

$\alpha$ -HALO- $\beta$ -DICARBONYL COMPOUNDS. NOVEL CARBOXYL PROTECTING REAGENTS

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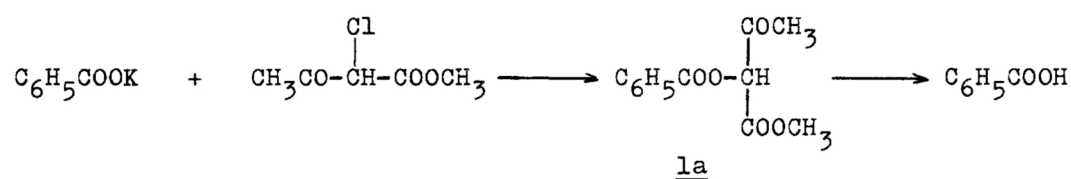
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$\alpha$ -Halo- $\beta$ -dicarbonyl compounds are useful reagents for the protection of carboxylic acids, particularly penicillin 3-carboxylic acid. The protected carboxylic acids can be successfully converted into the free acids by treatment with nitrosating reagents such as sodium nitrite and alkyl nitrite. The probable mechanism of this deprotection is also described.

In the course of work on penicillin and cephalosporin, we needed a carboxyl protecting group that would be moderately stable in both acidic and basic media and could be removed under mild conditions. The protective groups generally used in this area are trichloroethyl, t-butyl, p-methoxybenzyl, p-nitrobenzyl, benzhydryl, and phenacyl esters<sup>1)</sup>. However, successful removal of these esters of the 3-carboxylic acid of penicillin have not been reported, except for benzyl<sup>2)</sup> and phenacyl<sup>3)</sup> esters, because of the extremely labile  $\beta$ -lactam ring of penicillin. We now wish to report useful reagents for the protection of penicillin 3-carboxylic acids; namely the use of  $\alpha$ -halo- $\beta$ -dicarbonyl compounds.

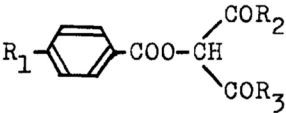
As a model experiment, 1-methoxycarbonyl-2-oxopropyl benzoate (la) was prepared in good yield by the treatment of potassium benzoate with methyl  $\alpha$ -chloroacetoacetate in DMF at room temperature. This ester, la, was moderately stable under acidic and basic conditions. It is well known that nitrosation of  $\alpha$ -alkylsubstituted  $\beta$ -keto esters is accompanied by a loss of the acyl group to yield  $\alpha$ -oximino esters<sup>4)</sup>. Therefore, nitrosation of la is to be expected to effect cleavage of the ester group. The best results were obtained by using an excess of sodium nitrite or alkyl nitrite in aqueous solvent; when la was treated at 0-5°C

with 3 equivalents of sodium nitrite in aqueous acetone, a nearly quantitative yield of benzoic acid was regenerated. This reaction did not proceed under the



anhydrous conditions or in an immiscible solvent with water (e.g., methylene chloride). Results obtained with other  $\beta$ -dicarbonyl esters of benzoic acid or p-toluic acid are summarized in the following table.

Table

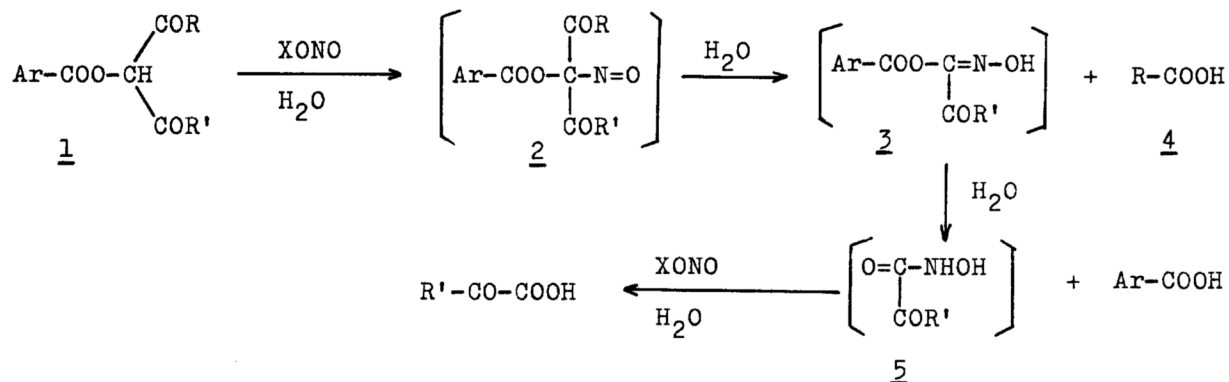
|           |  |                               |                                                                                     | Nitrosating<br>Reagents      | Yield (%) of<br>benzoic or p-toluic acid |
|-----------|-----------------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------------------------------------|------------------------------|------------------------------------------|
|           | R <sub>1</sub>                                                                    | R <sub>2</sub>                | R <sub>3</sub>                                                                      |                              |                                          |
| <u>1a</u> | H                                                                                 | CH <sub>3</sub>               | OCH <sub>3</sub>                                                                    | NaNO <sub>2</sub><br>n-PrONO | 90<br>88                                 |
| <u>1b</u> | H                                                                                 | CH <sub>3</sub>               | CH <sub>3</sub>                                                                     | NaNO <sub>2</sub><br>n-PrONO | 90<br>92                                 |
| <u>1c</u> | CH <sub>3</sub>                                                                   | C <sub>6</sub> H <sub>5</sub> | OC <sub>2</sub> H <sub>5</sub>                                                      | NaNO <sub>2</sub>            | 91                                       |
| <u>1d</u> | CH <sub>3</sub>                                                                   | C <sub>6</sub> H <sub>5</sub> | CH <sub>3</sub>                                                                     | NaNO <sub>2</sub>            | 90                                       |
| <u>1e</u> | H                                                                                 | OCH <sub>3</sub>              | OCH <sub>3</sub>                                                                    | NaNO <sub>2</sub>            | trace                                    |
| <u>1f</u> | H                                                                                 | CH <sub>3</sub>               |  | NaNO <sub>2</sub>            | trace                                    |

The failure of the deprotection of 1e and 1f is probably due to less acidity of the methine protons of 1e and 1f.

In the general procedure, to a solution of 1a (1.18 g, 5 mmol) in acetone was added at 5°C a solution of sodium nitrite (1.0 g, 15 mmol) in water (5 ml) with stirring. The stirring was continued for 3 h at room temperature, and then the acetone was evaporated under reduced pressure. The resulting solution was washed with ethyl acetate, and then adjusted to pH 2 with dilute hydrochloric acid. The white precipitate was collected by filtration to give benzoic acid (0.55 g, 90.5%).

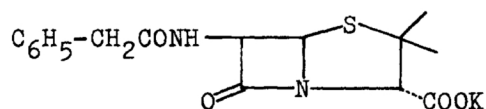
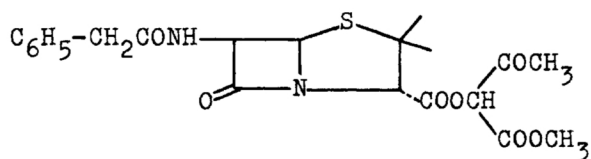
For the elucidation of the mechanistic pathway, isolation of the degradation

products derived from the  $\beta$ -dicarbonyl moieties of the esters, la and lc, was examined. After la was allowed to react with sodium nitrite in aqueous acetone, the solution was evaporated to dryness under reduced pressure and the remaining solid was then treated with p-nitrobenzyl bromide in DMF. Column chromatography on silica gel of the crude product gave 85% yield of p-nitrobenzyl benzoate: mp 87-88°C (lit<sup>5</sup>), mp 89°C), 67.5% yield of p-nitrobenzyl acetate: mp 77°C (lit<sup>6</sup>), mp 78°C), and 45.2% yield of methyl p-nitrobenzyl oxalate: mp 107-108°C. Similar experiment with lc also provided the mixture of p-nitrobenzyl p-toluate, p-nitrobenzyl benzoate, and ethyl p-nitrobenzyl oxalate. Therefore, the deesterification may be rationalized as shown in the following mechanistic scheme.



The first step is undoubtedly nitrosation at the methine carbon atom to form 2. Subsequently, 2 would be hydrolyzed into the carboxylic acid, 4, and the O-acyl hydroxamic acid, 3, in a manner similar to that reported for the nitrosation of  $\alpha$ -alkylsubstituted  $\beta$ -keto esters<sup>4)</sup>. The further hydrolysis of 3 will lead to benzoic acid and the hydroxamic acid, 5. Although the presence of 5 in the reaction mixture was not detected, this can be explained on the basis of the fact that the authentic oxalmonohydroxamic acid monomethyl ester was oxidatively hydrolyzed into methyl hydrogen oxalate on the treatment with sodium nitrite under the same conditions as that of the deesterification reaction.

The utility of these protecting reagents is shown nicely by the protection of the 3-carboxylic acid of penicillin. Thus, potassium 6-phenylacetamidopenicillanate (6) was allowed to react with methyl  $\alpha$ -chloroacetoacetate in DMF at room temperature overnight to yield 1-methoxycarbonyl-2-oxopropyl 6-phenylacetamidopenicillanate (7): mp 118°C (decomp.); IR (Nujol): 1785, 1755, 1640  $\text{cm}^{-1}$ ; UV (ethanol)  $\lambda_{\text{max}}$  257 nm ( $\epsilon$ , 10.7) and 263 nm ( $\epsilon$ , 7.8); Calcd. for

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$C_{21}H_{24}N_2O_7S$ : C, 56.25; H, 5.35; N, 6.25%. Found: C, 56.04; H, 5.48; N, 6.35%.

Treatment of 7 with 1.3 equivalents of sodium nitrite in aqueous acetone afforded the free acid, 6, in 85% yield.

#### References

- 1) J.F.W.McOmie, Ed., "Protective Groups in Organic Chemistry", Plenum Press, London and New York, Chapter 5 (1973).
- 2) J.C.Sheehan and E.J.Corey, J. Am. Chem. Soc., 74, 4555 (1952).
- 3) J.C.Sheehan and G.D.Daves Jr., J. Org. Chem., 29, 2006 (1964).
- 4) O.Touster, Org. React., Vol. 7, Chapter 6 (1953); M.M.Rogic', J.Vitrone, and M.D.Swerdloff, J. Am. Chem. Soc., 99, 1156 (1977).
- 5) E.J.Bourne, M.Stacey, J.C.Tatlow, and J.M.Tedder, J. Chem. Soc., 1949, 2976.
- 6) W.W.Hartman and E.J.Rahrs, Org. Synth., Coll. Vol. 3, 650 (1955).

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