

The twilight zone of Vanillic Acid nitration: how the purity requirements for a pharma-grade intermediate faces off with a well-known standard reaction

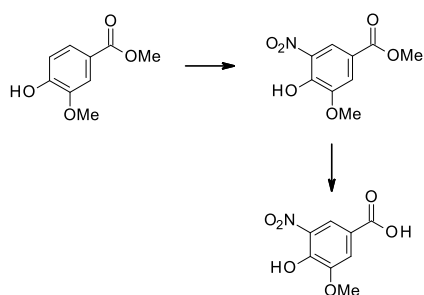
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Nitration of organic molecules is a very common strategy to functionalize and prepare intermediates from the laboratory up to the industrial scale. Side-reactions and by-products of this reaction are very well-known and understood. In fact, plenty of literature can be found on this subject. Nonetheless, requirements of purity for active pharmaceutical ingredients (APIs) are continuously increasing because of the knowledge of the potential subsequent fate of impurities in starting materials and intermediates. This implies that impurity management is a growing issue in the pharmaceutical industry.

5-Nitrovanillic acid is a very simple molecule and its use spans from adhesive composition¹ to counterfeit-proof paper², as well as intermediates for the synthesis of catechol-O-methyltransferase (COMT) inhibitors for the treatment of Parkinson's disease, such as Tolcapone³ or novel drugs like Opicapone⁴.

Preparation of 5-nitrovanillic acid (Scheme 1) has been reported since the early XXth century⁵ but, even though the reaction mechanism and side-products are very well known, systematic identification of all the impurities deriving from nitration of vanillic acid is still incomplete. Such identification is needed to set up an appropriate control strategy and avoid quality problems in subsequent steps or on the finished product. Here, isolation (Figure 1) and full characterization (Figure 2) along with independent synthesis of critical impurities present in 5-nitrovanillic acid is reported.



Scheme 1

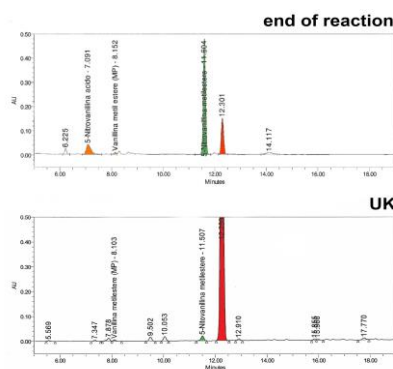


Figure 1

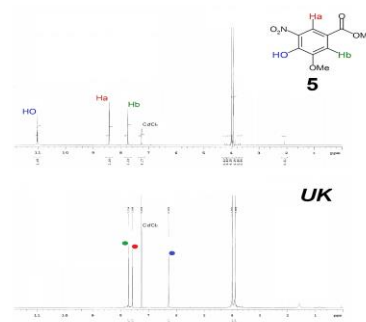


Figure 2

References:

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