Pergamon

Tetrahedron Letters, Vol. 38, No. 40, pp. 6981-6984, 1997

0040-4039/97 $17.00 + 0.00

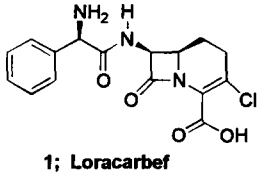
PII: S0040-4039(97)01669-9

Use of an Iodonium Ylide in the Synthesis of p-Nitrobenzyl (6R, 7S) 3-hydroxy-8-oxo-7-phenoxyacetamido-1-azabicyclo[4.2.0]octa-2-ene-2-carboxylate

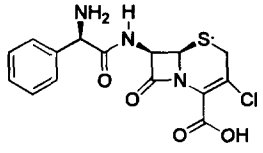
Radhe K. Vaid* and Thomas E. Hopkins
Contribution from Lilly Research Laboratories; Development and Technical Services
Eli Lilly and Company; Clinton Laboratories; Clinton, IN 47832

Abstract: p-Nitrobenzyl (6R,7S)-3-hydroxy-8-oxo-7-phenoxyacetamido-1-azabicyclo [4.2.0]octa-2-ene-2-carboxyate (**6**) was synthesized utilizing rhodium(II)- or acid-catalyzed cyclization of iodonium ylide (**5**). The iodonium ylide (**5**) was easily prepared from the corresponding β-keto ester (**4**) and [(diacetoxy)iodo]benzene in good yield. © 1997 Elsevier Science Ltd.

Loracarbef (**1**), the 1-carba analog of Cefaclor (**2**) is an orally active antibiotic marketed by Eli Lilly and Company.[1,2] In the synthesis of carbacephalosporins the stereospecific construction of the bicyclic ring system is a

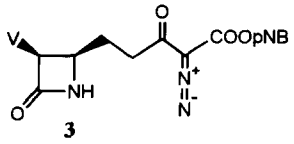


1; Loracarbef



2; Cefaclor

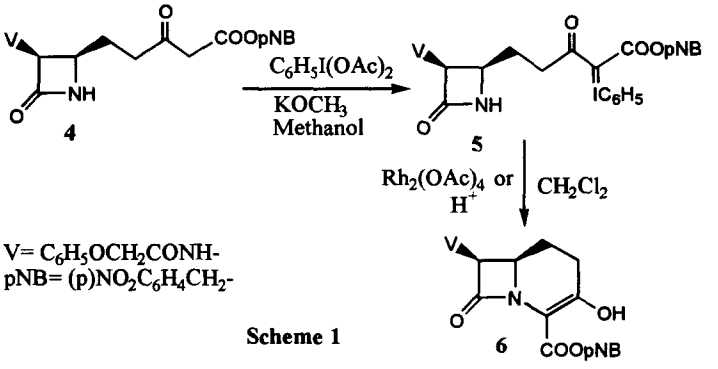
major challenge. One of the previous approaches investigated involved Rh(II)-catalyzed intramolecular carbene insertion from corresponding α-diazo derivative of p-nitrobenzyl (2R,*cis*)β, 4-dioxo-3-phenoxyacetamido-2-azetidinepentane carboxylate (**3**).[3] The nature and synthesis of the α-diazo β-dicarbonyl compound **3** on a large scale makes this route less attractive.



3

V= $C_6H_5OCH_2CONH$-; pNB= -$CH_2C_6H_4NO_2$(p)

Iodonium ylides derived from β-dicarbonyl compounds have been used for cyclopropanation and insertion reactions.[4] Recently, the use of an iodonium ylide in an intramolecular insertion reaction to construct the bicyclic ring system of carbapenems has been also reported.[5] In this paper, we report an efficient and facile method for the stereospecific synthesis of p-nitrobenzyl (6R, 7S)- 3-hydroxy-8-oxo-7-phenoxyacetamido-1-azabicyclo[4.2.0]octa-2-ene-2-carboxylate, **6**, (a key intermediate to the carbacephalosporins) from iodonium ylide, **5** *via* the use of hypervalent iodine compounds[6]. (Scheme 1)



Scheme 1

The preparation of the iodonium ylide **5** was accomplished using the following methodology. A solution of [(diacetoxy)iodo]benzene (0.644g, 0.0020mole) in methanol (20ml) was treated with potassium methoxide (0.28gm, 0.041mole) in methanol. The β-ketoester, **4** (0.94gm, 0.0020mole) was added to the resulting solution. The contents were stirred at room temperature for 1.5 hr during which the iodonium ylide **5** precipitated. The reaction mixture was diluted with 15 ml of cold water and the product was isolated by filtration and dried under vacuum. Thus, 1.28gm of **5** was obtained in 88.3% yield. The ylide **5** was characterized by a variety of analytical techniques.[7] The ylide, **5**, was used without further purification in the ring closure step.

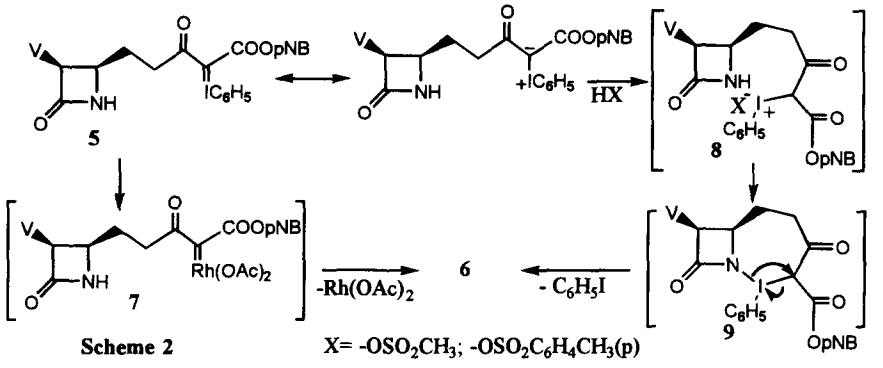
The ring closure reaction was studied using several transition metal catalysts. The results obtained for each catalyst are listed in Table 1. The use of commonly employed Cu(I)Cl and copper acetylacetone as catalysts in the iodonium ylide reactions did not yield the desired product, **5**. The use of Cu(I)I or $Cu(I)OSO_2CF_3$ and $Pd(OAC)_2$ in the ring cyclization reaction also lead to the formation of a complex mixtures.

Based upon i) the analogy between β-dicarbonyl iodonium ylides and α-diazo β-dicarbonyl compounds[6], and ii) the reported success in the ring closure in carapenems using idonium ylides[5], we attempted the use of dirhodium(II) tetraacetate for the ring closure of iodonium ylide (**5**). The cyclization reaction proceeded smoothly at room temperature to give the desired product (**6**) in 87% yield.[8]

Table 1 Transition metal-catalyzed cyclization of iodonium ylide, 5.

Catalyst	Reaction Time	Results (Yield)
$Rh_2(OAc)_4$	12-15 minutes	87%
Cu(I)Cl	2hrs	complex mixture
$Cu(I)OSO_2CF_3$	3hr	complex mixture
Cu(I)I	1hr	complex mixture
$Pd(OAc)_2$	10hr	complex mixture

Mechanistically, the formation of **6** from **5** using dirhodium(II) tetraacetate may involve the formation of Rh(II)-carbene complex in a similar way to the Rh(II)-catalyzed cyclization of an α-diazo β-keto ester. (Scheme 2) This would involve the nucleophilic attack of the ylide carbon on the electrophilic rhodium followed by the extrusion of phenyl iodide resulting in the formation of the metal carbene complex, **7**. The lone pair of the azetidine nitrogen would then attack the now electrophilic carbon followed by proton migration. Rhodium diacetate would then be reductively eliminated, making it available for the next catalytic cycle.



Scheme 2 X= $-OSO_2CH_3$; $-OSO_2C_6H_4CH_3$(p)

It is also known that iodonium ylides of β-dicarbonyl compounds upon protontion undergo rupture of C-I bond with subsequent nucleophilic substitution.[5,9] In a similar manner, we expected that protonation of the ylide with a strong acid followed by nucleophilic addition of β-lactam nitrogen and subsequent reductive elimination of iodobenzene may afford the desired product **6**. Thus, the use of methanesulfonic acid, p-toluenesulfonic acid, in the cyclization reaction with the ylide resulted in the formation of **6** in 50 and 55% yield, respectively, after column chromatography[10]. The use of trifluoroacetic acid or triflic acid in the cyclization reaction with **5** led to the formation of a complex mixtures.

The formation of **6** from **5** in presence of acid may involve i) protonation of ylide **5** to form intermediate **8**, ii) nucleophilic addition of azetidine nitrogen to electrophilic iodine to form **9** and iii) C-N bond formation with reductive elimination of iodobenzene to yield **6** (Scheme 2).

In conclusion, we have successfully demonstrated a novel and efficient synthesis of 7β-phenoxyacetamido-3-hdroxycarbaceph-4-carboxylate (**6**, a key intermediate in the synthesis of carbacephalosporins) utilizing rhodium (II) or acid catalyzed cyclization of the iodonium ylide (**5**). Since, the synthesis involves no hazardous compounds and requires simple operations, it could be readily applied to manufacturing purposes.

Acknowledgments: We are thankful to Dr. W. Luke for providing compound **4**, Mr. R. Boyer Jr. is also acknowledged for providing the NMR data, Drs. F. Perry and G. Tharp for helpful discussions.

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* Author to whom correspondence should be addressed.

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7. mp 123-125°C. IR (KBr) cm^{-1}: 3414, 3289, 1762, 1670 (broad), 1602, 1560, 1521; ^1H NMR($CDCl_3$) δ: 1.88(m, 2H), 3.01(m, 1H), 3.03(m, 1H), 3.98(m, 1H, J=5.3Hz), 4.67(dd, 2H, OCH_2CO-), 5.27(S, 2H, -$CH_2COOpNB$), 5.35(dd, 1H, J=5.3Hz), 6.75(1H, NH), 6.85(m, 2H), 7.02(m, 1H), 7.35(m, 6H), 7.59(m, 1H), 7.75(d, 2H), 7.84(m, 1H), 8.22(d, 2H); ^{13}C NMR($CDCl_3$, δ) 27.72, 29.67, 34.22, 54.61, 58.15, 64.90, 67.06, 112.45, 114.74, 121.95, 123.70, 128.02, 129.64, 129.80, 130.22, 131.50, 131.63, 132.80, 137.45, 144.08, 147.47, 157.19, 163.99, 167.76, 168.90, 188.94. UV(95% EtOH) 349 and 258nm. M^+(m/z) 671; Analysis: Found C 51.67, H 3.85, N 6.28, I 18.51 $C_{29}H_{26}N_3O_8I$ requires C51.88, H 3.91, N 6.26, I 18.91.

8. To a solution of iodonium ylide **5** (0.70gm, 0.001moles) in methylene chloride (30ml) was added $Rh_2(OAC)_4$ dimer (1.3mg, 0.0031mmol) at room temperature. The contents were stirred for 10-12minutes and then concentrated to an oil. The oil was dissolved in ether and isopropanol (40:60) and contents were stirred in a ice bath for 20-25minutes. A white solid was obtained, filtered and washed with 7ml of ether. Thus, 0.44gm of **6** was obtained. Yield = 87%. mp= 163-165°C, Authentic sample.[1,11] mp = 163-165°C; ^1H NMR ($CDCl_3$) δ: 1.72(m, 1H), 2.00(m, 1H), 2.5(m, 2H), 3.95(m, 1H), 4.56(s, 2H), 5.25, 5.55(d, d, 2H), 5.5.36(dd, 1H), 6.92(d,2H), 7.02(m, 1H), 7.29(m, 3H), 7.60(d, 2H), 8.25(d, 2H), 10.90(s, 1H).

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10. To a solution of iodonium ylide **5** (0.35gm, 0.0005moles) in methylene chloride and ethanol (10 ml:20 ml) was added acid (0.0016mmol) at room temperature. The reaction contents were stirred for 1hr. and concentrated to an oil. The oil was chromatographed using a silica column, ethyl acetate and hexane (70:30) as eluents. Thus, **6** was obtained in 50% and 53% yields from **4** using methanesulfonic acid and p-toluenesulfonic acid, respectively.

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(*Received in USA* 21 *July* 1997; *revised* 11 *August* 1997; *accepted* 12 *August* 1997)