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THE REACTION OF 3-DESACETOXY-7-ISOCYANATOCEPHALOSPORANIC ESTER WITH THE ANION DERIVED FROM t-BUTYL PHENYLACETATE; THE SYNTHESIS OF α-CARBOXYPHENYLACETAMIDOCEPHALOSPORINS

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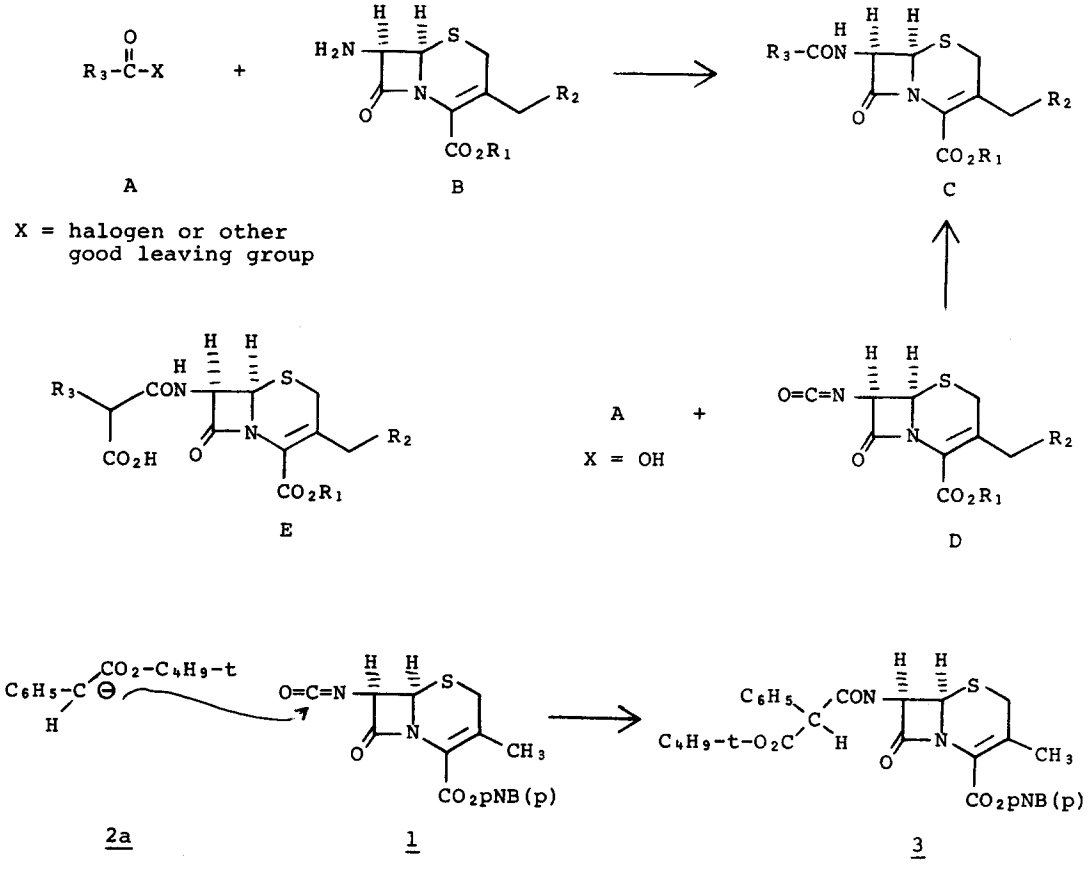
Modifying C_7-amide side chains of cephalosporins is one of the most important factors contributing to enhanced antimicrobial activity. The traditional method utilized for coupling acyl side chains to the cephalosporin nucleus has been the classical acylation (A + B → C). Recently, a method has been reported for the preparation of C which involves the reaction of the 7-isocyanatocephalosporanic derivative (D) with an acid A.[1] Conceptually, the isocyanate functionality is a very reactive electrophile which could be used for the synthesis of the biologically active cephalosporins (E) characterized by the α-carboxy functionality of the amide side chain. I wish to report here the results of my investigation as to the synthetic potential of the isocyanate in the synthesis of cephalosporins of type E.[2]

The reaction of 1 with the anion derived from t-butyl phenylacetate (2a) theoretically could present three possible problems: (1) isomerization of the Δ_3 double bond of the dihydrothiazine ring; (2) epimerization of C_7; (3) cleavage of the β-lactam. The reaction of 2a (prepared by the reaction of 2 with 1 equivalent of lithium diisopropylamide in tetrahydrofuran at -80°) with 1 at -80° afforded, upon protonation during acetic acid work-up and purification by preparative thin layer chromatography, a 60% yield of 3;[3,4] nmr τ_{CDCl_3} [H_7, 4.25 (quartet), H_6, 5.03 (doublet, J=4 Hz), ($t\text{-}C_4H_9\text{-}O_2C\text{-}\underline{C}\text{-}\underline{H}$), 5.47 (two singlets), ($\text{-}CH_3$), 7.84 (singlet)]. Significantly, no double bond isomerization, C_7-epimerization, or rupture of the β-lactam was observed. These data support the previous findings in these laboratories that the β-lactam is stable to strong nucleophiles at low temperature.[5]



References

1. Koninkliske Nederlandsche Gist, Belgian Patent 760,494 (1971).
2. For a similar synthesis, see P. W. Henniger, U. S. Patent 3,741,958 (1973).
3. The cephalosporin is isolated as a mixture of diastereomers as a result of the ready isomerization of the malonate side chain.
4. Compound 3 is identical to that which was prepared by an alternate synthesis.
5. G. A. Koppel and R. E. Koehler, J. Amer. Chem. Soc. 95, 2403 (1973).