Introduction

N-substituted imidazoles and their derivatives (Figure 1) are pharmaceutically important due to their pharmacodynamic properties. In the last two decades, interest for the study of these precursors of pharmaceuticals has grown due to the increase of infections of fungal origin. This increase has been caused by the massive introduction of new drugs (antibiotics, corticosteroids and immunosuppressants), surgical procedures (catheterization, transplants, prosthesis) and as a result of new disease developments, such as those caused by the human immunodeficiency virus (HIV). In an industrial process development environment, empirical approaches are typically used to optimize reaction time, selectivity and chemical reaction yields.
This note demonstrates the use of Raman monitoring of the synthesis of 1-alkyl-2-methylimidazoles under both acid and basic heterogeneous media. This methodology can be applied to multiple reactions in the preparation of other N-alkylated purines, which serve as precursors in the primary route to pharmaceutically important acyclic nucleoside analogues with antiviral properties, such as penciclovir, acyclovir and famciclovir, by substituting adenine with different alkylation agents (Figure 1).

**Experimental**

The N-alkylation reaction for the synthesis of 1-alkyl-2-methylimidazoles was run in a batch reactor under thermal activation at 333 K, and under continuous stirring. The reaction was carried out in solvent-free conditions using an excess of the alkylating agent and both acid and basic solid catalysts, hydrated niobia Nb₂O₅·nH₂O and Cs-Norit activated carbon. The reaction was monitored by Raman spectroscopy using a PerkinElmer® RamanStation™ 400F system with a 100 mW 785 nm excitation line capturing 50 accumulations of 1 second, every five minutes. Activity was measured by gas chromatography with a capillary column.

Figure 3 illustrates representative Raman spectra during the reaction with the acid (left) and basic (right) catalyst. Representative bands are commented.

Monitoring alkylation heterocycle reactions traditionally require parallel analyses by chromatography. However, this can be time consuming and may not provide direct real time analysis of reaction progress. In addition, chromatography cannot provide the molecular information on reaction mechanisms and intermediates.

Raman spectroscopy is a powerful non-invasive tool for real time in-situ monitoring of organic reactions when the reactants, products or intermediates are Raman active and are present in adequate concentrations. With this technology, any liquid-phase reaction can be monitored, even in the presence of a solid catalyst.

Solid acids and bases are commonly used for the manufacture of fine chemicals by catalyzing, e.g. alkylation reactions, the different determining reaction pathways. In the case of N-alkylations, several solid acid catalysts, such as alumina and zeolites, and also solid bases, such as clays and alkali doped carbons, have been proposed for this reaction due to the convenience and environmentally friendly characteristics of the solid catalysts. Both the acid and base-catalyzed alkylation of 2-methylimidazoles yield the N-alkyl-2-methylimidazole following a different mechanism of imidazole alkylation (Figure 2).
Real-time assessment of single N-alkylation is fundamental for an efficient synthesis of pharmaceutical precursors. A representation of the intensities of Raman bands is illustrated in Figure 4, which shows how Raman monitoring indicates the time for complete alkylation of imidazole, preventing further alkylation into the ionic liquid phase. Raman intensity trends show that maximum conversion to monoalkylated imidazole happens at ca. 1.5 hours in acidic medium and at ca. 2.25 hours in basic medium. The dialkylation to imidazolium salts after monoalkylation has been done and is significantly faster and more important in acidic medium.

Figure 3. Raman spectra of the N-alkylation of 2-methylimidazole with 1-bromobutane at 333 K using acid (top) and basic (bottom) solid catalysts, Nb₂O₅·nH₂O and Cs-Norit respectively.

Figure 4. Real-time normalized Raman intensity of representative Raman bands during 2-methylimidazole alkylation with 1-bromobutane in acid (left) and basic (right) media.

Conclusions
Real-time Raman spectroscopic monitoring during alkylation reactions provides detailed molecular information on the reaction mechanism and possible intermediates, while remaining non-invasive. Thus, it is possible to see progressive alkylation of 2-methylimidazole in the N-position under both acid and basic media. This methodology can be applied to a wide range of processes. This is critical to understanding reaction mechanisms and to provide a tool for real-time reaction monitoring and feedback for reaction control.

PerkinElmer Raman instruments are based on an Echelle spectrometer design that produces a full spectral range (3500-230 cm⁻¹) at high resolution (better than 4 cm⁻¹). This system provides scientists, engineers and technicians with means to follow the course of an organic or inorganic reaction in real time.
References


