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A Convenient Protective Method for the 7-Amino Function on a Cephem Derivative in Wittig Vinylation

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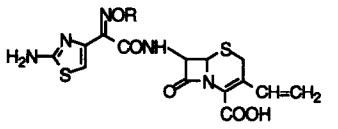
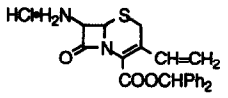
Abstract: A novel preparative pathway for diphenylmethyl 7 β-amino-3-vinylceph-3-em-4-carboxylate from 3-chloromethyl derivative is described. As a convenient protecting group for the 7-amino function in a Wittig reaction, six membered azine derivatives incorporating the 7-amino group were developed as a surrogate of conventional protecting groups.

Much effort to find orally active and broad spectrum antibiotics in our research labolatories resulted in the discovery of two therapeutically available agents, cefixime (**1**)[1, 2] and cefdinir (**2**).[1, 3] These drugs are prepared from a common intermediate, diphenylmethyl 7 β-amino-3-vinylceph-3-em-4-carboxylate (**3**), which has usually been synthesized by Wittig reaction of the 3-phosphonium halide derived from the 3-halomethyl compound. In this reaction it is necessary to protect the reactive 7-amino group. Although the most well-known protecting group is the acyl group,[4] strict temperature control is required to obtain a high yield in the deprotection (using the usually condition of phosphorous pentachloride followed by alcoholysis of the resulting iminochloride). To improve this process the *ortho*-salicyl aldehyde Schiff base was successfully introduced as a readily removable protecting group of the 7-amino function.[2] In light of this result, our synthetic effort was directed toward the utilization of the more accessible, simple aldehyde, formaldehyde.



cefixime (**1**) R = CH_2COOH



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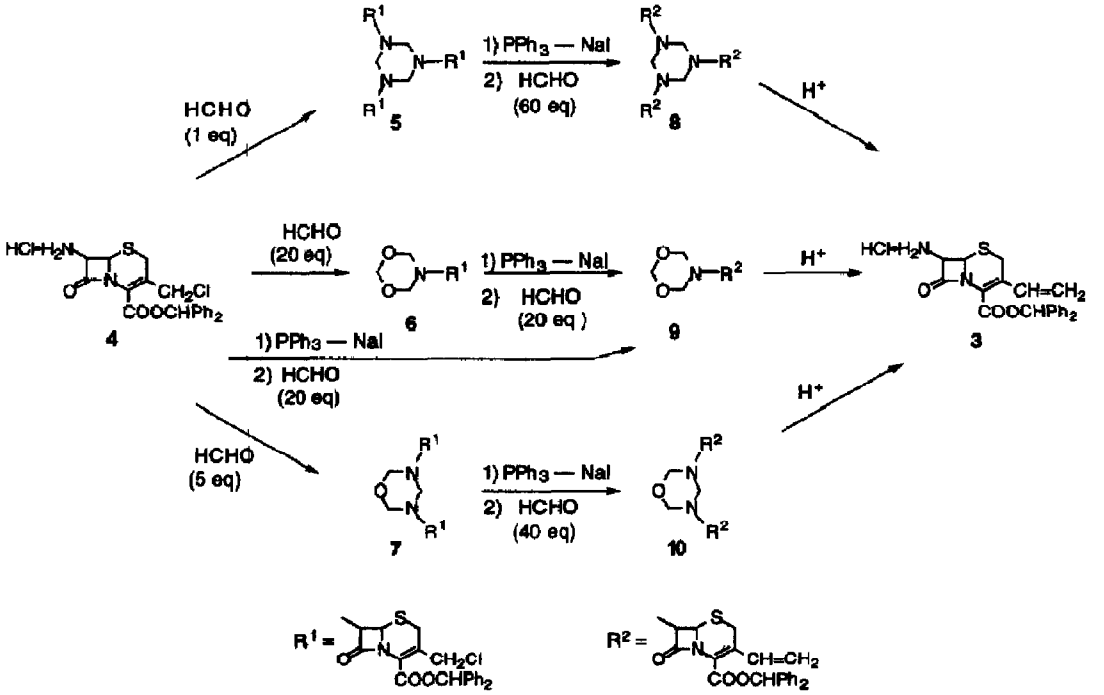
cefdinir (**2**) R = H

The reaction of a primary amine with formaldehyde to give 6-membered rings, i. e., hexahydro-*s*-triazine, tetrahydro-1,3,5-oxadiazine and dihydro-1,3,5-dioxazine, via the formation of an aldimine, has been reported.[5—7] To our knowledge, however, the application as a protective group has not been investigated. We describe here the usefulness of these azine rings for amino protection in Wittig vinylation.

Treatment of 7-amino-3-chloromethylcephem derivative (**4**)[2] with an equivalent of 37% aqueous formalin in dichloromethane at room temperature afforded the *s*-triazine derivative (**5**) in nearly quantitative yield (98%).[8a] Reaction using a large excess (20 fold moles) of formalin provided the 1,3,5-dioxazine derivative (**6**) in good yield (75%).[8b] On the other hand, despite use of varying amounts of formalin (3—20 equivalents), selective

preparation of 1,3,5-oxadiazine derivative (**7**) was not achieved, and the isolation of **7** from a reaction mixture with **6** was performed by chromatography on silica gel in 37% yield.[8c] After the compound **5** was converted to the phosphonium salt by reacting with one equivalent each of triphenylphosphine and sodium iodide per chloride in N,N-dimethylacetamide at room temperature, the salt was allowed to react with formalin in dichloromethane at pH 8—9 to furnish the 3-vinyl derivative (**8**) in 73% yield.[8d] Compound **6** was also converted to the 3-vinyl derivative (**9**) under the same conditions in 76% yield.[8e] The Wittig reaction using compound **7** under similar conditions afforded vinyl derivative (**10**), but in unsatisfactory yield (41%).[8f, 9] As an alternative synthetic method for **9** starting from **4**, the reaction sequence was reversed; formation of phosphonium salt followed by cyclization to the dioxazine ring, succeeded in a two step yield of 54%.[8e] All three cyclic moieties, *s*-triazine (**8**), dioxazine (**9**) and oxadiazine (**10**), could smoothly be removed on treatment with hydrochloric acid in dichloromethane at room temperature to regenerate the 7-amino function in good yields, 83%, 92% and 91%, respectively.[8g]



Thus we have introduced a convenient protecting method for the amino function by using the readily available and very inexpensive material formalin. As a cyclic amino protecting group, triazone derivatives prepared from 1,3-disubstituted urea was recently reported.[10] However, the reaction conditions described in the paper, such as heating the reactant and using an organic base, are too harsh to cephalosporins which are known as thermo and base sensitive. The reactions described here proceeded under mild conditions without notable degradation of the cephem skeleton.[9] Therefore applications to other synthetic reactions can be expected.

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8. **Experimental procedure and physical data:** ^{1}H NMR spectra were recorded in DMSO-d_6. Analytical results (C, H, N) are within ±0.4% of the theoretical values. All reactions were carried out at room temperature and the organic layers reacted were washed with H_2O, dried over $MgSO_4$ and concentrated to dryness under reduced pressure. Silica gel was used for the carrier on chromatography and the eluent used was EtOAc / toluene (1 : 10).

   (a) 1,3,5-Tris[3-chloromethyl-4-diphenylmethoxycarbonylceph-3-em-7 β-yl]-hexahydro-1,3,5-triazine (**5**)
   General procedure for protection: A suspension of **4** (9.3 g, 20 mmol) in CH_2Cl_2 (100 ml) was adjusted to pH 2 with 1N NaOH. Formalin (37%, 1.7 ml, 22 mmol) was added to the resulting solution and the mixture was stirred for 2 h. The organic layer separated was washed, dried, and concentrated to give a residue which was purified by chromatography to afford **5** (8.6 g, 98%). An analytical sample was obtained by washing with Et_2O, mp 125 ℃ (decomp). ^{1}H NMR: δ 3.49 (3H, d, J = 18 Hz), 3.74 (3H, d, J = 18 Hz), 4.01 (6H, s), 4.46 (6H, s), 5.12 (6H, s), 7.00 (3H, s), 7.17—7.58 (30H, m); MS: m/z 1279 (M^++1).

   (b) 5-(3-Chloromethyl-4-diphenylmethoxycarbonylceph-3-em-7 β-yl)-dihydro-1,3,5-dioxazine (**6**)
   mp 124—125 ℃. ^{1}H NMR: δ 3.50 (1H, d, J = 18 Hz), 3.77 (1H, d, J = 18 Hz), 4.44 (2H, s), 4.58 (2H, d, J = 11 Hz), 4.94 (2H, d, J = 11 Hz), 5.14 (2H, s), 5.25 (1H, d, J = 5 Hz), 5.48 (1H, d, J = 5 Hz), 6.98 (1H, s), 7.14—7.60 (10H, m).

   (c) 3,5-Bis[3-chloromethyl-4-diphenylmethoxycarbonylceph-3-em-7 β-yl]-tetrahydro-1,3,5-oxadiazine (**7**)
   mp 133—135 ℃. ^{1}H NMR: δ 3.50 (2H, d, J = 18 Hz), 3.74 (2H, d, J = 18 Hz), 4.16 (2H, s), 4.46 (4H, s), 4.58 (2H, d, J = 11 Hz), 4.82 (2H, d, J = 11 Hz), 5.13 (2H, d, J = 5 Hz), 5.39 (2H, d, J = 5 Hz), 7.01 (2H, s), 7.12—7.59 (20H, m).

   (d) 1,3,5-Tris[4-diphenylmethoxycarbonyl-3-vinylceph-3-em-7 β-yl]-hexahydro-1,3,5-triazine (**8**)
   General procedure of Wittig reaction: A mixture of **5** (10 g, 7.8 mmol), PPh_3 (6.8 g, 26 mmoles) and NaI (3.9 g, 26 mmol) in *N,N*-dimethylacetamide (25 ml) was stirred for 1 h. After CH_2Cl_2 (200 ml) and formalin (37%, 40 ml) were added, the mixture was adjusted to pH 8—9 with 1N NaOH with stirring for 2 h. The organic layer separated was washed, dried and concentrated to give a residue, which was purified by chromatography to afford **8** (6.9 g, 73%). An analytical sample was obtained by reprecipitation with MeOH from a solution in Me_2CO, mp 134 ℃ (decomp). ^{1}H NMR: δ 3.54 (3H, d, J = 18 Hz), 3.88 (3H, d, J =

18 Hz), 4.03 (6H, s), 5.11 (6H, s), 5.32 (3H; d, J = 11 Hz), 5.63 (3H, d, J = 17 Hz), 6.81 (3H, d, J = 11 and 17 Hz), 6.99 (3H, s), 7.16—7.54 (30H, m); MS: m/z 1212 (M^+).

(e) 5-(4-Diphenylmethoxycarbonyl-3-vinylceph-3-em-7 β -yl)-dihydro-1,3,5-dioxazine (**9**)

mp 175—176 ℃. ^{1}H NMR: δ 3.56 (1H, d, J = 18 Hz), 3.90 (1H, d, J = 18 Hz), 4.58 (2H, d, J = 11 Hz), 4.94 (2H, d, J = 11 Hz), 5.14 (2H, s), 5.25 (1H, d, J = 5 Hz), 5.28 (1H, d, J = 12 Hz), 5.46 (1H, d, J = 5 Hz), 5.63 (1H, d, J = 18 Hz), 6.76 (1H, dd, J = 12 and 18 Hz), 6.97 (1H, s), 7.20—7.57 (10H, m).

Alternative procedure: A mixture of **4** (1.9 g, 4.1 mmol), PPh_3 (1.3 g, 4.9 mmol) and NaI (0.7 g, 4.7 mmol) in *N*,*N*-dimethylacetamide (6 ml) was stirred for 1 h. After CH_2Cl_2 (40 ml) and formalin (6.7 ml, 89 mmoles) were added, the mixture was stirred for 1h and then adjusted to pH 8—9 with 1N NaOH with stirring for 2 h. The organic layer separated was washed, dried and concentrated to give a residue, which was successively washed with hexane and then MeOH to afford **9** (1.0 g, 54%).

(f) 3,5-Bis[3-chloromethyl-4-diphenylmethoxycarbonylceph-3-em-7 β -yl]-tetrahydro-1,3,5-oxadiazine (**10**)

mp 165—166 ℃. ^{1}H NMR: δ 3.53 (2H, d, J = 18 Hz), 3.90 (2H, d, J = 18 Hz), 4.19 (2H, s), 4.60 (2H, d, J = 10 Hz), 4.82 (2H, d, J = 10 Hz), 5.14 (2H, d, J = 5 Hz), 5.29 (1H, d, J = 12 Hz), 5.41 (2H, d, J = 5 Hz), 5.63 (1H, d, J = 18 Hz), 6.80 (1H, dd, J = 12 and 18 Hz), 6.99 (2H, s), 7.19—7.53 (20H, m).

(g) Diphenylmethyl 7 β-amino-3-vinylceph-3-em-4-carboxylate hydrochloride (**3**): hydrolysis of cyclic compounds (**8**—**10**)

A mixture of a cyclic compound (**8**, **9**, or **10**) (2 mmol) and 6N HCl (12.5 ml) in CH_2Cl_2 (25 ml) was stirred for 1 h. The resulting precipitate was collected by filtration and washed with CH_2Cl_2 to afford **3**. Yield; 83% from **8**, 92% from **9**, and 91% from **10**, respectively. The physical propaties were consistent with an authentic sample.[2]

9. It seems that the low yields in the case of compound **10** are due to the instability of oxadiazine ring as described reference 4.

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