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MILD PALLADIUM (0)-CATALYZED DEPROTECTION OF ALLYL ESTERS. A USEFUL APPLICATION IN THE SYNTHESIS OF CARBAPENEMS AND OTHER β-LACTAM DERIVATIVES.

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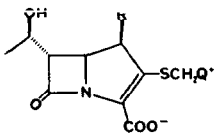
Summary: Carbapenem and other β-lactam allyl ester derivatives are efficiently deprotected with pyrrolidine in the presence of catalytic amount of Pd(0).

As a part of an ongoing effort in the synthesis of carbapenem antibiotics such as 1, we undertook to develop an efficient and high yielding process for the crucial deprotection step of the C-3 carboxylate function. Although a large body of options exist for the deprotection of esters[1], only a few give satisfactory results with carbapenems as substrates[2]. In this respect, PNB esters are commonly used but their removal involves a rather tedious work-up (i.e. reversed phase chromatography then lyophilization) and yields are often only moderate. Obviously, it is not the method of choice when large amounts of carbapenem derivatives are required.

In our opinion, allylic esters as protective groups offer the best alternative for our purpose because of their ease of displacement by nucleophiles when activated with Pd(0)[3]. Although a few procedures have been reported in this regard, in our hands none of them gave satisfactory results with the carbapenem allyl ester derivatives (e.g. 2)[4]. We now wish to report herein that very nucleophilic amines such as pyrrolidine smoothly deprotect allyl esters at 0°C in the presence of catalytic amount of $Pd(PPh_3)_4$. As shown in the table, carbapenem allyl esters 2[5] were deprotected within a few min and in very good yield[7]. Also the carbapenem zwitterions 1 crystallized out of the reaction mixture and were isolated in fairly pure form after a simple filtration. Due to the ease of this procedure large scale experiments have been successfully carried out.

In a similar manner penicillin G allyl ester was deprotected in very good yield (15 min, 0°C), the free acid 3 was obtained in 93% after acidification of the reaction mixture[8]. Deprotection of the acetoxycephem 4 also procedeed smoothly (25 min, 0°C, 88%); no nucleophilic displacement of the acetoxy function was noticed, showing the chemoselectivity of this process. Simple allyl esters such as allyl benzoate and allyl *trans*-cinnamate were deprotected in quantitative yield.



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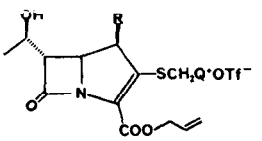

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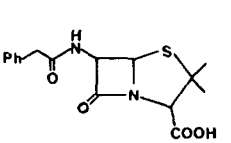

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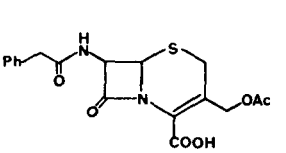
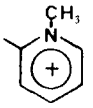
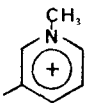
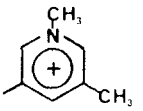
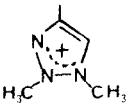
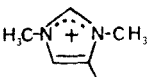


4

TABLE: Carbapenems 1 obtained from allyl esters 2[7].

R :	H	CH_3	CH_3	CH_3	CH_3
Q⁺ :					
yield :	70	80	66	90	72
time (min) :	10	10	15	5	15

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2. (a) Ohtani, M.; Watanabe, F.; Narisada, M.; J. Org. Chem., 1984, 49, 5271. (b) Shih, D.H.; Baker, F.; Cama, L.; Christensen, B.G., Heterocycles, 1984, 21, 29.

3. Trost, B.M.; Verhoven, T.R. In ''Comprehensive Organometallic Chemistry'', Wilkinson, G., Ed.; Pergamon Press; Oxford, 1982, Vol 8, p. 819-834.

4. (a) Jeffrey, P.D.; McCombie, S.W., J. Org. Chem., 1982, 47, 587. (b) Kunz, H.; Waldmann, H., Angew. Chem. Int. Ed. Engl., 1984, 23, 71. When allyl esters 2 were subjected to procedure of ref 4a decomposition occurred very rapidly whereas procedure of ref 4b failed to give zwitterions 1.

5. The unquaternized carbapenem precursors of 2 were prepared by application of the methods described in the literature[2b, 6] then salts 2 were prepared *in situ* by the addition of methyltrifluoromethane sulfonate (1 eq) in acetonitrile at 0°C prior to the deprotection.

6. Déziel, R.; Favreau, D.; Tetrahedron Lett., 1986, 47, 5687.

7. In a typical procedure; to an ice cooled solution of allyl esters 2 (80.0 mmol), $Pd(PPh_3)_4$ (2.0 mmol) and PPh_3 (4.0 mmol) in acetonitrile (300 mL) was added a solution of pyrrolidine (84.0 mmol) in acetonitrile (50 mL). After stirring for 10 min, cold acetone (500 mL) was added. The resulting precipitate was isolated by filtration and recrystallized from methanol to give zwitterions 1 for which spectral data are in agreement with the assigned structure.

8. Allyl esters of 3 and 4 were deprotected in dichloromethane, the reaction mixture was then diluted with EtOAc and extracted with sodium bicarbonate solution (c.a. 15%). The combined aqueous phases were acidified to pH 2 with 5% hydrochloric acid solution. The mixture was then extracted with dichloromethane to give 3 and 4 in 93% and 88% yield respectively.

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