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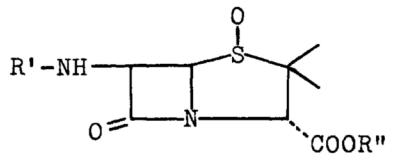
α-HALO-β-DICARBONYL COMPOUNDS. NOVEL CARBOXYL PROTECTING REAGENTS. THE APPLICATION TO THE SYNTHESIS OF CEPHALEXIN FROM PENICILLIN

Hitoshi IKEDA, Hajime NITTA, Mariko HATAMURA,
Minoru HATANAKA, and Toshiyasu ISHIMARU*
The Institute of Scientific and Industrial Research, Osaka University, Yamadakami, Suita, Osaka 565

α-Halo-β-dicarbonyl compounds are successfully used as the carboxyl protective reagents in the synthesis of cephalexin from penicillin.

Our preceding report[1] has described that α-halo-β-dicarbonyl compounds are useful reagents for the protection of carboxylic acids, and that the regeneration of the free acids from the protected acids is carried out under mild conditions by nitrosation using sodium nitrite or alkyl nitrite in aqueous acetone. Now, we wish to report that these protective groups are applicable to the well-known thermal rearrangement of penicillin sulfoxide into deacetoxycephlosporin[2]. In this rearrangement, the 3-carboxyl group of penicillin sulfoxide must be protected in order to avoid the accompanying decarboxylation[2a]. Several esters have been used for this purpose[3]. Our new protective groups provided a convenient process for the synthesis of cephalexin from penicillin.

Heating 1-methoxycarbonyl-2-oxopropyl 6-phenylacetamidopenicillanate 1-oxide (1a) for 5 h in boiling dioxane in the presence of pyridinium dichloromethane-phosphate[4] gave 1-methoxycarbonyl-2-oxopropyl 7-phenylacetamido-3-deacetoxy-cephalosporanate (2a) in 81% yield: mp 149.5°C (decomp.); IR (Nujol) 1760 cm^{-1} (β-lactam); Calcd. for $C_{21}H_{22}N_2O_7S$: C, 56.49; H, 4.97; N, 6.27%. Found: C, 56.23; H, 4.98; N, 6.48%. Subsequently, the phenylacetyl group was removed from 2a in a usual way; 2a was first treated with phosphorus pentachloride in methylene chloride containing pyridine at 5-10°C for 1.5 h, following with an excess of methanol at -20°C, and then with ice water for 1 h, to provide 2b, which was not characterized. The crude 2b was then coupled with D-α-t-butoxycarbonylamino phenylacetic acid via the mixed anhydride with ethyl chloroformate to give



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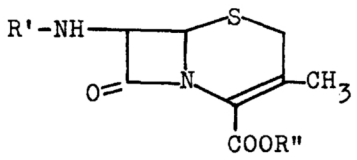

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a. R'= $C_6H_5CH_2CO-$, R"= $-CH(COOCH_3)-COCH_3$

b. R'= H, R"= $-CH(COOCH_3)-COCH_3$

c. R'= $C_6H_5-CH(NH\text{-}Boc)-CO-$, R"= $-CH(COOCH_3)-COCH_3$

d. R'= $C_6H_5-CH(NH\text{-}Boc)-CO-$, R"= H

e. R'= $C_6H_5-CH(NH_2)-CO-$, R"= H

2c (in 74% yield from 2a): mp 145-147°C (decomp.). Treatment of 2c with 5 equivalents of sodium nitrite in aqueous acetone containing 5 equivalents of acetic acid at 35°C for 30 min gave 2d in 74% yield; mp 135°C (decomp.). Subsequent removal of the N-t-butoxycarbonyl group by treatment with p-toluenesulfonic acid monohydrate in acetonitrile afforded cephalexin (2e) in 93% yield.

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* To whom correspondences should be addressed.

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