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Review Article

Three-component reaction of amines, epoxides, and carbon dioxide: A straightforward route to organic carbamates

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ABSTRACT

The efficient utilization of carbon dioxide (CO_2) as a C1-building block in organic synthesis has attracted considerable attention in view of sustainable chemistry and green chemistry concepts. Recently, three-component reaction of amines, epoxides, and carbon dioxide has emerged as a powerful strategy for the synthesis of biologically important organic carbamates. In this review, we try to provide a comprehensive and updated overview of recent developments in this interesting research arena with special emphasis on the mechanistic aspects of the reactions. The review is divided into two major sections. The first section focuses exclusively on synthesis of acyclic carbonates, while the second covers construction of cyclic carbamates.

1. Introduction

Organic carbamates, identified by the presence of the −OC(O(NH− linkage, are among the most important class of organic compounds which are widely found in natural products [1], pharmaceutically active compounds [2], and agrochemicals (pesticides, herbicides, insecticides, fungicides *etc.*) [3]. Because of their chemical stability and ability to permeate cell membranes, many currently marketed drugs contain carbamate structures. For examples (Fig. 1), Tedizolid **1** with the brand name of Sivextro is a five-membered cyclic carbamate marketed worldwide for the treatment of skin infections in adults, including "MRSA" staph infections [4]. The drug works by inhibition of protein synthesis by binding to the V-domain of the 23S rRNA component of the 50S ribosomal subunit [5]. Toloxatone **2** is a monoamine oxidase A (MAOA) inhibitor, marketed as an antidepressant under the trade name Humoryl [6]. Ritonavir **3** (Norvir) is a promising antiretroviral drug used for the treatment of HIV infection, in combination with other drugs [7]. Felbamate **4** with trade name Felbatol is an anticonvulsant drug used in the treatment of epilepsy [8].

Organic carbamates classically have been synthesized starting from amines using highly toxic phosgene or isocyanate derivatives which may cause serious environmental pollution and safety problems [9]. Over the past three decades, carbon dioxide (CO_2) has emerged as an ideal C1-building block to replace phosgene because it is abundant, inexpensive, nontoxic, nonflammable, and renewable [10–21]. Along this line, great efforts have been directed toward the synthesis of organic carbamates through three-component reaction of amines, epoxides, and carbon dioxide (Fig. 2). Interestingly, to our best knowledge, a comprehensive review has not appeared so far on this chemistry. In continuation of our recent works [10], this review survey research works on the preparation of cyclic and acyclic carbamates from amines, epoxides, and CO_2. The first section focuses exclusively on synthesis of acyclic carbonates, while the second covers construction of cyclic carbamates. It is noted that special emphasis is laid on mechanistic aspects of the reactions.

2. Synthesis of acyclic carbamates

2.1. Catalyst-free reactions

The first report on the synthesis of acyclic carbamates through three-component reaction of carbon dioxide, epoxides, and amines was published in 1978, by Yoshida and Inoue [22]. They showed that treatment of 1,2-epoxycyclohexane **5** with aliphatic amines **6** in solvent-free conditions under the CO_2 atmosphere (~50 atm) furnished corresponding hydroxy-carbamates **7** together with amino alcohols **8** as the by-products (Scheme 1 a). In this study, both primary and secondary aliphatic amines underwent coupling to the target carbamates in moderate yields. It should be mentioned that the application of this procedure to epoxyethane and 1,2-epoxypropane proved to be difficult

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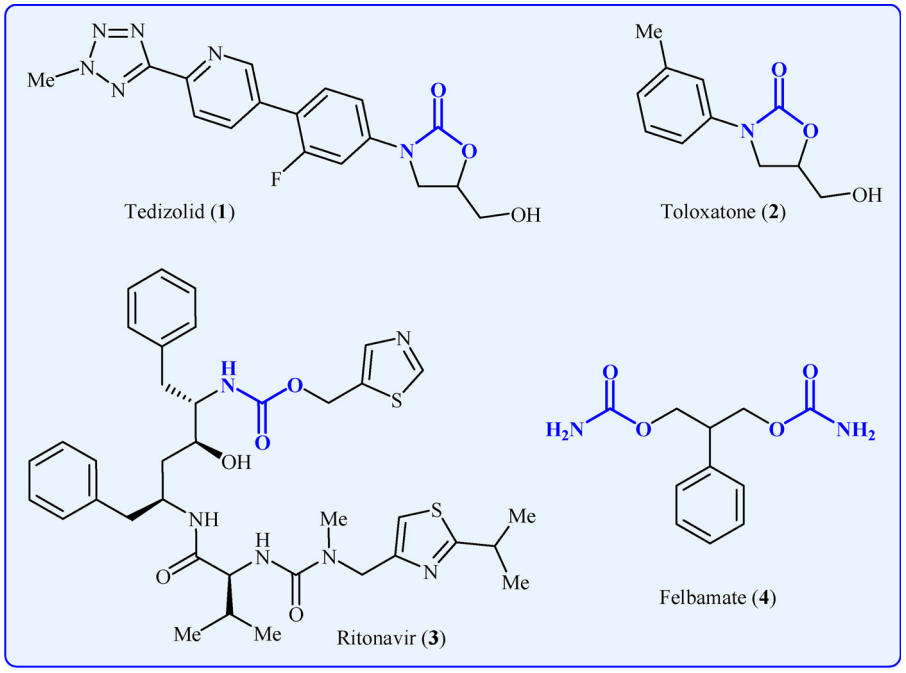


Fig. 1. Selected examples of drugs containing cyclic or non-cyclic carbamate moiety.

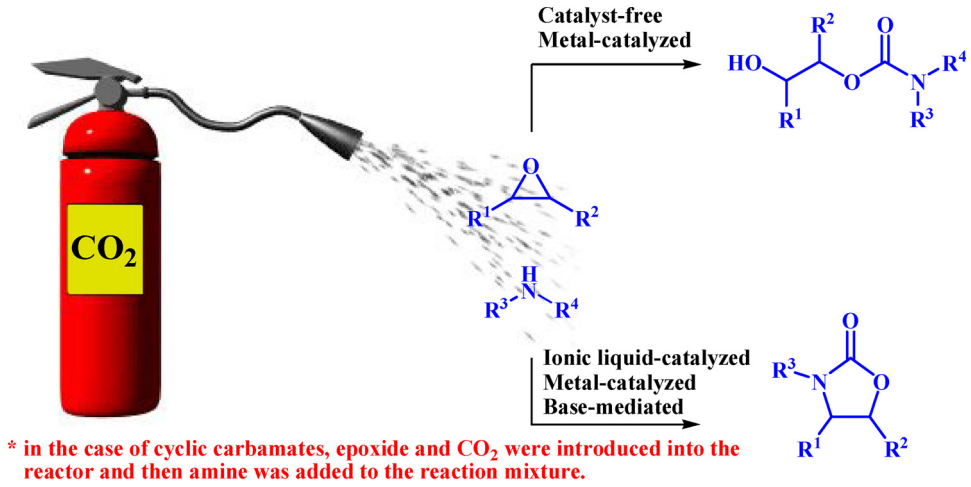
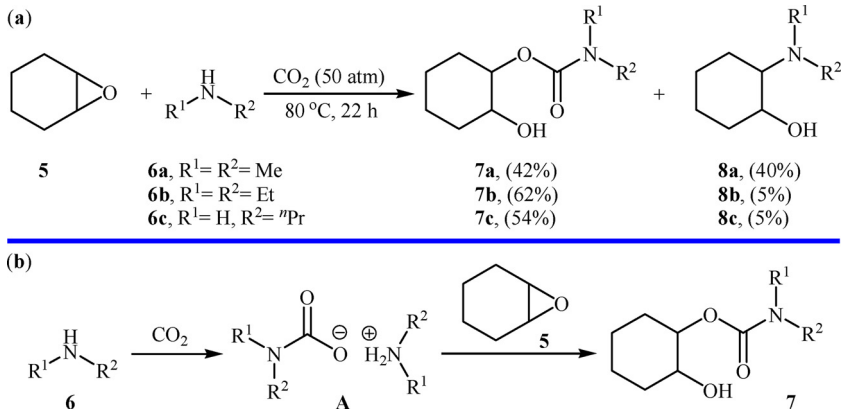


Fig. 2. Synthesis of cyclic and acyclic carbamates from amine, epoxide, and carbon dioxide.



Scheme 1. (a) Synthesis of organic carbamates **7** through catalyst-free three-component reaction of carbon dioxide, epoxide **5**, and amines **6**; (b) Mechanistic proposal for the formation of carbamates **7**.