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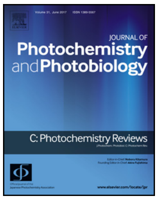

Review

The Paternò-Büchi reaction—Mechanisms and application to organic synthesis

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ABSTRACT

The [2 + 2] photocycloaddition between an electronically excited carbonyl compound and an alkene leading to oxetanes (Paternò-Büchi reaction) is one of the most investigated organic photochemical reaction. Regio-, stereo- and site selectivities are discussed as a consequence of the reaction mechanism. Spin multiplicity and electron transfer have a significant impact on the outcome of the reaction. Typical carbonyl and alkene reaction partners are presented indicating scope and limitation of the reaction. The Paternò-Büchi reaction possesses particular interest for being applied to organic synthesis, considering the difficulty for non-photochemical reactions to obtain oxetanes, with or without stereoselectivity. Mechanistic details are particularly focused. It has been applied as key step in various multi-step syntheses.

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1. Introduction

Photochemical reactions are widely applied to organic synthesis [1,2]. The big interest in these reactions in the academic and the industrial field is due to the fact that with these transformations, a large variety of compounds or compound families become available which cannot be prepared using ground state reactions. When a chemical compound is electronically excited by light absorption, its electron configuration changes and completely different chemical reactivity is induced [3,4]. Thus, a large variety of four membered cyclic compounds [5] such as oxetanes can be synthesized using photochemical reactions.

Oxetanes or 1,3-propylene oxides are cyclic ethers found in many natural products. For example, (−)-Oxetanocin inhibits the replication of HIV and possesses also antitumor and antibacterial activities (Fig. 1) [6]. Merrilactone A is a sesquiterpene which possesses a neurotrophic activity [7]. Thromboxane A_2, produced by blood platelets, has several biological functions but once in aqueous solution, the oxetane is easily opened to yield Thromboxane B_2, which is biologically inactive [8]. Oxetanes are also considered as ring shortened analogues of sugars which give rise to the synthesis of many biologically active compounds [9].

The first photochemical reaction achieved between a carbonyl compound and an alkene was published in 1909 by Paternò and Chieffi [10]. The solution has been exposed to sunlight for 104 days. This experiment was reproduced in 1954 by Büchi et al. and oxetanes were characterized [11]. Yang et al. were in 1964 the first to determine the regioselectivity of this reaction [12], henceforth called: the Paternò-Büchi reaction.

Systematic and reliable structure determination of a variety of oxetanes became possible when NMR, particularly, the Nuclear Overhauser Effect (NOE) was used [13]. Many recent reviews discuss different aspects of the Paternò-Büchi reaction [14].

Oxetanes have a ring strain energy of 110 $\mathrm{kJ\,mol^{-1}}$ [15]. As a strained ring and because of the polarity of C—O bonds, the opening of oxetanes may lead to degradation, in particular in acidic conditions. However, under controlled conditions the opening can lead to the formation of 3-hydroxy-acetals, 3-hydroxy-ethers or 3-hydroxy-aldehydes [16]. Jarosz and Zamojski studied these reactions with organic and Lewis acids [17]. For example, the lactone **4** is obtained from the oxetane **3** with hydrochloric acid (Scheme 1) [18]. Oxetanes can also be opened with aryl borates to yield chiral compounds [19].

Several methods have been reported for the non-photochemical synthesis of oxetanes [20]. The main one is an intramolecular nucleophilic substitution [21,22]. Other ways have also been described [23,24], but the specificity of the substrates used in these reactions restricts their general application.

This present review describes in detail the complex mechanisms of the Paternò-Büchi reaction. The understanding of these mechanisms allow the explanation, if not the prediction, of the selectivity of the reaction. A huge number of different carbonyl compounds and alkenes undergoing the Paternò-Büchi reaction are presented in order to illustrate the large scope of this photochemical reaction, the structural diversity of the oxetane products and the interest for application to organic synthesis.

2. Mechanisms of the Paternò-Büchi reaction

When a molecule absorbs a photon, it reaches an excited state where the electronic configuration differs from the ground state. In 1971, Turro et al. described this as an “electronic isomer” of the ground state [25]. The chemical structure undergoes then conformational changes to reach an energy minimum in this new electronic state. This stabilization can further be increased by the inversion of the spin of an electron. The molecule reaches therefore a triplet state. The change of state (singlet → triplet or triplet → singlet) is called intersystem crossing (ISC). At any time, a compound in an excited state can return to its ground state, via physical or chemical processes of deactivation.

2.1. Mechanisms involving a diradical intermediate

Most frequently, one or several diradical intermediates are involved in the mechanism of a Paternò-Büchi reaction (Scheme 2). The carbonyl compound is excited to a singlet state (usually $n\pi^*$) and then reaches a triplet state after an ISC, which is often fast, in particular in the case of aromatic ketones. However, some carbonyl compounds possess a singlet excited state lifetime which is long enough to react with another molecule. That is the case, for example, of aliphatic aldehydes or naphtaldehydes. The multiplicity of the reactive intermediate has a significant influence on the selectivity of the reaction (Section 3). The diradical intermediate ^{1}**D**, formed by attack of the singlet excited carbonyl compound on the alkene, mainly leads to its triplet counterpart ^{3}**D**. After a second ISC, which is controlled by a spin-orbit coupling, this diradical ^{3}**D** can undergo either cyclization to the oxetane or cleavage of the new C—O covalent bond to regenerate the substrates in their ground state. Computational studies have proven that the same ground state products can also be formed directly from ^{1}**D**, through the crossing of a conical intersection CCI [26].

Once the diradical intermediate is formed, its stability plays an important role in the selectivity. Indeed, the competition between the formation of the oxetane and the return to the substrates is critical for the selectivity [27]. Generally, the oxetane will mainly be generated from the diradical possessing the longest lifetime, so from the most stable diradical. However, a long lifetime of the diradical intermediate allows the bonds rotation and therefore the loss of the alkene stereochemistry (see below).

The photoinduced reaction between benzophenone **6** and alkene **7** (Scheme 3) nicely prove the existence of the diradical intermediate [28]. The tetrahydrooxepine derivative **11** can only be formed by a rearrangement of the diradical **8** leading to the intermediate **10**.