

MILD CONVERSION OF PRIMARY ALCOHOLS AND ALDEHYDES TO ACID FLUORIDES WITH CAESIUM FLUOROXYLSULPHATE

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Abstract - Caesium fluoroxy sulphate in acetonitrile medium at 35°C converts primary alcohols and alkyl, as well as aryl aldehydes, to acid fluorides in high yield.

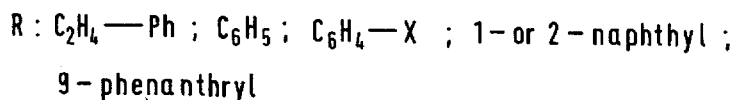
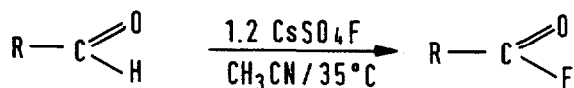
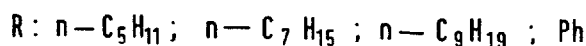
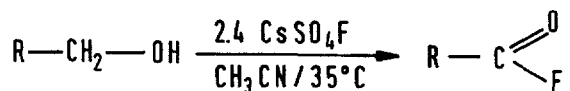
It has already been demonstrated that CsSO₄F is a convenient reagent for the selective fluorofunctionalisation under mild conditions of aromatics¹, alkenes², alkynes³, alkanes⁴, uracil derivatives⁵, and aryltrialkyltin compounds⁶, while the reaction of CsSO₄F with dibenzothiophene or triphenylphosphine resulted in the formation of sulphone and triphenylphosphine oxide, respectively⁵. Reported results show that the course of the reaction strongly depends on the structure of the organic molecules and the functional groups present, the reagent to substrate molar ratio, solvent polarity, catalyst used, reaction temperature, as well as the general reaction procedure, so that any of above mentioned variables can cause the reaction to follow a different path, which in general, leads to two kinds of products, i.e. fluorosubstituted or oxidised derivatives.

We now report that when benzyl alcohol is treated with an equimolar amount of CsSO₄F in acetonitrile medium, in the crude reaction mixture the presence of nearly 50% of benzoyl fluoride, and a few percent of benzaldehyde was established, the rest being starting material. The total conversion of benzyl alcohol to benzoyl fluoride needed 2.4 mmols of caesium fluoroxy sulphate per mmol of benzyl alcohol, and after purification over 85% of pure acid fluoride was isolated. We expanded our study to various other types of alcohols. In a typical experiment to a solution of 1 mmol of alcohol (Scheme) in acetonitrile (2 ml) we added 0.6 g (2.4 mmols) of CsSO₄F and, while the reaction temperature was kept between 30-35°C, we stirred the reaction mixture for 2 hours. It was then diluted with 20 mls of CH₂Cl₂, the insoluble inorganic residue filtered off, the methylene chloride solution washed with water, dried over anhydrous Na₂SO₄, and the solvent evaporated in vacuo. Analysis of the crude reaction mixtures by ¹⁹F and ¹H NMR, using octafluoro-naphthalene as an internal standard, and glc, revealed the presence of 85-90% of the corresponding acid fluoride, isolated in 80-85% yield after purification, while 2-5% of aldehyde was detected in the crude reaction mixtures.

Under the same reaction conditions only a 20% molar excess of CsSO₄F was sufficient to convert 4-tert-butylcyclohexanol, as an example of secondary alcohol, into 4-tert-butylcyclohexanone, while the reaction with a tertiary alcohol, 2-cyclohexyl-2-propanol, resulted in a crude reaction mixture of up to six products, none of them containing fluorine.

The results described above, indicate that caesium fluoroxy sulphate readily oxidises primary alcohols to aldehydes, which further transform to acid fluorides, the fluorination process being the faster reaction step. Therefore, we studied the reactions of CsSO₄F with various aldehydes under the conditions already described, and acid fluorides in over 80% yield were isolated (Scheme). The substituents

SCHEME



on the aromatic ring (X: p-OCH₃, p-CH₃, p-Cl, p-COOH, p-COOCH₃, p-NO₂, m-NO₂) only influence the reaction rate. Para methoxy-benzaldehyde was transformed to para methoxybenzoyl fluoride in 30 minutes, while meta nitrobenzaldehyde needed 6 hours to be completely converted to meta nitrobenzoyl fluoride. No other significant product could be detected in the crude reaction mixtures, showing that the aldehyde functional group is the most reactive site of the molecule, even when the aromatic ring is activated. Further, we established the considerable influence of radical inhibitor nitrobenzene on the course of the reaction. Conversion of benzaldehyde and p-methoxybenzaldehyde to the acid fluoride was considerably inhibited as a function of the molar ratio of radical inhibitor to aldehyde, showing that the reaction course runs mainly via free radical intermediates.

In the case of the two aldehydes, so far tested, the reactions with CsSO₄F proceeded differently. After the reaction of phenylacetaldehyde with a 20% molar excess of CsSO₄F, we isolated the benzyl fluoride and phenylacetyl fluoride in a 2:1 relative ratio, while in the case of 9-anthraldehyde, 9-fluoroanthracene was isolated as the main product in 30% yield, accompanied by the starting material and less than 5% of unidentified fluorinated products.

The testing of the reactivity of CsSO₄F towards more sophisticated alcohols and aldehydes and some kinetic measurements are now in progress in order to define the limiting value of the method, and to elucidate some mechanistic aspects of the reaction.

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(Received in UK 4 September 1989)