CHEMISTRY LETTERS, pp. 183 - 186, 1985.

REACTION OF CEPHALOSPORIN 3'-TRIPHENYLPHOSPHONIUM YLIDE. SYNTHESIS OF A NOVEL TRICYCLIC CEPHALOSPORIN

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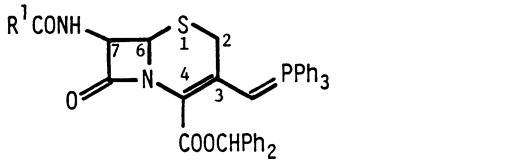
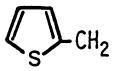
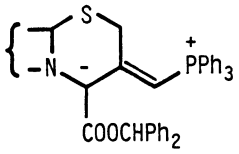
Reaction of cephalosporin 3'-triphenylphosphonium ylide with glyoxal gave a good yield of new cephalosporin derivative which possessed tricyclic framework bridged between the C-2 and C-3' positions.

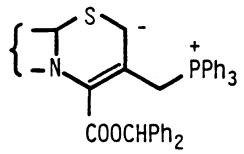
The reaction of cephalosporin 3'-triphenylphophonium ylide **1** with aldehyde is a useful method for the carbon-chain elongation at C-3' of cephalosporin.[1] However, utilization of the ylide in the synthesis of cephalosporin derivatives is considerably limited due to its poor reactivity and attendant formation of the C-2 and C-4 substituted products arising from the resonance-stabilized tautomers (e.g., **A** and **B**). In the previous communication, we have reported an interesting reaction of the ylide or its sulphoxide with acrylaldehyde leading to the tricyclic cephalosporins **2** and **3**.[2] Here we report other regioselective reactions of the



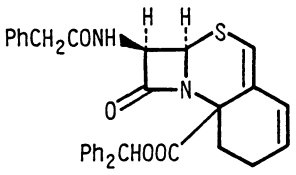
1 R^1 = $PhCH_2$, 



A



B



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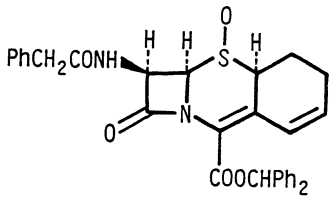


3

ylide **1** with trifluoroacetaldehyde and glyoxal, the latter giving a novel tricyclic cephalosporin which is bridged by a cyclopentene ring between C-2 and C-3.

Slow addition of 3 equiv. of anhydrous trifluoroacetaldehyde to an ice-cooled suspension of **1** (R^1=CH_2Ph) in dichloromethane (Table 1, Run 1) gave a mixture of **4**

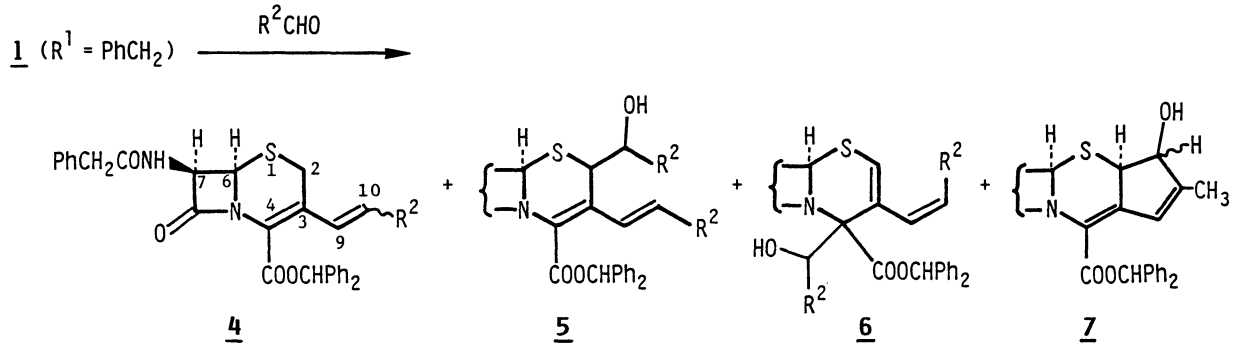
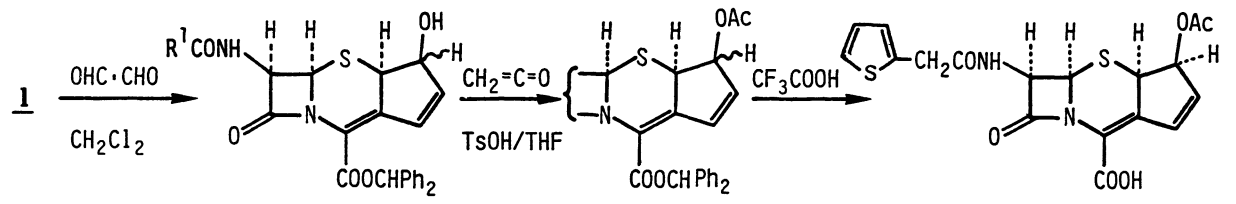


Table 1. Reaction of the ylide 1 ($R^1=CH_2Ph$) with aldehydes (R^2CHO)

Run	R^2	Solvent	Temp θ_m/°C	Time h	Ratio 1/R^2CHO	Isolated yield/% 4	5	6	7
1	CF_3	CH_2Cl_2	0	1	1:3	15	4	15	-
2	CF_3	CH_2Cl_2	40	0.5	1:3	66	0	0	-
3	CH_3CO	CH_2Cl_2	0	1	1:3	19	19	4	7
4	CH_3CO	DMF	-20	2	1:1.2	0	12	0	46
5	CH_3CO	CH_2Cl_2/aq-$NaHCO_3$	40	0.5	1:3	57	4	0	0

($R^2=CF_3$), 5 ($R^2=CF_3$), and 6 ($R^2=CF_3$).[3,4] The configuration of the double bond is trans for 5 ($J_{9,10}$=16.4 Hz) and cis for 6 ($J_{9,10}$=12.2 Hz), while 4 is a mixture of cis and trans isomers. In contrast, when the reaction was carried out at 40 °C, the compound 4 was obtained exclusively (Run 2). Thus the regioselectivity of this reaction is largely dependent on the reaction temperature. The C-2 and C-4 substituted products appear to arise from an initial aldol reaction followed by the Wittig reaction with another trifluoroacetaldehyde molecule, because 4 did not react with trifluoroacetaldehyde under the same reaction conditions as reported by Shingler et al.[1] The exclusive formation of 4 at 40 °C seems to indicate that the aldol reaction at C-2 or C-4 is kinetically controlled process.[5] Therefore, we next examined the reaction of the ylide with α-dicarbonyl compounds such as methyl glyoxal and glyoxal, in which formation of a cyclic compound might be expected.

The ylide reacted with 3 equiv. of 40% aqueous solution of methyl glyoxal at



8, $R^1=PhCH_2$
9, R^1=thienylmethyl

10

11

0 °C to give similar products, **4** (R^2=CH_3CO), **5** (R^2=CH_3CO), and **6** (R^2=CH_3CO), together with a small amount of the desired cyclic compound **7** (Run 3). The tricyclic cephalosporin **7** was obtained in a good yield when 1.2 equiv. of methyl glyoxal was slowly added at -20 °C to a suspension of the ylide in DMF (Run 4). Alternatively, a rise of reaction temperature to 40 °C resulted in almost exclusive formation of **4** (R^2=CH_3CO) similarly to the case of trifluoroacetaldehyde.

In contrast to the temperature dependence of the product distribution in the reaction of **1** with methyl glyoxal, reaction of the ylide with glyoxal gave only a tricyclic compound **8** in 50% yield even at room temperature, implying that formation of the C-2 aldol product was spontaneously followed by the internal Wittig reaction.

The resulting tricyclic compounds **7** and **8** were an inseparable mixture of two isomers in the ratios, 1:1 for **7** and 5:1 for **8**. Therefore, structural assignment of **8** was performed without separating each isomer by ^1H NMR spectrum (Fig. 1), in which the signals could be clearly assigned by means of ^1H-^1H shift correlated spectroscopy (COSY 45).[6] The two-dimensional NOE spectrum (Fig. 1) revealed that both H-2 signals in two isomers showed NOE with H-6, indicating that both isomers had *cis* ring-juncture at C-2. Furthermore, from a measurement of coupling constants (the major isomer: $J_{2,11}$=4.6 Hz, the minor isomer: $J_{2,11}$=6.0 Hz), it is estimated that the hydroxyl group of the major isomer **8a** is *trans* to H-2 and that of the minor isomer **8b** *cis* to H-2.

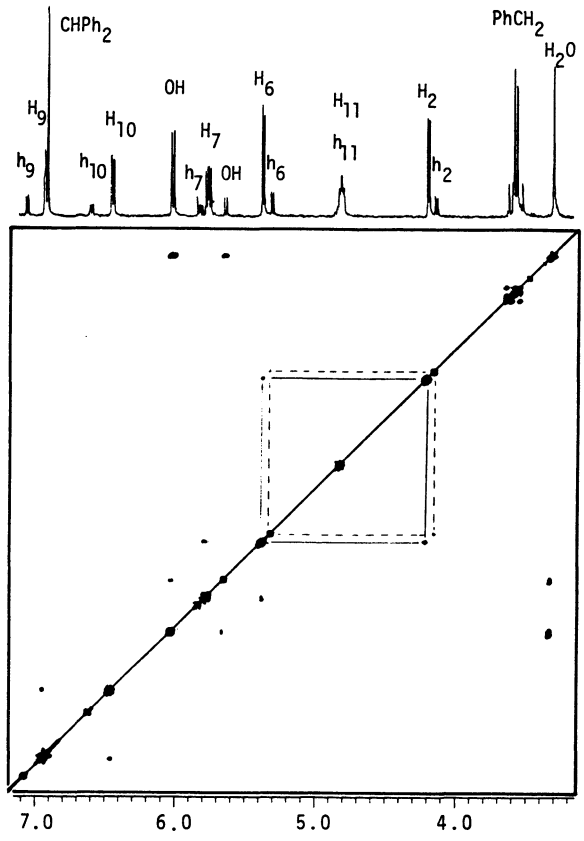
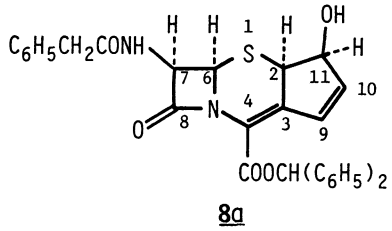
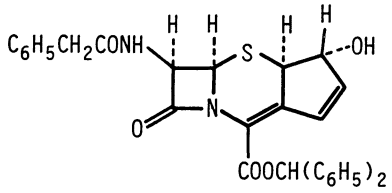


Fig. 1. Two-dimensional NOE spectrum of the isomeric mixture of **8a** and **8b** (in DMSO-d_6, Bruker AM 360 spectrometer).

Assignment is shown by capital letters for the major isomer **8a** and by small letters for the minor isomer **8b**.



8a



8b

To test biological activity of the interesting tricyclic compound,[7] we prepared compound **9** from **1** (R^1=thienylmethyl) in a similar manner. Attempted derivatization of the hydroxyl group including displacement by halogen (PCl_5-pyridine) and methylation (diazomethane-BF_3) were unsuccessful presumably owing to ready decomposition of the expected derivatives under the reaction conditions employed. However, acetylation with ketene gave a good yield of **10**. Careful treatment of **10** with trifluoroacetic acid and subsequent purification of the crude product by column chromatography afforded a single isomer **11**, which showed activity (MIC 1.56-3.13 μg/ml) against Gram-positive organisms, *S. aureus*, *S. epidermidis*, and *B. subtilis*, but no significant activity against Gram-negative organisms even in a concentration of 50 μg/ml.

References

1) A.H. Shingler and N.G. Weir, "Recent Advances in The Chemistry of β-Lactam Antibiotics," ed by J. Elks, J. Chem. Soc., Special Publication No.28, London (1977), p.153.

2) M. Hatanaka, Y. Yamamoto, and T. Ishimaru, J. Chem. Soc., Chem. Commun., in press.

3) All new compounds gave spectral and analytical data consistent with the proposed structures.

4) Selected physical data: **4** (R^2=CF_3): λ_{max}(EtOH) 292 nm (ε10200); ^{1}H NMR spectrum showed that this product was a 2:1 mixture of *cis* and *trans* isomers (*cis*, $J_{9,10}$=12.3 Hz; *trans*, $J_{9,10}$=16.0 Hz). **4** (R^2=CH_3CO): λ_{max}(EtOH) 325 nm (ε 11800). **5** (R^2=CF_3): ν(Nujol) 3200, 1790, 1720, and 1660 cm^{-1}; λ_{max} (EtOH) 259 (ε 8000) and 300 nm (ε 7700). **5** (R^2=CH_3CO): ν(Nujol) 3300, 1780, 1720, and 1680 cm^{-1}; λ_{max}(EtOH) 330 nm (ε 8900). **6** (R^2=CF_3): λ_{max} (EtOH) 265 nm (ε7100). **6** (R^2=CH_3CO): λ_{max}(EtOH) 259 (ε6600) and 265 nm (ε 6600). **7**: Mp 232-233 °C (decomp); ν (Nujol) 3300, 1770, 1710, and 1660 cm^{-1}; λ_{max}(EtOH) 312 nm (ε 16800). **8**: Mp 210-212 °C (decomp); λ_{max}(EtOH) 305 nm (ε16500). **9**: Mp 233-235 °C (decomp). **10**: Mp 194-198 °C (decomp). **11**: Mp 203-209 °C (decomp); ν(Nujol) 1785, 1760, 1705, and 1655 cm^{-1}; λ_{max} (EtOH) 296 nm (ε18400); δ(DMSO-d_6, 360 MHz) 2.09(3H, s, $COCH_3$), 3.78(2H, s, $COCH_2$), 4.43(1H, d, J=4.9 Hz, H_2), 5.30(1H, d, J=4.9 Hz, H_6), 5.69(1H, dd, J=4.9 and 8.1 Hz, H_7), 5.79(1H, m, H_{11}), 6.35(1H, dd, J=2.0 and 5.8 Hz, H_{10}), and 6.93-7.36(4H, m, thienyl and H_9).

5) Low solubility of the ylide **1** interfered with further detailed experiments.

6) The numbering system employed in this paper is shown in the structural formulas of **2** and **8a**.

7) For the tricyclic cephalosporins previously reported, see: F.H. Jung, W.R. Pilgrim, J.P. Poyser, and P.J. Siret, "Topics in Antibiotic Chemistry," ed by P.G. Sammes, Ellis Horwood Ltd., Chichester (1980), Vol.4, p.104.

(Received November 8, 1984)