

Sodium 2-Ethylhexanoate: A Mild Acid Scavenger Useful in Acylation of Amines

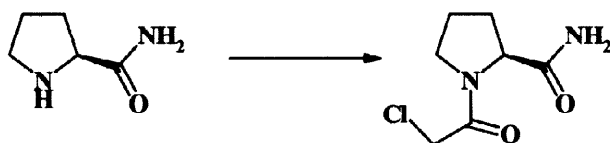
John Fitt, Kapa Prasad,* Oljan Repič, and Thomas J. Blacklock

Process R&D, Chemical and Analytical Development,
Novartis Pharmaceuticals Corporation,
59 Route 10, East Hanover, NJ 07936, U.S.A.

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Abstract: A highly useful method for the acylation of amines with acid chlorides utilizing sodium 2-ethylhexanoate as the base is described. This procedure is superior to the Schotten-Baumann conditions whenever the product is water soluble. © 1998 Elsevier Science Ltd. All rights reserved.

Sodium 2-ethylhexanoate is an inexpensive reagent that can be easily made from sodium hydride with 2-ethylhexanoic acid and is also readily available commercially at < \$10/kg from several sources.¹ This reagent is unique in the sense that it is readily soluble in common organic solvents like ethers, toluene, etc; this property has been used advantageously to make the crystalline sodium salt of amoxicillin² and several other carboxylic acid salts³ where the conjugate salt is insoluble in the exchange media. During our work on deriving a simple, practicable, high yielding, and environmentally friendly method for the acylation of prolinamide with acid chlorides, we faced the usual set of concerns. Classical Schotten-Baumann acylation conditions

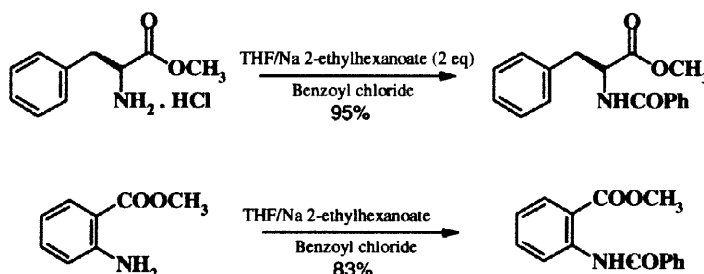


were found to be impractical as the starting material and the products are highly water-soluble and sparingly soluble in organic solvents, causing significant isolation problems. In the literature, for N-chloroacylation of heteroanthranilates, 1,2-epoxypropane⁴ was successfully used as a HCl scavenger. Application of these conditions to our system worked well, however, the reaction in THF was heterogeneous from beginning to the end, and epoxypropane is carcinogenic, low boiling and environmentally unacceptable. In view of this, we considered the use of sodium 2-ethylhexanoate as an organic-soluble base, the driving force being the irreversible formation of sodium chloride. Thus mixing of a suspension of prolinamide in THF with stoichiometric amounts of sodium 2-ethylhexanoate resulted in a clear solution, and the addition of chloroacetyl chloride resulted in the precipitation of the desired product along with NaCl in quantitative yield. As NaCl does not interfere, the subsequent reaction was carried out with this mixture with no further purification. The use of one equivalent of 2-ethylhexanoic acid as an additive in addition to sodium 2-ethylhexanoate allowed using the less expensive *t*-butyl methyl ether as the solvent instead of THF, as the lipophilic additive increased the solubility of prolinamide. To our knowledge this is the first example of the use of sodium 2-ethylhexanoate as a base in the acylation of amines with an acid chloride. As the method is so practical, we investigated it further with other acid chlorides and found it to be quite general (see Table). Depending on the need and the nature of the product,

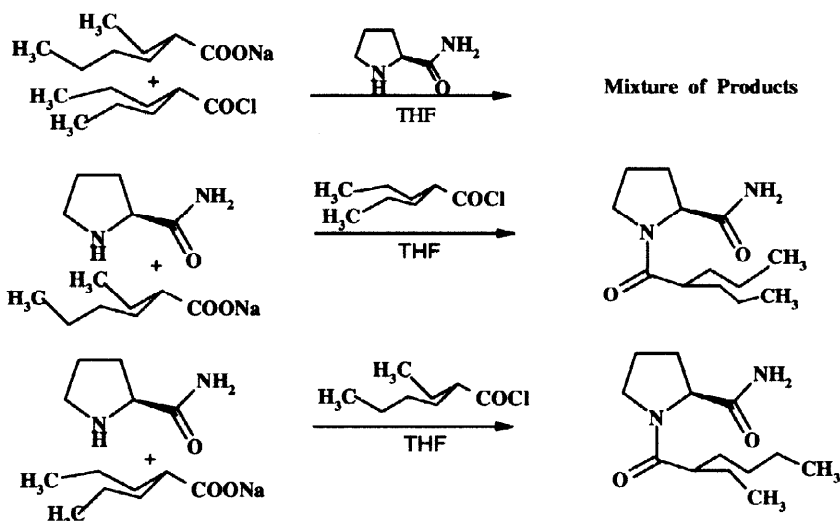
either the sodium chloride is washed out with water or the product is separated by extraction into organic solvents.

Table:

Acid Chloride	Acylated Product (yield %)
CH_3COCl	80
ClCH_2COCl	>90
$t\text{-BuCOCl}$	>90
PhCH_2COCl	>90



Utilizing sodium 2-ethylhexanoate as base, anthranilates and amino acid esters were also acylated in high yield as shown above. Concerning the mechanism of these acylations, it appears that there is no involvement of the mixed anhydride formation since preforming the anhydride by mixing sodium 2-ethylhexanoate with acid chloride as shown below, followed by the addition of prolinamide, gave a mixture of two acylation products. The addition of acid chloride at the end resulted in the isolation of a single acylation product, and the other product, which would result if a mixed anhydride was involved, was not detectable by NMR.



In conclusion, we described a simple, mild, and very efficient method for acylation of amines with acid chlorides utilizing sodium 2-ethylhexanoate, a mild, organic-soluble, and inexpensive base.

References

- For example, Aceto Corporation (1 Hollow Lane, Lake Success, New York 11042) supplies sodium 2-ethylhexanoate at <\$10/kg when ordering a minimum of 25 kg.
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