

PROCESS FOR CATALYZING THE OXIDATION OF ORGANIC COMPOUNDS

This application claims the benefit of provisional applications No. 60/148,079 filed Aug. 10, 1999 and Ser. No. 60/150,101 filed Aug. 20, 1999.

FIELD OF THE INVENTION

The study of drug metabolism is an important part of the very expensive drug R&D process. In humans and other mammals, many drugs are metabolized through oxidative reactions catalyzed by heme- and cytochrome-containing enzymes. Cytochrome P450 mono-oxygenases, the main enzymes involved in drug oxidative metabolism, have in their active site a heme moiety.

Synthetic metalloporphyrins can serve favorably to mimic oxidative catalytic reactions occurring in biological systems, with the aim of producing and identifying oxidative products of drug candidates, in quantities allowing in vivo studies.

PCT application WO 90/08455 discloses a process for the preparation of oxidative products using various combinations of a synthetic metalloporphyrin, a co-oxidizing reagent, and a solvent. The solvent is generally a CH₃CN/CH₂Cl₂ combination. One of the major inconveniences of processes of this type is the fact that they frequently provide incomplete yields of the sought-after individual products as well as low conversion percentages. As a result, they can rarely be used in a reliable fashion in integrated discovery processes. In fact, their use is generally limited to experimental validation.

SUMMARY OF THE INVENTION

In accordance with the present invention, the inventor has unexpectedly found that the yields of oxidative reactions involving metalloporphyrins and which can be useful for the synthesis of metabolites of organic compounds of interest could be increased in a substantial manner through the use of an inert aprotic solvent.

Thus, one of the objects of the present invention is a process for the oxidation of organic compounds. This process comprises reacting the selected organic compound with catalytic amounts of a metalloporphyrin and of an oxidizing agent in the presence of an inert aprotic solvent and recovering the desired products obtained therefrom.

The process of the invention is extremely useful in pharmaceutical research and development as it can be used to perform preliminary evaluations of the metabolic processes which are likely to occur when a given compound is tested in vivo. These preliminary evaluations can be performed rapidly without having to carry out expensive and time consuming in vivo experiments. Furthermore, the process of the present invention provides better yields of individual products than those obtained using prior art processes. In other words, the process of the present invention opens the possibility of obtaining and analyzing in a more systematic fashion a higher number of individual potential metabolites for a given selected compound on which the process is carried out.

DETAILED DESCRIPTION OF THE INVENTION

The present invention therefore concerns a process for the efficient oxidative preparation of metabolites of organic compounds. The invention comprises reacting an organic compound of interest with a catalytic amount of a metalloporphyrin and an oxidizing agent, in a non-reactive aprotic solvent.

As mentioned previously, several drugs are metabolized through oxidative reactions. The process of the instant invention is therefore applied favorably to organic compounds of interest possessing one or several functional groups which will react to oxidation conditions. Some of these functional groups are described below but as the skilled person will readily appreciate, the list provided is not intended to be exhaustive. In fact, the process of the invention can be used on any organic compound which can be oxidized in some way by enzymes involved in drug oxidative metabolism.

Preferably, compounds containing heteroatoms, such as nitrogen or sulfur, can be efficiently oxidized through the process of the invention, particularly to a higher oxidation state, and more particularly to their highest oxidation state. For example, primary amines can be readily converted to their corresponding hydroxylamines, nitroso- or nitro-derivatives; and tertiary amines to their corresponding N-oxides.

Also, C—H bonds can be conveniently hydroxylated into C—OH bonds by metalloporphyrin-catalyzed oxidations according to this invention. Examples include labile C—H bonds, such as those in benzylic positions or C—H bonds wherein the carbon atom is adjacent to a heteroatom (e.g. N, S, O, or the like). Those are particularly reactive to these conditions.

In this manner, primary alcohols can be converted to their corresponding aldehydes; in turn aldehydes can be converted to their corresponding acids, and said acids may further undergo decarboxylation.

Through the process of the invention, secondary alcohols can be converted to their corresponding ketones.

Carbon-carbon double bonds can be epoxidized by metalloporphyrin-catalyzed oxidation according to this invention, and aromatic groups can be oxidized into corresponding phenols or quinones.

The main parameters involved in the process of the invention are the starting material which is usually an organic compound of interest, the reactants which usually include a metalloporphyrin, an oxidizing agent and an inert aprotic solvent, and the reaction conditions which comprise the reaction temperature and the reaction time. Each of these parameters will be discussed in further detail below.

Metalloporphyrins

Synthetic metalloporphyrins are described in international patent application WO 96/08455. The term "metalloporphyrin", as used herein, refers to porphyrin compounds of formula (I):