A Convenient Synthesis of 2,2-Diarylcyclobutanones by Cerium(IV) Ammonium Nitrate (CAN) Mediated Oxidation of Methylenecyclopropanes (MCPs)

Vijay Nair,* T. D. Suja, Kishor Mohanan

Organic Chemistry Section, Regional Research Laboratory (CSIR), 695019 Trivandrum, India
Fax +91(471)2491712; E-mail: vijaynair_2001@yahoo.com

Received 15 March 2006

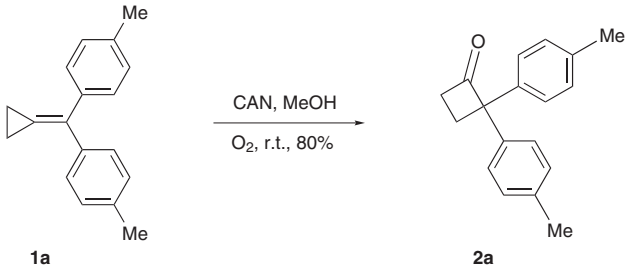
Abstract: Oxidative ring expansion of methylenecyclopropanes with CAN under oxygen atmosphere was investigated. A facile conversion affording 2,2-diarylcyclobutanones occurred in good yields.

Key words: CAN, methylenecyclopropane, cyclobutanone, oxygen, oxidative ring expansion

A number of cyclobutane derivatives are known to be biologically active,[1] an example being the antidepressant activity of certain 3,3-diphenylcyclobutylamine derivatives.[2] In view of this, synthesis of cyclobutane derivatives, like cyclobutanones assumes importance. Only a handful of general methods are available for the synthesis of cyclobutanones,[3] which include [2+2] cycloaddition of olefins to ketenes or ketene equivalents,[4] ring enlargement of bicyclooxapentanes,[5a] cyclopropylsilyl enol ethers,[5b] and cyclopropanones,[5c] and a $TiCl_4$–Et_3N mediated reaction of diaryl ketones with iminium ions generated by the oxidation of diisopropylbenzylamine using iodine.[5d]

Methylenecyclopropanes (MCPs) constitute a unique class of four-carbon synthons exhibiting a multitude of reactivity patterns.[6] The transition metal mediated reactions of MCPs have been well studied.[7] We surmised that MCPs are well suited for ring enlargement reactions, possibly delivering cyclobutanones under oxidative conditions. A recent report by Shao and Shi indeed described the Lewis acid assisted ring expansion reaction of MCPs in presence of azodicarboxylates to furnish cyclobutanone derivatives.[8] However, the strategy of subjecting MCPs to a one-electron oxidation reaction to generate a radical cation susceptible for ring expansion has received only limited attention.[9] In recent years, work in our laboratory and elsewhere has shown that cerium(IV) ammonium nitrate (CAN) is a useful reagent for oxidative single-electron-transfer processes[10] leading to a number of novel carbon–carbon and carbon–heteroatom bond-forming reactions.[11] In addition, a number of CAN-mediated transformations of strained hydrocarbons possessing cyclopropane and cyclobutane rings, including a number of monoterpenes, have been reported.[12] In this context, it was of interest to investigate the use of CAN as a reagent for the one-electron oxidation of MCPs. This work has led to a synthesis of 2,2-diarylcyclobutanones and the results are presented here.

Our studies commenced with exposing 2,2-ditolylmethylenecyclopropane (**1a**)[13] to a solution of CAN in methanol under argon. Chromatographic separation of the reaction mixture afforded 2,2-ditolylcyclobutanone (**2a**) albeit only in 15% yield. With the assumption that the carbonyl oxygen originated from the adventitious oxygen presented in the argon, we reinvestigated the reaction under oxygen atmosphere. In this experiment cyclobutanone **2a** was formed in 80% yield from **1a** (Scheme 1). The cyclobutanone **2a** was characterized on the basis of spectroscopic data which was completely identical with those reported for the authentic cyclobutanone.[8,14]



1a **2a**

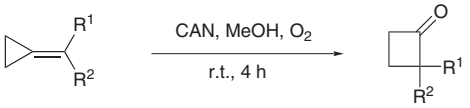
Scheme 1

To examine the scope of the reaction, a number of diaryl-substituted MCPs were subjected to oxidative ring expansion under identical conditions. In all cases cyclobutanones were obtained in good yields; the results are summarized in Table 1.

A mechanistic postulate for the reaction may be outlined as follows. The initial event is likely to be the single-electron oxidation of MCP **1a** by CAN to furnish radical cation **3**. It is reasonable to assume that the radical centre of the latter gets converted to hydroperoxide **4** by trapping molecular oxygen followed by hydrogen abstraction from methanol. The cationic site may be quenched by nitrate from CAN to form the intermediate **5**. The decomposition of hydroperoxide to alkoxy radical and its reduction by Ce(III) with the latter undergoing oxidation to Ce(IV) can deliver the alkoxide **6**. Rearrangement of the alkoxide **6** with the elimination of nitrate will complete the sequence of reactions leading to product **2a** (Scheme 2). It may be mentioned that the key steps in the mechanistic pathway outlined here are precedented in our earlier work.[15,16]

SYNTHESIS 2006, No. 15, pp 2531–2534
Advanced online publication: 28.06.2006
DOI: 10.1055/s-2006-942445; Art ID: Z05206SS

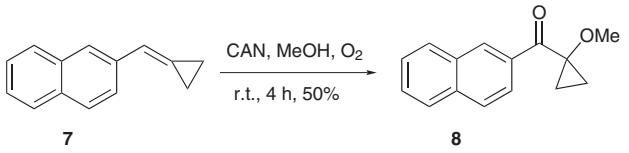
Table 1 CAN-Mediated Reaction of Diarylmethylenecyclopropanes with Oxygen and Methanol



Entry	R^1	R^2	Product	Yield (%)
1	Ph	Ph	**2b**	75
2	Ph	2-MeC_6H_4	**2c**	62
3	Ph	4-MeC_6H_4	**2d**	82
4	Ph	1-naphthyl	**2e**	73
5	Ph	2-naphthyl	**2f**	78
6	4-ClC_6H_4	4-ClC_6H_4	**2g**	57
7	4-$MeOC_6H_4$	Ph	**2h**	48

Interestingly, CAN-mediated reaction of the monosubstituted MCP **7** afforded methoxy-substituted aryl cyclopropyl ketone **8** along with a trace amount of cyclobutanone (Scheme 3). In this case, molecular oxygen presumably reacts at the benzylic site of the radical cation formed from **7**.[15] This may be attributed to the fact that the benzylic position of the radical cation is less sterically hindered when compared to the radical cations formed from diarylmethylenecyclopropanes.

In conclusion, we have uncovered an efficient CAN-mediated oxidative transformation of MCPs leading to the formation of cyclobutanones. The reaction may be of interest both from the mechanistic and synthetic standpoints.



Scheme 3

NMR spectra were recorded in $CDCl_3$ at 300 (^1H) and 75 (^{13}C) MHz on a Bruker 300 MHz FT-NMR spectrometer. Chemical shifts (δ) are reported relative to TMS (^1H) and $CDCl_3$ (^{13}C) as the internal standards. IR spectra were recorded on Bomem MB Series FT-IR spectrophotometer. Melting points were recorded on a Büchi melting point apparatus and are uncorrected. High-resolution mass spectra were recorded under EI/HRMS (at 5000 resolution) using JEOL JMS 600H mass spectrometer. Gravity column chromatography was performed on silica gel (100–200 mesh) in hexanes-EtOAc mixtures as eluent. Solvents were distilled prior to use. CAN used for the reactions was purchased from Aldrich Co. and was used without purification. Diarylmethylenecyclopropanes used were prepared from corresponding benzophenones according to the literature procedure.[13]

Diarylcyclobutanones; General Procedure

A solution of CAN (1.26 g, 2.3 mmol) in anhyd MeOH (20 mL), saturated with O_2 was added dropwise to an oxygenated solution of MCP **1** (1 mmol) in MeOH (10 ml) at r.t. The mixture was stirred for 4 h. It was then diluted with H_2O and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with brine and dried (Na_2SO_4). The residue obtained was subjected to column chromatography on silica gel using hexanes–EtOAc mixture (95:5) to afford pure product.

2a

Colorless viscous oil.

IR (neat): 1780, 1649, 1606, 1512, 1220, 1080 cm^{-1}.

^1H NMR: δ = 2.28 (s, 6 H), 2.77 (t, *J* = 8.4 Hz, 2 H), 3.13 (t, *J* = 8.4 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 4 H), 7.83 (d, *J* = 8.1 Hz, 4 H).

^{13}C NMR: δ = 21.3, 21.9, 25.9, 43.5, 75.9, 126.6, 129.1, 129.6, 130.5, 135.6, 136.6, 139.6, 142.9, 208.9.

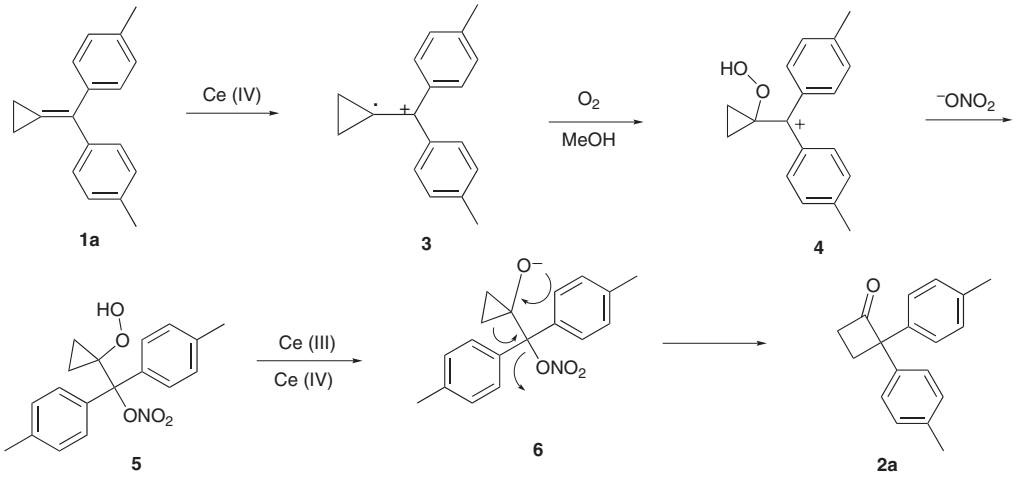
HRMS (EI): *m*/*z* calcd for $C_{18}H_{18}O$: 250.1358; found: 250.1368.

2b

Colorless viscous oil.

IR (neat): 3021, 1780, 1605, 1491, 1450, 1404, 1188, 1079 cm^{-1}.

^1H NMR: δ = 2.80 (t, *J* = 8.4 Hz, 2 H), 3.12 (t, *J* = 8.4 Hz, 2 H), 7.15–7.36 (m, 10 H).



Scheme 2

^{13}C NMR: δ = 25.7, 43.3, 76.2, 126.4, 126.9, 128.7, 142.1, 207.8.

HRMS (EI): *m*/*z* calcd for $C_{16}H_{14}O$: 222.1045; found: 222.1057.

2c
Colorless viscous oil.

IR (neat): 2931, 1780, 1605, 1583, 1478 cm^{-1}.

^{1}H NMR: δ = 2.03 (s, 3 H), 2.52–2.59 (m, 1 H), 3.01–3.24 (m, 3 H), 7.14–7.64 (m, 9 H).

^{13}C NMR: δ = 21.2, 24.6, 42.8, 76.5, 125.7, 126.4, 126.7, 126.8, 127.5, 128.6, 132.2, 136.2, 138.9, 140.3, 207.7.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}O$: 236.1201; found: 236.1222.

2d
Colorless viscous oil.

IR (neat): 1780, 1604, 1591, 1423 cm^{-1}.

^{1}H NMR: δ = 2.31 (s, 3 H), 2.79 (t, *J* = 8.7 Hz, 2 H), 3.13 (t, *J* = 8.7 Hz, 2 H), 7.07–7.35 (m, 9 H).

^{13}C NMR: δ = 21.0, 25.6, 43.3, 75.9, 126.2, 126.3, 126.8, 128.6, 129.4, 136.4, 139.2, 142.3, 208.5.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}O$: 236.1201; found: 236.1233.

2e
Colorless viscous oil.

IR (neat): 1778, 1605, 1510, 1421, 1220 cm^{-1}.

^{1}H NMR: δ = 2.67–2.75 (m, 1 H), 3.21–3.37 (m, 3 H), 7.15–7.89 (m, 12 H).

^{13}C NMR: δ = 25.6, 43.5, 76.3, 115.9, 124.3, 125.0, 125.7, 126.4, 126.9, 127.2, 128.7, 129.1, 131.8, 132.3, 133.3, 134.9, 139.4, 207.8.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}O$: 272.1201; found: 272.1201.

2f
Colorless viscous oil.

IR (neat): 1778, 1605, 1591, 1510, 1421 cm^{-1}.

^{1}H NMR: δ = 2.88 (t, *J* = 8.4 Hz, 2 H), 3.21 (t, *J* = 8.7 Hz, 2 H), 7.24–7.93 (m, 12 H).

^{13}C NMR: δ = 25.6, 43.5, 76.3, 115.7, 124.2, 125.5, 125.7, 126.4, 126.9, 127.7, 128.7, 129.1, 130.3, 130.4, 135.2, 137.2, 139.5, 208.4.

HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}O$: 272.1201; found: 272.1201.

2g
Colorless solid.

Mp 98–99 °C.

IR (KBr): 1780, 1651, 1489, 1400, 1088 cm^{-1}.

^{1}H NMR: δ = 2.78 (t, *J* = 8.4 Hz, 2 H), 3.18 (t, *J* = 8.4 Hz, 2 H), 7.26–7.27 (m, 8 H).

^{13}C NMR: δ = 25.7, 43.5, 74.9, 127.6, 129.0, 133.2, 140.1, 207.1.

HRMS (FAB, [M + H]): *m*/*z* calcd for $C_{16}H_{12}Cl_2O$: 291.02; found: 291.02.

2h
Colorless viscous oil.

IR (neat): 3063, 2988, 1776, 1645, 1600, 1515 cm^{-1}.

^{1}H NMR: δ = 2.82 (t, *J* = 8.4 Hz, 2 H), 3.14 (t, *J* = 8.4 Hz, 2 H), 3.75 (s, 3 H), 6.80–7.34 (m, 9 H).

^{13}C NMR: δ = 25.7, 43.3, 55.1, 75.6, 113.8, 126.4, 126.8, 127.5, 128.7, 138.4, 142.4, 158.4, 208.6.

HRMS (EI): *m*/*z* calcd for $C_{17}H_{16}O_2$: 252.1150; found: 252.1140.

8
Yellow viscous liquid.

IR (neat): 3063, 1689, 1571, 1510 cm^{-1}.

^{1}H NMR: δ = 1.26 (dd, *J* = 4.2, 8.1 Hz, 2 H), 1.48 (dd, *J* = 4.2, 8.1 Hz, 2 H), 3.19 (s, 3 H), 7.25–8.33 (m, 7 H).

^{13}C NMR: δ = 16.5, 57.2, 69.2, 125.1, 126.5, 127.8, 128.1, 128.2, 129.8, 130.9, 135.5, 198.8.

HRMS (EI): *m*/*z* calcd for $C_{15}H_{14}O_2$: 226.0994; found: 226.0984.

Acknowledgment

T.D.S. and K.M. thank the Council of Scientific and Industrial Research, Government of India for research fellowships, Mrs. Soumini Mathew for NMR spectra and Mrs. S. Viji for HRMS data.

References

(1) (a) Norbeck, D. W.; Kern, E.; Hayashi, S.; Rosenbrook, W.; Sham, H.; Herrin, T.; Plattner, J. J.; Erisckson, J.; Clement, J.; Swanson, R.; Shipkowitz, N.; Hardy, D.; Marsh, K.; Arnett, G.; Shannon, W.; Broder, S.; Mitsuya, H. *J. Med. Chem.* **1990**, *33*, 1281. (b) Brown, B.; Hegedus, L. S. *J. Org. Chem.* **1998**, *63*, 8012.
(2) Carnmalm, B.; Ramsby, S.; Renyi, A. L.; Ross, S. B.; Orgen, S. O.; Stjernstorm, N. E. *J. Med. Chem.* **1978**, *21*., 78.
(3) For a review, see: Salaun, J. In *Science of Synthesis*, Vol. 26; Cossy, J., Ed.; Thieme: Stuttgart, **2004**, 557.
(4) (a) Brandi, W. T. *Tetrahedron* **1981**, *37*, 2949. (b) Snider, B. B. *Chem. Rev.* **1988**, *88*, 793. (c) Sierra, M. A.; Hegedus, L. S. *J. Am. Chem. Soc.* **1989**, *111*, 2335.
(5) (a) Trost, B. M.; Bogdanowicz, M. J. *J. Am. Chem. Soc.* **1973**, *95*, 5321; and references cited therein. (b) Trost, B. M.; Brandi, A. *J. Am. Chem. Soc.* **1984**, *106*, 5041. (c) Turro, N. J.; Gagosian, R. B. *J. Am. Chem. Soc.* **1973**, *92*, 5321; and references cited therein. (d) Periasamy, M.; Jayakumar, K. N.; Bharathi, P. *J. Org. Chem.* **2005**, *70*, 5420.
(6) Synthesis of MCPs: (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213.
(7) (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111. (b) Brase, S.; de Meijere, A. *Angew. Chem., Int. Ed. Eng.* **1995**, *34*, 2545.
(8) Shao, L. X.; Shi, M. *Eur. J. Org. Chem.* **2004**, 426.
(9) Huang, J.-W.; Shi, M. *J. Org. Chem.* **2005**, *70*, 3859.
(10) (a) Heiba, E. I.; Dessau, R. M. *J. Am. Chem. Soc.* **1971**, *93*, 524. (b) Baciocchi, E.; Civitarese, G.; Ruzziconi, R. *Tetrahedron Lett.* **1987**, *28*, 5357. (c) Nair, V.; Mathew, J.; Prabhakaran, J. *Chem. Soc. Rev.* **1997**, 127.
(11) (a) Nair, V.; Mathew, J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 187. (b) Nair, V.; Nair, L. G.; George, T. G.; Augustine, A. *Tetrahedron* **2000**, *56*, 7607. (c) Nair, V.; Sheeba, V.; Panicker, S. B.; George, T. G.; Rajan, R.; Balagopal, L.; Vairamani, M.; Prabhakar, S. *Tetrahedron* **2000**, *56*, 246. (d) Nair, V.; Rajan, R.; Rath, N. P. *Org. Lett.* **2002**, *4*, 1575.
(12) (a) Young, L. B. *Tetrahedron Lett.* **1968**, 5105. (b) Takemoto, Y.; Ohra, T.; Furuse, S.-I.; Koike, H.; Iwata, C. *J. Chem. Soc., Chem. Commun.* **1994**, 1529. (c) Nair, V.; Panicker, S. B.; Mathai, S. *Res. Chem. Intermed.* **2003**, *29*, 227. (d) Nair, V.; Rajan, R.; Mohanan, K.; Sheeba, V. *Tetrahedron Lett.* **2003**, *44*, 4585.
(13) (a) Utimoto, K.; Tamura, M.; Sisido, K. *Tetrahedron* **1973**, *29*, 1169. (b) Siriwardhana, A. I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* **2003**, *44*, 4547.

(14) While this manuscript was under completion, Chen et al. reported the synthesis of 2,2-diarylcyclobutanones using the CAN-mediated reaction of MCPs in MeOH–THF–H_2O mixture: Chen, W.; Huang, X.; Zhou, H.; Ren, L. *Synthesis* **2006**, 609A. Comparison of the results reveals that our reactions afford about 25–30% higher yields of the products. In addition, on the basis of work in our laboratory and elsewhere,[15,16] it is strongly felt that the mechanistic postulate of Chen et al. is untenable.

(15) Nair, V.; Balagopal, L.; Rajan, R.; Mathew, J. *Acc. Chem. Res.* **2004**, *37*, 21; and references cited therein.

(16) Rossle, M.; Wermer, T.; Frey, W.; Christoffers, J. *Eur. J. Org. Chem.* **2005**, 5031; and references cited therein.