A Facile Access to 3-Allyl- and 3-Benzyl-3-cephems *via* Reductive Addition/Cyclization of Allenecarboxylate with Allyl and Benzyl Halides in an Al/Pb/Ni Redox System

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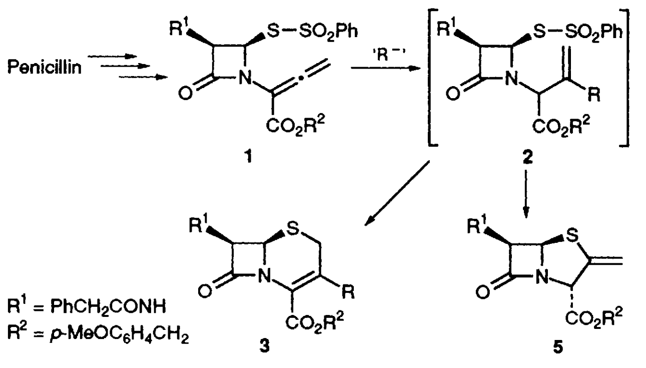
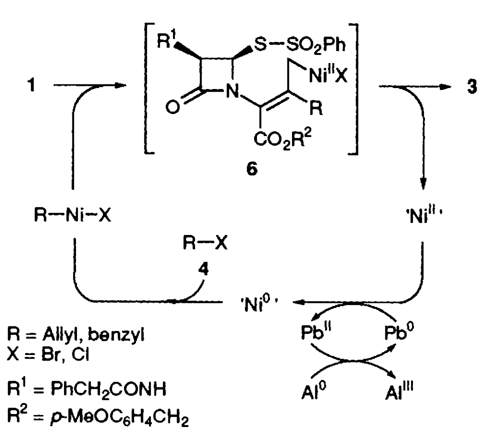
A sequential reductive addition/cyclization reaction of allenecarboxylate, derived from penicillin G, with allyl and benzyl halides was successfully performed by the aid of aluminium metal and catalytic amounts of $PbBr_2$ and $[NiCl_2(bipy)]$ to afford 3-allyl- and 3-benzyl-3-cephems, respectively.

Since the pioneering work of Morin *et al.*,[1] conversion of penicillins into cephalosporins has been the keen subject of the synthesis of cephem antibiotics and various synthetic approaches have emerged.[2] In previous papers, we disclosed a conceptually new strategy for the penicillin → cephalosporin conversion involving a sequential addition/cyclization reaction of allenecarboxylate **1**, derived from penicillin G, leading to 3-substituted cephems **3** (Scheme 1).[3] Independently, Kant and Farina reported an analogous access to the 3-substituted cephems **3**.[4] In these procedures, heteroatom nucleophiles, organocuprates, and organostannannes were employed as nucleophiles (R^-) which were introduced at the C-3 position of the cephem framework. Herein we disclose a new device for construction of a cephem framework promoted by reductive addition of allyl or benzyl halides **4** to the allenecarboxylate **1** in an $Al/PbBr_2/[NiCl_2(bipy)]$ three-metal redox system as illustrated in Scheme 2.

The addition/cyclization can be performed by treatment of a mixture of the allenecarboxylate **1** and allyl or benzyl halides **4** with aluminium and catalytic amounts of $PbBr_2$ and $[NiCl_2(bipy)]$. A typical reaction procedure is as follows: A mixture of the allenecarboxylate **1**,[3] allyl bromide **4a** (R = allyl, X = Br; 5 equiv.) aluminium (2.5 equiv.), $PbBr_2$ (0.05 equiv.), and $[NiCl_2(bipy)]$ (0.1 equiv.) in *N*-methyl-2-pyrrolidone (NMP) was stirred at 35–40 °C. The reaction proceeded smoothly and was complete in 45 min to afford 3-allyl-3-cephem **3a** (R = allyl) in 85% yield along with a small amount of 2-*exo*-methylenepenam **5** (Table 1, entry 1). The formation of **5** can be reasonably understood by assuming reductive cleavage of the S–S bond of **1** followed by intramolecular attack of thus formed thiolate ion to the allene moiety.[5] The presence of aluminium and catalytic amounts of $PbBr_2$ and $[NiCl_2(bipy)]$ is indispensable for the formation of **3a**, since lack of any of the components resulted in the formation of no appreciable amount of **3a**. In place of the $Al/PbBr_2/[NiCl_2(bipy)]$ combination, use of other metal/metal salt combinations, *e.g.*, $Zn/NiCl_2$[6] and $SnCl_2/[PdCl_2(PhCN)_2]$,[7] was attempted for performing the reaction of **1** and **4a** but no detectable amount of the desired product **3a** was found.



Scheme 1

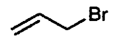
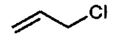
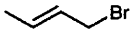
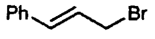
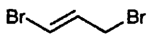
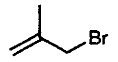
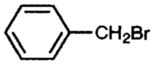
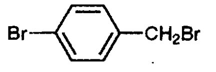


Scheme 2

Although the reaction mechanism is not clear at present, it is likely that an $Al^0–Al^{III}$, $Pb^0–Pb^{II}$, and $Ni^0–Ni^{II}$ three-metal redox system may promote a sequential addition/cyclization reaction of the allenecarboxylate **1** *via* **6** as illustrated in Scheme 2. The Ni^0 would be initially formed and regenerated in the $Al/PbBr_2/[NiCl_2(bipy)]$ system, in which, aluminium would release the required electrons through a $Pb^0–Pb^{II}$ redox mediatory system.[8]

The $Al/PbBr_2/[NiCl_2(bipy)]$ system can be successfully applied to the synthesis of the cephems **3** bearing allylic or benzylic C-3 substituents (entries 2–8). The reaction of **1** with 2-butenyl, 3-phenyl-2-propenyl, and 3-bromo-2-propenyl bromides **4** took place in a regioselective manner to afford the corresponding α-substituted products **3**, exclusively (entries 3–5). When benzylic halides were used in place of the allyl

Table 1 Reaction of allenecarboxylate **1** with allyl and benzyl halides **4**[a]

Entry	R–X	Yield (%)[b] 3	5
1		85	Trace
2		61	Trace
3		82	–
4		60	–
5		31	4
6		73	–
7		83	–
8		62	–

[a] Carried out in a similar manner to that described in the text. [b] Isolated yields after column chromatography.

halides, the 3-benzyl-3-cephems **3** were obtained in moderate yields (entries 7 and 8). Similar reactions of **1** with vinyl bromide and phenyl iodide were also attempted but no detectable amounts of cyclized products **3** (R = vinyl, phenyl) were observed. Presumably, disproportionation of the vinyl and phenyl nickel(II) complexes (R–Ni–X) would take place preferentially to give buta-1,3-diene and biphenyl, respectively.[6,7]

In conclusion, we have developed a new methodology for the construction of the cephem framework **3** based on reductive addition/cyclization of the allenecarboxylate **1** with allyl and benzyl halides **4** in the Al/$PbBr_2$/[$NiCl_2$(bipy)] system. Further applications of the three-metal redox system are in progress.

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References

1 R. B. Morin, B. G. Jackson, R. A. Mueller, E. R. Lavagnino, W. B. Scanlon and S. L. Andrews, *J. Am. Chem. Soc.*, 1963, **85**, 1896.

2 *Recent Advance in the Chemistry of β-Lactam Antibiotics*, ed. G. I. Gregory, The Royal Society of Chemistry, London, 1980; *Topics in Antibiotics Chemistry* ed. P. G. Sammes, Ellis Horwood Ltd, Chichester, vol. 4, 1980.

3 H. Tanaka, Y. Kameyama, S. Sumida, T. Yamada, Y. Tokumaru, T. Shiroi, M. Sasaoka, M. Taniguchi and S. Torii, *Synlett*, 1991, 888; H. Tanaka, Y. Kameyama, S. Sumida and S. Torii, *Tetrahedron Lett.*, 1992, **33**, 7029.

4 V. Farina and J. Kant, *Tetrahedron Lett.*, 1992, **33**, 3559, 3563.

5 H. Tanaka, Y. Kameyama and S. Torii, *Synlett*, 1992, 878.

6 M. Zembayashi, K. Tamao, J. Yoshida and M. Kumada, *Tetrahedron Lett.*, 1977, **47**, 4089; K. Takagi, N. Hayama and K. Sasaki, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 1887; K. Takagi, H. Mimura and S. Inokawa, *Bull. Chem. Soc. Jpn.*, 1984, **57**, 3517; M. Iyoda, M. Sakaitani, H. Otsuka and M. Oda, *Chem. Lett.*, 1985, 127; I. Colon and D. R. Kelsey, *J. Org. Chem.*, 1986, **51**, 2627; A. Jutand and A. Mosleh, *Synlett*, 1993, 568.

7 J. P. Takahara, Y. Masuyama and Y. Kurusu, *J. Am. Chem. Soc.*, 1992, **114**, 2577.

8 H. Tanaka, A. Kosaka, S. Yamashita, K. Morisaki and S. Torii, *Tetrahedron Lett.*, 1989, **30**, 1261; H. Tanaka, S. Sumida, N. Kobayashi, N. Komatsu and S. Torii, *Inorg. Chim. Acta*, 1994, in the press.