5, 56.8, 55.1, 50.9, 49.5, 48.3, 46.4, 43.9, 21.6, 18.0. HRMS (EI) calcd for $C_{27}H_{29}NO_5S$: 479.1766, found: 479.1729. X-ray data for compound **2a**: $C_{27}H_{29}NO_5S$, $M = 479.57$, monoclinic, space group $P21/c$, $a = 9.8467(10)$, $b = 11.4829(12)$, $c = 22.122(2)$ Å, $\beta = 96.881(2)°$, $Z = 4$, $D_c = 1.283$ g/cm^3, $F_{000} = 1016$, $R1 = 0.0448$, $wR2 = 0.1205$. CCDC 293076.
15. (a) Harre, M.; Raddatz, P.; Walenta, R.; Winterfeldt, E. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 480–492; (b) Noyori, R.; Suzuki, M. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 847–876.
16. Compound **4a**: Colorless crystalline solid; mp 121–123 °C. IR (KBr) ν_{max}: 2952, 2842, 1735, 1680, 1600, 1480, 1455, 1239, 1199, 1104, 1024, 754 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ: 7.80 (d, $J = 7.8$ Hz, 2H), 7.51 (t, $J = 7.2$ Hz, 1H), 7.39 (t, $J = 3.8$ Hz, 2H), 7.26–7.23 (m, 1H), 7.11 (t, $J = 8.1$ Hz, 1H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.62 (d, $J = 8.1$ Hz, 1H), 4.49 (d, $J = 5.7$ Hz, 1H), 3.78 (s, 3H), 3.69 (s, 3H), 3.64 (s, 3H), 3.14 (s, 3H), 2.96–2.91 (m, 3H), 2.51–2.43 (m, 1H), 2.34–2.24 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 197.3, 163.9, 161.0, 143.4, 142.3, 139.1, 130.9, 129.8, 129.7, 128.7, 125.9, 124.4, 114.0, 111.4, 52.7, 50.4, 48.9, 45.2, 32.0, 30.3, 29.4, 23.5, 21.6, 14.2. HRMS (EI) calcd for $C_{25}H_{28}O_7$: 440.1835, found: 440.1841. X-ray data for compound **4a**: $C_{25}H_{28}O_7$, $M = 440.47$, monoclinic, space group $P21/n$, $a = 7.9660(7)$, $b = 14.0858(13)$, $c = 20.7638(18)$ Å, $\beta = 94.291(2)°$, $Z = 4$, $D_c = 1.259$ g/cm^3, $F_{000} = 936$, $R1 = 0.0690$, $wR2 = 0.1388$. CCDC 293077.