Alkylation and Arylation at the C-3' Side Chain Position of Cephalosporins *via* a Pummerer Intermediate

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Dedicated to the memory of Professor Nicholas Alexandrou

The Pummerer intermediate generated from a 3-exomethylene-1-oxocephem with trifluoroacetic anhydride was trapped intermolecularly in the presence of a Lewis acid by some aromatic or olefinic nucleophiles.

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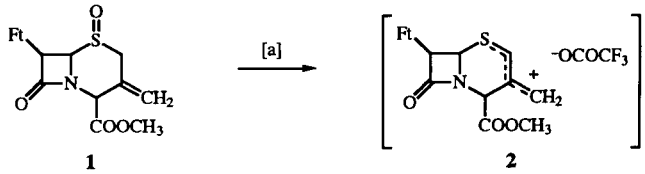
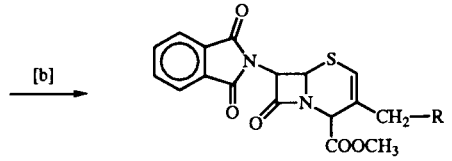
Among the β-lactam drugs the modified cephalosporin antibiotics have a much wider antibacterial spectrum and more potent activity. Chemical advances in manipulating these sensitive materials and studying their physicochemical properties have depended heavily on the use of modern analytical and purification techniques, and on the development of more selective reagents, and milder and practical preparative procedures. Extensive chemical modifications at the C-3' position have largely centered on the replacement of the acetoxy group with heteroatom-based nucleophiles. On the other hand, reports of substitution at C-3' side chain position by weak carbon nucleophiles are in scarcity in the chemical literature [1].

Herewith we report a way of introducing substituents at C-3' side chain position by making the cepham ring susceptible to such weak nucleophilic attacks. To achieve this goal we first transformed a penam ring to the corresponding 3-exomethylenecepham derivative, followed by treatment of the allylic sulfoxide produced with a sulfoxide activator agent to generate a Pummerer intermediate. This vinylthionium ion was then trapped by an aryl or alkyl weak base in the presence of a Lewis acid [2]. Thus, the 3-exomethylene derivative **1** prepared by transformation of a penicillin derivative [3] was treated with a quadruple amount of trifluoroacetic anhydride in the presence of the specific non-nucleophilic Brönsted base 2,6-di-*tert*-butyl-4-methylpyridine at room temperature which generated the desired Pummerer intermediate **2**. Exposure of this susceptible vinylthionium ion to the substrate benzene at room temperature in the presence of tin tetrachloride afforded the arylated cephalosporin **3** in moderate yield along with a polar residue according to tlc. Similarly we prepared the arylated cephalosporins **4-6** but in poor yields.

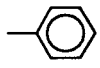
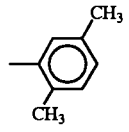
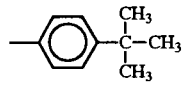
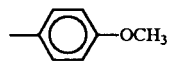
When the milder Lewis acid boron trifluoride diethyl etherate was employed instead, the above reactions did not proceed. Conversely, the boron trifluoride diethyl etherate worked better in all cases, except when benzene was used as a substrate, and improved the yield of the products considerably (see Table) but only when acetonitrile was used as a solvent. Interestingly when these last reaction conditions were employed using the masked base allyltrimethylsilane as a substrate the alkylated product **7** was obtained in 63% yield. However, when trimethylsilyl trifluoroacetate or trimethylsilyl trifluoromethanesulfonate were used as activators in place of trifluoroacetic anhydride, the starting material was recovered. On the other hand, when the allylic-sulfoxide **1** was treated with 1.1 equivalents of trifluoroacetyl triflate in dichloromethane the starting material was quickly destroyed to give a very polar species even at very low temperatures (-90°).



1 **2**



3-7

Compound	R	X	Method	Time (h) [c]	Yield (%)
3		H	A B	24 8	41 32
4		H	A B	24 5	21 48
5		H	B	4	19
6		H	A B	24 3	26 52
7	—$CH_2CH{=}CH_2$	$Si(CH_3)_3$	B	7	63

[a] 2,6-Di-*tert*-butyl-4-methylpyridine, trifluoroacetic anhydride. [b] RX, Lewis acid. [c] Time after the addition of Lewis acid.

It is worthy of note that in all these cases the generated vinylthionium ion was captured with allylic transposition.

All physical data and elemental analysis data were consistent with the structures of the products **3-7**. Particularly in the ^{1}H-nmr spectra all compounds showed the characteristic peaks of the cepham ring system as well as the individual peaks of the attached aryl and alkyl groups. The 2-H of compounds **3**, **5**, **6** and **7** is deshielded and appears at about 6 ppm as a broad singlet probably arising from a weak allylic coupling. But in compound **4** the 2-H absorption appears as a doublet with a coupling constant of 1.2 Hz. The 4-H appears at about 5 ppm. The two protons of the 3-methylene give a characteristic singlet at ~3.5 ppm.

EXPERIMENTAL

General Procedures for the Preparation of Methyl 7-phthalimido-2-cephem-4-carboxylates **3-7**.

Method A.

The exomethylenecephem **1** (R = sulfoxide, 1 mmole, 0.37 g) was dissolved in 10 ml of dry dichloromethane under argon at room temperature, followed by the addition of 0.23 g (1.1 mmoles) of 2,6-di-*tert*-butyl-4-methylpyridine and 0.56 ml (4 mmoles) of trifluoroacetic anhydride. The mixture was stirred for about 20 hours, then the aromatic compound was added in large excess and finally 0.12 ml (1 mmole) of tin tetrachloride. After completion of the reaction, the crude product was added dropwise to water and extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered through silica and concentrated. The product was purified by liquid chromatography on silica using mixtures of dichloromethane-hexane as a solvent.

Method B.

The exomethylenecephem **1** (R = sulfoxide, 1 mmole, 0.37 g) was dissolved in 5 ml of dry acetonitrile under argon, followed by 0.25 g (1.2 mmoles) of 2,6-di-*tert*-butyl-4-methylpyridine. The mixture was cooled to 0° (ice-water) and 0.15 ml (1.1 mmoles) of trifluoroacetic anhydride was added. After stirring for 20 hours the nucleophilic substrate was added in excess (5-10 mmoles) followed by 0.25 ml (2 mmoles) of boron trifluoride etherate. The bath was removed and the temperature was allowed to rise to 20°. When the reaction was complete, the crude product was added dropwise to water and extracted with dichloromethane. The organic layer was dried over sodium sulphate, filtered through silica and concentrated. The product was purified by liquid chromatography on silica using mixtures of dichloromethane-hexane as a solvent.

Methyl 3-Benzyl-7-phthalimido-2-cephem-4-carboxylate (**3**).

This compound was obtained as white crystals, mp 203-203.5°; ^{1}H nmr (deuteriochloroform): δ 3.61 (broad s, 2H, 3-CH_2-), 3.68 (s, 3H, -$COOCH_3$), 4.95 (s, C4-H), 5.43 (d, J = 4 Hz, C6-H), 5.68 (d, J = 4 Hz, C7-H), 5.97 (s, C2-H), 7.3 (m, 5H, 3'-Ph), 7.75-7.90 (m, 4H, Ft-).

Anal. Calcd. for $C_{23}H_{18}N_2O_5S$ (434.47): C, 63.58; H, 4.18; N, 6 45. Found: C, 63.23; H, 4.25; N, 6.19.

Methyl 3-(*p*-Xylene)methyl-7-phthalimido-2-cephem-4-carboxylate (**4**).

This compound was obtained as a white powder, mp 151-153°; ^{1}H nmr (deuteriochloroform): δ 2.21 (s, 3H, CH_3-), 2.30 (s, 3H, CH_3-), 3.52 (broad s, 2H, 3-CH_2-), 3.77 (s, 3H, -$COOCH_3$), 5.00 (s, C4-H), 5.42 (d, J = 3.9 Hz, C6-H), 5.63 (d, J = 1.2 Hz, C2-H), 5.66 (d, J = 3.8 Hz, C7-H), 6.94-7.05 (m, 3H, 3'-Ar), 7.72-7.88 (m, 4H, Ft-).

Anal. Calcd. for $C_{25}H_{22}N_2O_5S$ (462.52): C, 64.92; H, 4.79; N, 6.06. Found: C, 65.04; H, 4.88; N, 5.77.

Methyl 3-(*p-tert*-Butylphenyl)methyl-7-phthalimido-2-cephem-4-carboxylate (**5**).

This compound was obtained as a white powder, mp 192-194°; ^{1}H nmr (deuteriochloroform): δ 1.29 (s, 9H, $(CH_3)_3C$-), 3.50 (broad s, 2H, 3-CH_2-), 3.78 (s, 3H, -$COOCH_3$), 4.99 (s, C4-H), 5.41 (d, J = 3.9 Hz, C6-H), 5.65 (d, J = 3.9 Hz, C7-H), 5.91 (broad s, C2-H), 7.1-7.2 (m, 4H, 3'-Ar), 7.72-7.88 (m, 4H, Ft-).

Anal. Calcd. for $C_{27}H_{26}N_2O_5S$ (490.57): C, 66.11; H, 5.34; N, 5.71. Found: C, 66.30; H, 5.41; N, 5.52.

Methyl 3-(*p*-methoxyphenyl)methyl-7-phthalimido-2-cephem-4-carboxylate (**6**).

This compound was obtained as white crystals, mp 189-192°; ^{1}H nmr (deuteriochloroform): δ 3.46 (broad s, 2H, 3-CH_2-), 3.67 (s, 3H, -OCH_3), 3.75 (s, 3H, -$COOCH_3$), 4.97 (s, C4-H), 5.41 (d, J = 3.9 Hz, C6-H), 5.63 (d, J = 3.9 Hz, C7-H), 5.94 (broad s, C2-H), 6.70-6.85 (A_2B_2, J = 8.5 Hz, 4H, 3'-Ar), 7.75-7.90 (m, 4H, Ft-).

Anal. Calcd. for $C_{24}H_{20}N_2O_6S$ (464.49): C, 62.06; H, 4.34; N, 6.03. Found: C, 62.17; H, 4.50; N, 5.83.

Methyl 3-(3-Butenyl)-7-phthalimido-2-cephem-4-carboxylate (**7**).

This compound was obtained as colorless leafs, mp 187-188°; ^{1}H nmr (deuteriochloroform): δ 2.2-2.4 (m, 4H, -CH_2CH_2CH=CH_2), 3.79 (s, 3H, -$COOCH_3$), 5.01 (s, C4-H), 5.03 (broad d, J_{cis} = 10.7 Hz, 1H, -CH_2CH_2CH=CH*H*), 5.07 (dd, J_{trans} = 16.8 Hz/J_2 = 1.5 Hz, 1H, -CH_2CH_2CH=C*H*H), 5.40 (d, 3.9 Hz, C6-H), 5.65 (d, 3.9 Hz, C7-H), 5.8 (m, 1H, -CH2CH2C*H*=CH_2), 5.92 (s, C2-H), 7.72-7.88 (m, 4H, Ft-).

Anal. Calcd. for $C_{20}H_{18}N_2O_5S$ (398.43): C, 60.29; H, 4.55; N, 7.03. Found: C, 60.44; H, 4.61; N, 6.79.

REFERENCES AND NOTES

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