Tetrahedron Letters 50 (2009) 5110–5112

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Phenylsulfonyl as a directing group for nitrile oxide cycloadditions and *m*CPBA epoxidations

Jeffrey D. Butler, Michael B. Donald, Zhensheng Ding, James C. Fettinger, Mark J. Kurth *

Department of Chemistry, University of California, One Shields Avenue, Davis, CA 95616, USA

ARTICLE INFO

Article history:
Received 1 May 2009
Revised 18 June 2009
Accepted 19 June 2009
Available online 25 June 2009

ABSTRACT

An unexpected selectivity trend in the nitrile oxide cycloaddition and epoxidation reactions of 4,4-disubstituted cyclopentenes is reported. A variety of facially distinct, 'X-' and 'Y-substituted' cyclopentenes were investigated.

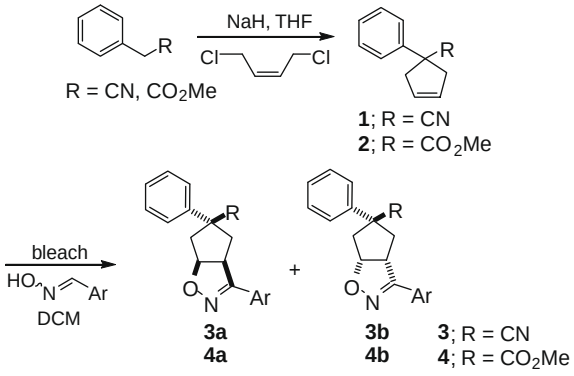
Nitrile oxide cycloadditions are exploited to deliver both the saturated (isoxazolines) and unsaturated (isoxazoles) heterocycles;[1] these products have considerable synthetic application as natural product precursors[2,3] and biological probes.[4,5] However, their usefulness is often handicapped by the inherent generation of regio- and/or stereoisomers.[6] Synthetic methodologies continue to be developed to address these issues,[6] with allylic H-bonding,[7,8] Lewis acids,[9] metal chelation,[10–12] and coulombic interactions[13] having been exploited as control elements. Examples of regioselective nitrile oxide cycloadditions to vinyl sulfone[14] and phosphonate[15] dipolarophiles are also represented in the literature. Computational and experimental studies[16] have provided insights in the cycloadditions of unsymmetrical dipolarophiles and regioselectivities are often explained by examining HOMO/LUMO interactions between the dipole and dipolarophile.[15] Herein, we report variable nitrile oxide cycloaddition selectivity in cyclopentene-based systems which are related to our previous report of a selective *m*CPBA-mediated epoxidation.[17]

Our investigation began as an effort to synthesize an array of 3a*H*-cyclopenta[*d*]isoxazoles. The effort began on two fronts as detailed in Schemes 1 and 2. Following Scheme 1, base-mediated dialkylation of 2-phenylacetonitrile (→**1**) and methyl 2-phenylacetate (→**2**) followed by nitrile oxide cycloaddition utilizing Huisgen's method (e.g., an aryl oxime + bleach in DCM) gave **3a**/**3b** and **4a**/**4b**. Despite the fact that the A-value[18] of phenyl (~3.0 kcal/mol) is significantly greater than the *A*-value of either nitrile or carbomethoxy (0.2 and 1.2 kcal/mol, respectively), there was essentially no facial selectivity observed in these cycloadditions (Table 1, entries 1–4).

However, in the parallel route (Scheme 2) utilizing chemistry similar to that presented in Scheme 1, sulfone **5** was prepared by S-alkylation of sodium benzenesulfinate with chloroacetonitrile in ethylene glycol.[19] Subsequent dialkylation (sodium hydride + *cis*-1,4-dichloro-2-butene) gave cyclopentene **6a** in 70% overall yield. Nitrile oxide cycloadditions (aryl oxime + bleach in DCM) with this dipolarophile delivered **9a** and **9b** in ⩾19:1 diastereoselectivity (Table 1, entry 5). The stereochemistry of **9a** (Ar = *m*-BrC_6H_4) was established by X-ray crystallography (see Fig. 1). Facial selectivity with a slightly more reactive nitrile oxide (entry 6) is comparable.

Initially, we expected the system with the largest *A*-value[18] discrepancy between the two substituents to deliver the greatest facial selectivity. However, when the *A*-values of phenylsulfonyl (~2.5 kcal/mol) and nitrile (~0.2 kcal/mol) are contrasted with those of the phenyl-substituted cases from Scheme 1, this simple expectation is not met.

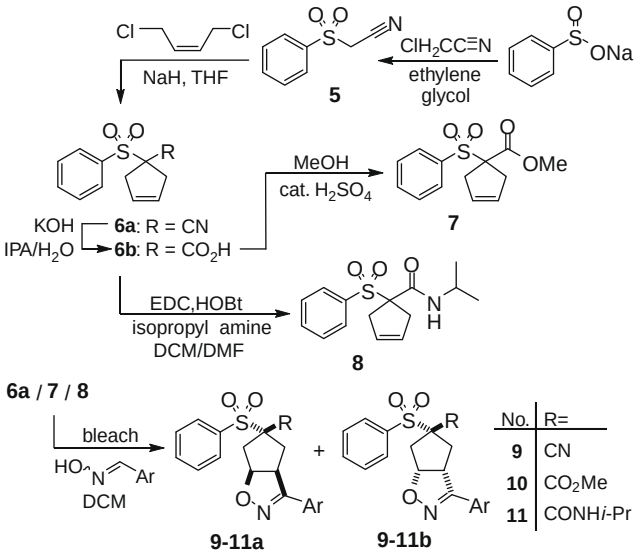
With these contrasting results (Table 1 entries 1–4 vs entries 5–6) in hand, we set out to make a small collection of phenylsulfonyl-substituted examples to further probe the limits of their unexpected facial selectivity. Ester (**7**) and amide (**8**) (phenylsulfon-4-yl)cyclopentene analogs were prepared by nitrile hydrolysis (**6a**→**6b**) followed by Fisher esterification (**6b**→**7**) and amidation



Scheme 1. Synthetic route to selected phenyl-substituted cyclopentenes and their isoxazoline derivatives.

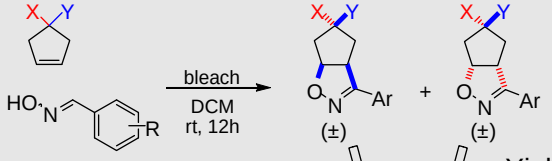
* Corresponding author. Tel.: +1 530 752 8192; fax: +1 530 752 8995.
E-mail address: mjkurth@ucdavis.edu (M.J. Kurth).

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.06.100



Scheme 2. Synthetic route to various phenylsulfonyl-substituted cyclo-pentenes and their 3a*H*-cyclopenta[*d*]isoxazole derivatives.

Table 1
Summary of nitrile oxide cycloaddition selectivity data



entry	X=	Y=	R=	% a*	% b*	Yield (%)**
1	Ph	CN	*m*-Br	55	45	86
2	Ph	CN	*p*-OCH_3	53	47	75
3	Ph	CO_2Me	*m*-Br	54	46	70
4	Ph	CO_2Me	*p*-OCH_3	52	48	60
5	SO_2Ph	CN	*m*-Br	95	5	68
6	SO_2Ph	CN	*p*-OCH_3	96	4	52
7	SO_2Ph	CO_2Me	*m*-Br	91	9	61
8	SO_2Ph	CO_2Me	*p*-OCH_3	93	7	57
9	SO_2Ph	CONH*i*-Pr	*m*-Br	85	15	64
10	SO_2Ph	CONH*i*-Pr	*p*-OCH_3	87	13	54
11	SO_2Ph	Ph	*m*-Br	83	17	80
12	SO_2Ph	Ph	*p*-OCH_3	73	27	79
13	SPh	CN	*m*-Br	51	49	41
14	SPh	CN	*p*-OCH_3	52	48	50
15	SO_2Me	CN	*m*-Br	90	10	54
16	SO_2Me	CN	*p*-OCH_3	89	11	60
17	$PO(OEt)_2$	Ph	*m*-Br	55	45	55
18	$PO(OEt)_2$	Ph	*p*-OCH_3	49	51	45
19	$PO(OEt)_2$	CN	*m*-Br	51	49	61
20	$PO(OEt)_2$	CN	*p*-OCH_3	50	50	50

* Percentages calculated by LC trace and NMR integration.
** Combined yield.

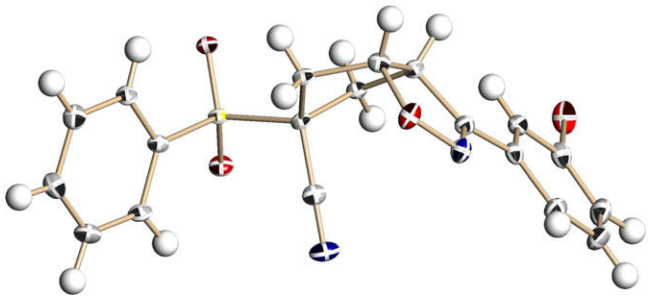


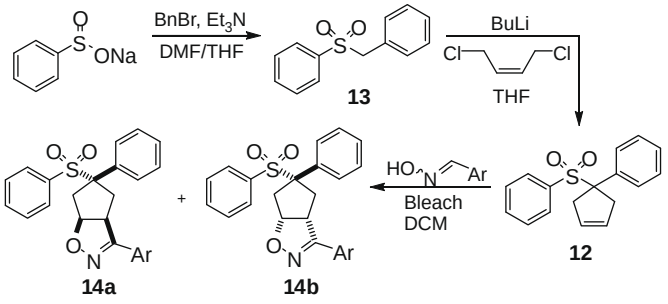
Figure 1. X-ray crystal structure of cycloadduct **9a**.

(**6b**→**8**), respectively. These dipolarophiles undergo nitrile oxide cycloadditions to give predominately diastereomers **10a** and **11a** with quite good selectivity (85:15–93:7; see Table 1, entries 7–10).

These facially selective cycloaddition results with (phenylsulfon-4-yl)cyclopentenes (e.g., Table 1, entries 5–10) led us to prepare analogs where the phenylsulfonyl substituent was matched with a phenyl substituent (**13**). This analog was chosen to explore the selectivity when both substituents (X and Y) have increased steric bulk.

Following the literature procedures,[17] the synthesis of **12** began with the S-alkylation of sodium benzenesulfinate with benzyl bromide, generating benzylsulfonylbenzene **13** in excellent yield. α,α-Dialkylation of **13** using strong base and *cis*-1,4-dichloro-2-butene gave **12** in 65% overall yield. Nitrile oxide cycloadditions were then performed (aryl oxime + bleach in DCM) to give **14a**/**14b** (Scheme 3). Employing 3-bromobenzaldehyde oxime resulted in an 83:17 ratio of diastereomers (Table 1, entry 11). The resulting mixture was recrystallized from ethyl acetate/hexanes and the major diastereomer was analyzed by X-ray crystallography to establish that this cycloaddition reaction also proceeded predominantly with the nitrile oxide adding trans to the phenylsulfone moiety (see Fig. 2).

In an attempt to probe whether coulombic interactions with the sulfone or steric effects of the phenyl ring leads to a destabilizing



Scheme 3. Synthetic route to (1-phenylcyclopent-3-enylsulfonyl)benzene (**12**) and 3a*H*-cyclopenta[*d*]isoxazole derivatives (**14a**/**14b**).

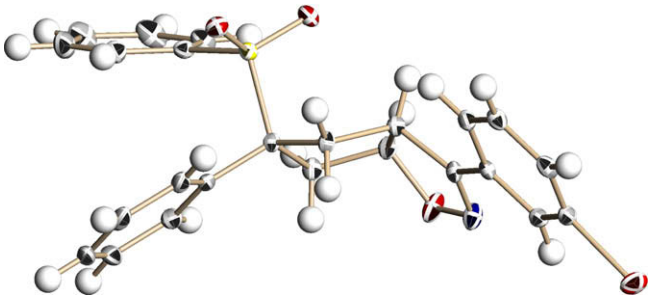


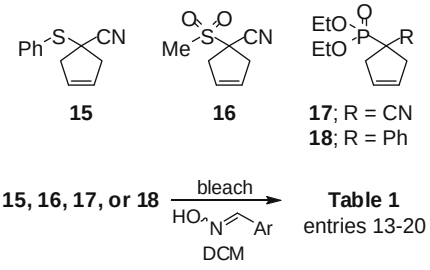
Figure 2. X-ray crystal structure of cycloadduct **14a**.

interaction with the nitrile oxide and hence the unexpectedly high trans (e.g., **9a**/**10a**/**11a**/**14a**) selectivity observed, we next prepared cyclopentenes with sulfide (**15**), methylsulfone (**16**), and diethyl phosphonate (**17** and **18**) substituents (Scheme 4).

Sulfide analog **15** shows little facial selectivity. In contrast, methylsulfone analog **16** shows good diastereoselectivity (Table 1, entries 13–16). The examples employing a diethyl phosphonate group in place of the phenylsulfonyl show little facial selectivity and, in this regard, are similar to the phenyl-substituted cases from Scheme 1. These data are tabulated in Table 1, entries 17–20.

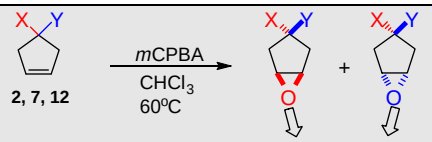
To extend and further generalize the facial directing properties of the phenylsulfonyl moiety in *m*CPBA-mediated epoxidations, we exposed a selection of our 4,4-disubstituted cyclopentenes (**2**, **7**, and **12**; Table 2) to epoxidation conditions yielding **19a**/**19b**, **20a**/**20b**, and **21a**/**21b**. The *m*CPBA-mediated epoxidation of **12** gives only **21a** and, in parallel, the epoxidation of **7** is also completely selective yielding only **20a**. Diastereomer **20a** was analyzed by X-ray crystallography to establish that epoxidation also proceeds trans to the phenylsulfone moiety (see Fig. 3). This is contrasted by the mediocre selectivity observed in the epoxidation of **2** which yields a 2.5:1 mixture of **19a** and **19b**.

Although the origin of this sulfone-based facial selectivity remains unclear, an interesting trend in our 4,4-disubstituted cyclopentenes is observed. All of the sulfone-substituted cyclopentenes are quite selective, even when steric disparity between the two cyclopentene substituents is not large (compare entries 5–12 and 15–16, Table 1). This suggests that cyclopentene conformation as well as sulfone-based coulombic interactions lead to the observed selectivity trend. As a consequence, the sulfide analog of sulfone **6a**, cyclopentene **15**, shows no selectivity (entries 5–6 and 13–14)[13] and exchanging the sulfone substituent for a phenyl substituent also leads to negligible selectivity (entries 1–4, Table 1). Likewise, exchanging the sulfone for a diethyl phosphonate leads to much reduced facial selectivity (entries 17–20, Table 1). Applications of these selective trends are currently under investigation and will be reported in due course.



Scheme 4. Synthetic route to selected cyclopentenes and their 3a*H*-cyclopenta[*d*]isoxazole derivatives.

Table 2
Synthetic scheme and tabulated selectivity data



Rxn	X=	Y=	% a	% b	Yield (%)
2 → **19**	Ph	CO_2Me	70	30	60
7 → **20**	SO_2Ph	CO_2Me	100	0	64
12 → **21**	SO_2Ph	Ph	100	0	75

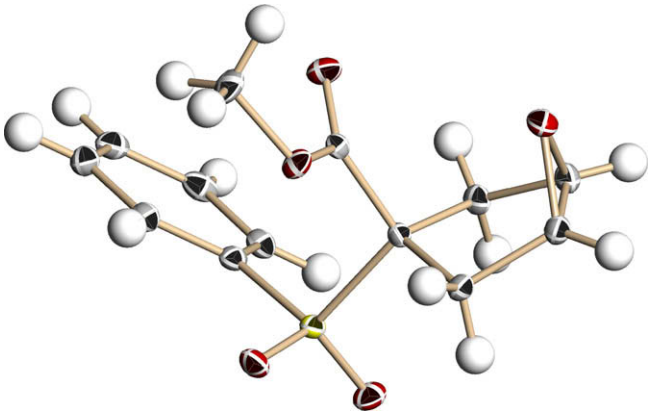


Figure 3. X-ray crystal structure of epoxide **20a**.

Acknowledgments

The authors thank the National Science Foundation (CHE-0614756) for their financial support of this work. NMR spectrometers used were partially funded by the National Science Foundation (CHE-0443516 and CHE-9808183).

Supplementary data

^{1}H NMR and ^{13}C NMR data are provided. Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 730064, 730065, and 730066. Copies of these data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.100.

References and notes

1. Mabrour, M.; Bougrin, K.; Benhida, R.; Loupy, A.; Soufiaoui, M. *Tetrahedron Lett.* **2006**, *48*, 443–447.
2. Furstner, A.; Fenster, M. D. B.; Fasching, B.; Godbout, C.; Radkowski, K. *Angew. Chem., Int. Ed.* **2006**, *45*, 5510–5515.
3. Nath, M.; Mukhopadhyay, R.; Bhattacharjya, A. *Org. Lett.* **2006**, *8*, 317–320.
4. Simoni, D.; Grisolia, G.; Giannini, G.; Roberti, M.; Rondanin, R.; Piccagli, L.; Baruchello, R.; Rossi, M.; Romagnoli, R.; Invidiata, F. P.; Grimaudo, S.; Jung, M. K.; Hamel, E.; Gebbia, N.; Crosta, O. L.; Abbadessa, O. V.; Di Cristina, A.; Dusonchet, L.; Meli, M.; Tolomeo, M. *J. Med. Chem.* **2005**, *48*, 723–736.
5. Del Corral, J. M. M.; Gordaliza, M.; Castro, M. A.; Lopez-Vazquez, M. L.; Garcia-Gravalos, M. D.; Broughton, H. B.; San Feliciano, A. *Tetrahedron* **1997**, *53*, 6555–6564.
6. Pellissier, H. *Tetrahedron* **2007**, *63*, 3235–3285.
7. Becker, N.; Carreira, E. M. *Org. Lett.* **2007**, *9*, 3857–3858.
8. Quadrelli, P.; Fassardi, V.; Cardarelli, A.; Caramella, P. *Eur. J. Org. Chem.* **2002**, 2058–2065.
9. Brinkmann, Y.; Madhushaw, R. J.; Jazzar, R.; Bernardinelli, G.; Kuendig, E. P. *Tetrahedron* **2007**, *63*, 8413–8419.
10. Sibi, M. P.; Itoh, K.; Jasperse, C. P. *J. Am. Chem. Soc.* **2004**, *126*, 5366–5367.
11. Tsuji, M.; Ukaji, Y.; Inomata, K. *Chem. Lett.* **2002**, 1112–1113.
12. Kanemasa, S.; Kobayashi, S.; Nishiuchi, M.; Yamamoto, H.; Wada, E. *Tetrahedron Lett.* **1991**, *32*, 6367–6370.
13. Kim, K. S.; Kim, B. H.; Park, W. M.; Cho, S. J.; Mhin, B. J. *J. Am. Chem. Soc.* **1993**, *115*, 7472–7477.
14. Rai, K. M. L.; Hassner, A. *Synth. Commun.* **1997**, *27*, 467–472.
15. Ye, Y.; Zheng, Y.; Xu, G.-Y.; Liu, L.-Z. *Heteroat. Chem.* **2003**, *14*, 254–257.
16. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Eur. J. Org. Chem.* **1998**, 1823–1832.
17. Cheng, W.-C.; Kurth, M. J. *J. Org. Chem.* **2002**, *67*, 4387–4391.
18. Corey, E. J.; Feiner, N. F. *J. Org. Chem.* **1980**, *45*, 765–780.
19. Sukata, K. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 613–614.