Pergamon

Tetrahedron Letters, Vol. 38, No. 18, pp. 3291-3292, 1997
© 1997 Published by Elsevier Science Ltd
All rights reserved. Printed in Great Britain
0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00588-1

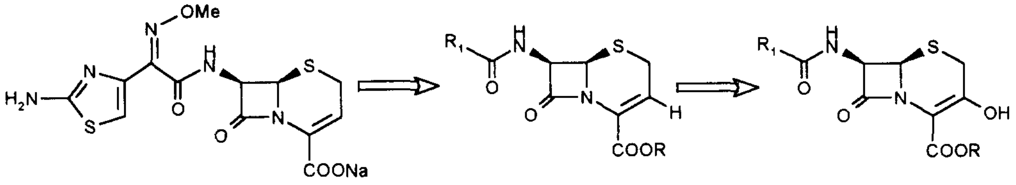
Palladium-Catalysed Reduction of 3-Substituted Cephems. A High Yield Approach to Ceftizoxime Synthetic Intermediates.

Walter Cabri*[1]
Bristol-Myers Squibb, Chemical Research & Development, via del Murillo, Sermoneta-04010 (LT), Italy

Maurizio Botta,* Federico Corelli* and Flavia Messina
Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Banchi di Sotto 55, Siena-53100, Italy

Abstract: A high palladium-catalysed approach to Ceftizoxime intermediate is described.
© 1997 Published by Elsevier Science Ltd.

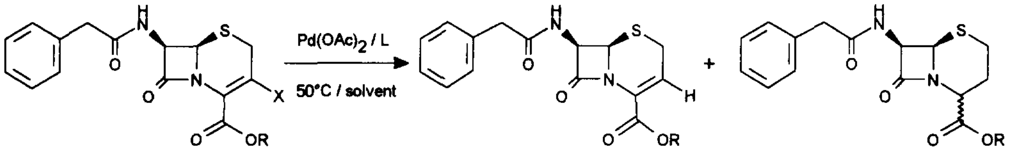
Ceftizoxime sodium **1** is a sterile, broad-spectrum, β-lactamase resistant third generation cephalosporin for parental administration.[2] Up to now several synthetic approaches have been described, however, the key step is always the conversion of the 3-OH cephem **3** into **2**.[3] In this context, the interesting synthesis described by Farina centred on the palladium-catalysed reduction of 3-trifluoromethanesulfonyl cephem suffers of some drawbacks.[4] In fact, following a Stille type protocol, the hydride source is the expensive and toxic nBu_4SnH.[5] On the other hand, the advantage of this procedure is the use of neutral conditions that avoid Δ2/Δ3 isomerization[6] and the decomposition of the sensitive β-lactam ring.



1 **2** **3**

We would like to report herein our results on the use of a cheap and non-toxic hydride source, namely Et_3SiH, for the synthesis of Ceftizoxime key intermediate by palladium-catalysed reduction.[7] We investigated the reduction of 3-Cl **4**[8] and 3-OTf **5**[9] cephem derivatives using catalysts generated in situ from $Pd(OAc)_2$ and the ligand.[10] The presence of a base was unnecessary because the reaction side products (Et_3SiCl or Et_3SiOTf) were not able to destroy the active Pd(0) complex. Independently from the leaving group, the reduction carried out in the absence of phosphine ligands afforded the over-reduced products **7** (Table I, entries 1 and 4). On the other hand, the reduction of chloride **4** using 1,1'-bis-diphenylphosphino ferrocene (DPPF) and PPh_3 as palladium ligands afforded compound **6** in 10% and 52%, respectively (entries 2 and 3). Switching to enol triflate **5**, using DPPF and six equivalents of Et_3SiH, cephem **6** was isolated in high yield (entry 5). Under these reaction conditions, the palladium-catalysed decomposition of Et_3SiH to H_2 and $(Et_3Si)_2$ becomes competitive with the oxidative-addition step. This side reaction was completely suppressed by using PPh_3 instead of DPPF. In fact, only one equivalent of Et_3SiH was necessary to achieve a complete reduction (entry 6). In dioxane, only traces amount of **6** were detected after 24 h with

Table I. Palladium-Catalysed reduction of 3-substituted cephem derivatives.[a]



R: 4-MeO-Bn 4 X: Cl 6 7
5 X: OTf

Entry	Substrate	L	Solvent	Et$_3$SiH/substrate molar ratio	t h	Conv[b] %	Product (yield, %)[c]
1	**4**	-	DMF	6	3	100	7 (21)[d]
2	**4**	DPPF	DMF	6	24	46[e]	**6** (10)
3	**4**	PPh$_3$	DMF	6	16	100	**6** (52)
4	**5**	-	DMF	6	24	100	7 (27)[d]
5	**5**	DPPF	DMF	6	3	100	**6** (80)
6	**5**	PPh$_3$	DMF	1	2	100	**6** (83)
7	**5**	PPh$_3$	dioxane	12	3	100	**6** (75)

a. See reference 10. b. Determined by ^{1}H NMR. c. Isolated yields. d. 7 was a 1/1 mixture of C-4 epimers by ^{1}H NMR. e. 34% of Δ2 cephem.

one equivalent of Et$_3$SiH. However, using a large excess of the reducing agent a complete conversion was obtained (entry 7).

Summing up, we have described a high yield synthesis of Ceftizoxime key intermediate **2** using environmentally friendly reagents. The use of cheap PPh$_3$ as ligand for the palladium-catalysed reduction gave the best results in terms of reaction rate and atom economy.

References and Notes

1. Present address: Secifarma, via Bissone,5 Baranzate di Bollate-20021 (MI), Italy.
2. Takaya,T.;Takasugi,H.;Tsuji,K;Chiba,T. Ger.Offen. 2810922 (1978).
3. Kobayashi,M.;Kato,M.; Ueda,I. *Chem. Pharm Bull.* **1988**, *36*, 582 and reference therein.
4. Farina,V. Baker,S.R.; Benigni,D.A. *J.Org.Chem.* **1990**, *55*, 5833.
5. Evans,C,J.; Karpel,L.S. *Organic Compound in Modern Technology*, Elsevier, New York, **1985**. Chapter 10.
6. Botta,M.;De Rosa,M.C.;Di Fabio,R.;Mozzetti,C.;Santini,A.;Corelli,F *Electronic. J. Theor. Chem.* **1996**, *1*, 52.
7. Bidentate phosphine ligands gave the best results in palladium-catalysed reduction of aryl sulfonates using triethylammonium formate as hydride source. Cabri.W; DeBernardinis,S.; Francalanci,F.; S.Penco; Santi,R. *J. Org. Chem.* **1990**, *55*, 350. Similar observation was made using Et$_3$SiH. Kotsuki,H.; Datta,P.K.; Hayakawa,H.; Suenaga,H. *Synthesis* **1995**, 1348.
8. Chauvette,R.R. US 3.925,372 (1975).
9. Farina,V.; Baker,S.R.;Hauck,S.I. *J.Org.Chem.* **1989**, *54*, 4962.
10. Table I, entry 6: To a DMF (2.0 mL) solution of **5** (176 mg, 0.3 mmol), under argon atmosphere, PPh$_3$ (16 mg, 0.06 mmol), Pd(OAc)$_2$ (3.5 mg, 0.015 mmol) and Et$_3$SiH (0.048 mL, 0.3 mmol) were sequentially added. After 2 h at 50°C the reaction mixture was poured into water and extracted with CH$_2$Cl$_2$ after usual work up and purification by flash chromatography **6** was isolated in 83% yield.

(*Received in UK* 19 *December* 1996; *revised* 25 *March* 1997; *accepted* 26 *March* 1997)