

New Entry into β -Lactams via Reaction of Dimethoxycarbene with Isocyanates

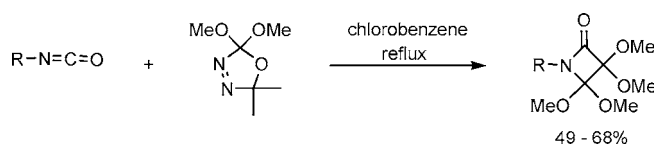
James H. Rigby,* Jean-Christophe Brouet, Patrick J. Burke, Stephanie Rohach, Shyama Sidique, and Mary Jane Heeg

Department of Chemistry, Wayne State University, Detroit, Michigan 48202-3489

jhr@chem.wayne.edu

Received May 4, 2006

ABSTRACT

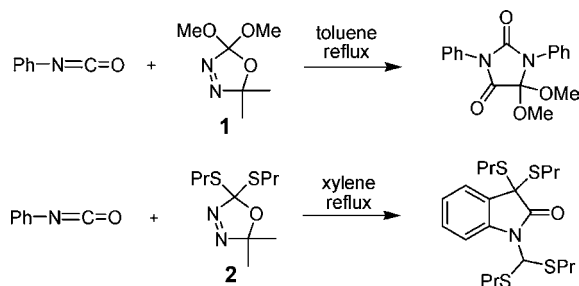


Highly substituted β -lactams have been isolated as the major product of the reaction of dimethoxycarbene with selected isocyanates. This reaction offers the potential for rapid access into a variety of highly functionalized species.

Nucleophilic carbenes have a characteristic reactivity profile that differs markedly from other classes of carbenes.¹ The nucleophilic character of these reactive intermediates stems from π -donation of heteroatom substituents flanking the divalent carbene center.² These species were traditionally difficult to generate but have become much more accessible with the advent of oxadiazoline precursors such as **1** and **2** (Scheme 1), which are reasonably stable and decompose under controlled thermolysis conditions.³

Hydantoin or indolone species have been previously reported as the primary products obtained from the reaction of nucleophilic carbenes with isocyanates. The specific pathway followed by these transformations depends on factors such as the type of carbene employed and the substitution pattern of the isocyanate. A typical example of this reactivity diversity is illustrated by the reaction of phenyl isocyanate with dimethoxycarbene,⁴ which leads to a hydantoin, or bis(propylthio)carbene,⁵ which affords the corresponding indolone (Scheme 1).

Scheme 1. Reported Products of Nucleophilic Carbenes and Phenyl Isocyanate



Disclosed herein is the production of yet a third species, a β -lactam, in moderate to good yields when dimethoxyoxadiazoline is decomposed in the presence of select isocyanates by virtue of a simple change in reaction conditions. Specifically, simply replacing toluene or xylene with chlorobenzene as solvent afforded a β -lactam as the principal product instead of the expected hydantoin.

With this advance, one can control whether a hydantoin or a β -lactam is produced preferentially (Scheme 2). This development has further expanded the utility of nucleophilic carbenes in heterocyclic synthesis.

(1) (a) Zhou, H.; Mloston, G.; Warkentin, J. *Org. Lett.* **2005**, *7*, 487. (b) Spino, C.; Rezaei, H.; Dupont-Gaudet, K.; Belanger, F. *J. Am. Chem. Soc.* **2004**, *126*, 9926. (c) Nair, V.; Bindu, S.; Sreekumar, V.; Chiaroni, A. *Org. Lett.* **2002**, *4*, 2821. (d) Rigby, J. H.; Wang, Z. *Org. Lett.* **2002**, *4*, 4289. (e) Dawid, M.; Mloston, G.; Warkentin, J. *Org. Lett.* **2001**, *3*, 2455.

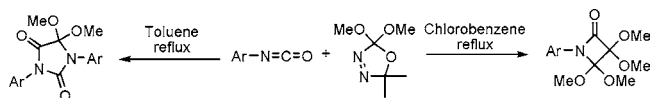
(2) (a) Couture, P.; Warkentin, J. *Can. J. Chem.* **1997**, *75*, 1281. (b) Arduengo, A. J., III; Goerlich, J. R.; Marshall, W. J. *J. Am. Chem. Soc.* **1995**, *117*, 11027. (c) Ge, C. J.; Jefferson, E. A.; Moss, R. A. *Tetrahedron Lett.* **1993**, *34*, 7549.

(3) (a) El-Saidi, M.; Kassam, K.; Pole, D. L.; Tadey, T.; Warkentin, J. *J. Am. Chem. Soc.* **1992**, *114*, 8751. (b) Rigby, J. H.; Danca, M. D. *Tetrahedron Lett.* **1999**, *40*, 6891.

(4) (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. *Chem. Ber.* **1973**, *106*, 2174. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1971**.

(5) Rigby, J. H.; Danca, M. D. *Tetrahedron Lett.* **1999**, *40*, 6891.

Scheme 2. Solvent Effects on Carbene Additions to Aryl Isocyanates



β -Lactams are the key substructural unit in one of the most important classes of antibiotics.⁶ As resistant bacteria continue to emerge, the synthesis and development of new β -lactam derivatives could provide new clinical candidates for the treatment of these strains. The current methodology produces highly substituted β -lactam derivatives that could be useful in this regard.

Table 1. Summary of Examples of β -Lactam Products^{a,b}

A	B	C	
R (A)	time (min)	% yield (B)	% yield (C)
1	45	49 ^c	0
2	20	68 ^c	0
3 ^d	45	57	3
4	45	65	14
5	45	55 ^c	20

^a All reactions were performed at 0.01 M in refluxing chlorobenzene. ^b Acyl azides rearrange in situ to form isocyanates. ^c The product structure was confirmed by X-ray diffraction studies in this case. ^d A small yield (6%) of an ortho ester product was also isolated. A product similar to this was reported in 2004 and is believed to follow a similar mechanism.⁷

The results of these studies are summarized in Table 1. The best yields were obtained at 0.01 M concentration. When the reaction was performed at higher concentrations, the yields of the β -lactam decreased and the yields of the hydantoin product increased.

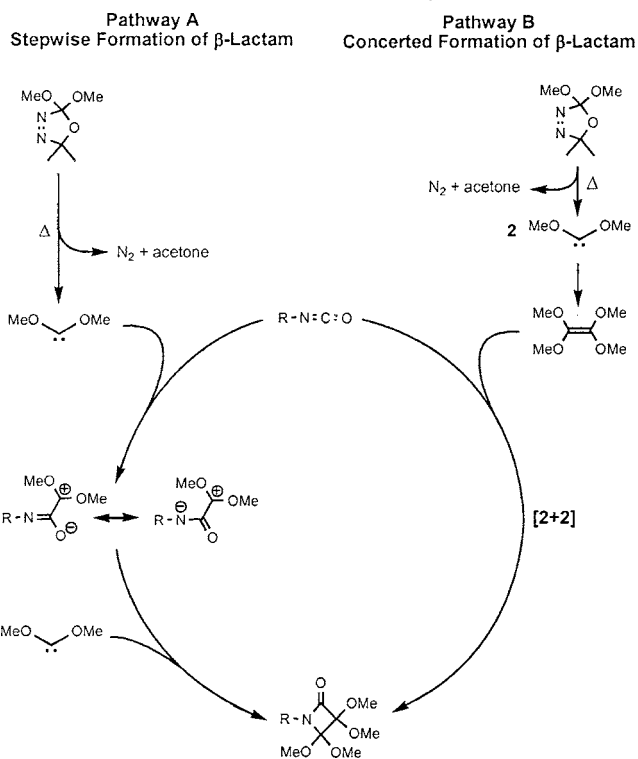
A 1964 publication by Hoffmann⁸ reported that a β -lactam product was isolated in the reaction of 1,2,3,4-tetramethoxy-

(6) Fisher, J. F.; Meroueh, S. O.; Mobashery, S. *Chem. Rev.* **2005**, *105*, 395.

ethylene and phenyl isocyanate. Subsequently, hydantoin products were principally observed in the reaction between phenyl isocyanate and various dimethoxycarbene precursors.⁹

On the basis of the Hoffmann report, it was initially assumed that this new reaction was taking place through a [2+2] cycloaddition of the isocyanate and the 1,2,3,4-tetramethoxyethylene that was rapidly formed by initial dimerization of dimethoxycarbene (pathway B, Scheme 3).

Scheme 3. Mechanistic Possibilities for β -Lactam Formation



To test this notion, control experiments were performed with the purified dimer of dimethoxycarbene. These control experiments led to some interesting results. The β -lactam product was isolated in small yields (less than 10%) when the reaction mixture was refluxed for several hours at concentrations greater than 0.5 M (pathway B, Scheme 3). However, none of the product was isolated when the reaction was performed with a purified carbene dimer at concentrations consistent with those under which the β -lactam product was observed. This led to the conclusion that under these conditions the β -lactam formation likely took place in a stepwise fashion (pathway A, Scheme 3), exclusive of the dimer. Indeed, the proposed mechanism is not without precedent as dimethoxycarbene (generated at 50 °C) has been recently reported to react with electrophilic alkenes, via a

(7) Dawid, M.; Reid, D. L.; Warkentin, J.; Mloston, G. *J. Phys. Org. Chem.* **2005**, *18*, 86

(8) Hoffmann, R. W.; Hauser, H. *Tetrahedron Lett.* **1964**, 197.

(9) (a) Hoffmann, R. W.; Steinbach, K.; Dittrich, B. *Chem. Ber.* **1973**, *106*, 2174. (b) Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 529. (c) Lemal, D. M.; Gosselink, E. P.; McGregor, S. D. *J. Am. Chem. Soc.* **1966**, *88*, 582.

zwitterionic intermediate, to provide functionalized cyclobutane products.^{1a}

The initial investigations that led to the observation of β -lactam products employed chlorobenzene as solvent. It is noteworthy that by simply changing the solvent one can access either a β -lactam or a hydantoin as the major product. For example, in the case of entry 4 (Table 1), when the solvent was changed from chlorobenzene to toluene, the product distribution changed from 65% β -lactam/14% hydantoin to 27% β -lactam/50% hydantoin. Furthermore, by increasing the reaction concentration in toluene from 0.01 to 0.04 M, we observed 80% hydantoin accompanied by 15% β -lactam. It is not completely understood why changing the solvent from toluene to chlorobenzene resulted in such a dramatic change in the course of the reaction. It is assumed that the more polar nature and the high boiling point of chlorobenzene are likely playing a role.

To evaluate these possibilities, the reaction depicted in entry 2 (Table 1) was performed in toluene, chlorobenzene, and ethylbenzene. When the solvent was changed from chlorobenzene (bp 132 °C, $\epsilon = 5.62$)¹⁰ to toluene (bp 111

(10) Gordan, A. J.; Ford, R. A. *The Chemists Companion: A Handbook of Practical Data, Techniques, and References*; John Wiley & Sons: New York, 1972.

°C, $\epsilon = 2.38$),¹⁰ no β -lactam was isolated. When the reaction was performed in ethylbenzene (bp 136 °C, $\epsilon = 2.41$),¹⁰ a solvent that approximates the boiling point of chlorobenzene and the polarity of toluene, a complex reaction mixture was obtained from which β -lactam was isolated in 33% yield. This result can be contrasted with the 68% yield of β -lactam when the reaction was performed in chlorobenzene. Further investigations into the mechanism of this reaction that are currently underway could lead to a better understanding of the effect that solvent has on this reaction.

In summary, a new reaction pathway has been observed between dimethoxycarbene and isocyanates, leading to the rapid formation of highly substituted β -lactam products in moderate to good yields.

Acknowledgment. The authors wish to thank the National Science Foundation for their generous support of this research.

Supporting Information Available: General experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>

OL061101Q