Among The Smallest Building Blocks in Organic Synthesis: Oxalate Half-Esters and Their Derivatives

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Among The Smallest Building Blocks in Organic Synthesis: Oxalate Half-Esters and Their Derivatives

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Abstract

Although oxalate half-esters and their derivatives are among the smallest units of building blocks in organic synthesis, they are very important for synthesis of a wide range of significant compounds. Utilized as building blocks for pharmaceuticals and natural products, they are typically prepared by partial hydrolysis of symmetric diesters or by partial alkylation of oxalyl chloride. Their structural properties that enable them to undergo radical deoxygenation are also applied to various significant reactions, further leading to synthesis of complex pharmaceuticals and natural products. Oxalate half-esters are also applied to the preparation of new polymers with novel properties.

Keywords: Oxalate; Building block; Half-ester; Organic synthesis

Introduction

Half-esters possess both an ester group and a carboxyl group within the same molecule. They are typically obtained by desymmetrization of symmetric compounds such as symmetric diesters. As the reactivities of these two functional groups are distinct, they and their derivatives constitute versatile building blocks, and have been utilized for the synthesis of a variety of significant compounds [1]. Among them, oxalate half-esters have no carbon unit between the ester group and the carboxyl group, and therefore have the smallest structures. Notably, such units are prevalent in natural products and in the body. They also play important roles in organic synthesis. This commentary outlines some examples of preparations and applications of oxalate half-esters and their derivatives (Figure 1).

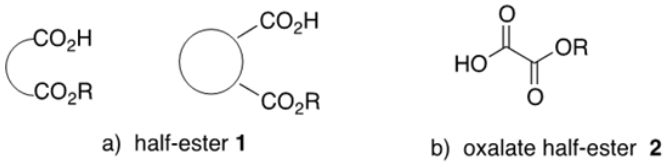

Figure 1: *a) General structure of half-ester.*

b) General structure of oxalate half-esters.

Preparation of Oxalate Half-Esters and Their Derivatives

The commercial availability of oxalate half-esters, 2, including their derivatives, is rather limited. Among the most classical and typical methods to obtain oxalate half-esters, 2, are partial saponification/hydrolysis of dialkyl oxalates, 3, although the yields are not particularly high (Figure 2). Their derivatives, such as acid chlorides, can also be prepared by partial alkylation of oxalyl chloride, 4, in the presence of a base, which can further produce non-symmetric diesters (double half-esters), for example. All these compounds have two different functional groups that exhibit distinct reactivities. Brown et al. synthesized some ^{13}C-labaled oxalates using these classical reactions for their NMR studies [2].

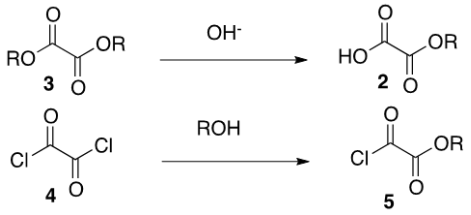

Figure 2: *Classical synthesis of oxalate half-ester and their derivatives.*

Our laboratory has previously reported highly efficient selective monohydrolysis of a series of symmetric diesters (Figure 3) [3-7]. These reactions work for selective monohydrolysis of symmetric dialkyl oxalates as well, although some tuning of reaction conditions based on our mechanistic hypothesis as well as the effects of co-solvents [6] and the type of base [7], etc., which we reported earlier significantly enhances the selectivity. These studies will be reported in due course.

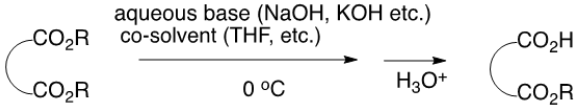

Figure 3: *Selective monohydrolysis of symmetric diesters reported by Niwayama, et al.*

Some oxalate half-esters and/or their derivatives were prepared through cyclic oxalate esters of diols such as glycols or cycloalkanediol as shown in Figure 4 [8-10]. They include non-symmetric cyclic oxalate diesters.

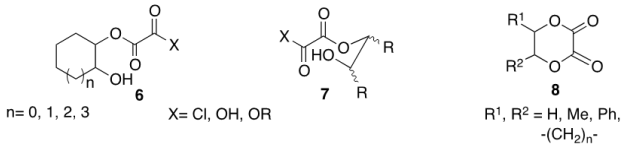

***Figure 4**: Some oxalate half-esters and the derivatives prepared through cyclic oxalate esters of diols.*

More recently, Wan et al. reported preparation of various non-symmetric oxalate diesters from α-bromo ketones, 9, diazo acetate, 10, and molecular oxygen mediated by visible light (Figure 5) [11]. This reaction is compatible with a wide range of α-bromo ketones and diazo acetates.

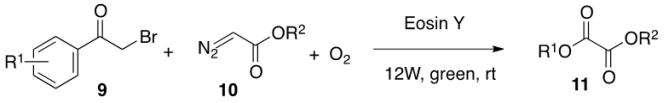

***Figure 5:** Synthesis of non-symmetric oxalate esters reported by Wan et al.*

Application of Oxalate Half-Esters and Their Derivatives

Oxalate half-esters and their derivatives have been applied as building blocks for synthesis of various significant compounds, such as natural products and pharmaceuticals. For example, the total synthesis of (-)- and *ent*-(+)-Vindoline and related alkaloids was accomplished by Boger et al., and they prepared an intermediary oxadiazole unit using a derivative of an oxalate half-ester, methyl oxalylhydrazide, 13 (Figure 6) [12].

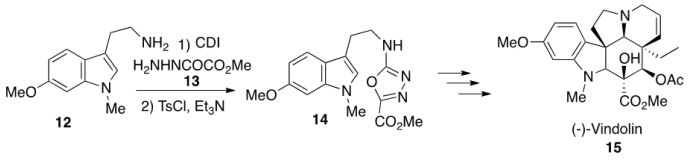

***Figure 6:** Synthesis of alkaloids reported by Boger et al.*

A series of pharmaceuticals with the structures of oxalamide derivatives has been synthesized for discovery of novel cyclophilin D inhibitors with the use of oxalate half-esters (Figure 7 (a)) [13]. These oxalyl linker portions, along with the amide or urea linker portions, have been found to play key roles in the enhancement of the inhibitory activities in the biochemical and biophysical assays, providing a suitable base for further optimization. In addition, since oxalates are among the smallest building blocks, they have been utilized as short linkers for the synthesis of pharmaceuticals as in the discovery of inhibitors of apoptosis as studied by Bristol-Myers Squibb (Figure 7 (b)) [14].

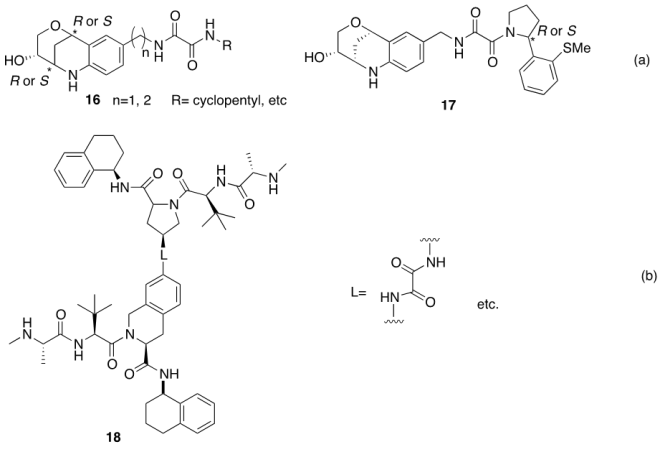

***Figure 7:** (a) Synthesis of pharmaceuticals for discovery of Cyclophilin D inhibitors and (b) apoptosis inhibitors*

Several other structure-activity relationship (SAR) studies including oxalates for various biological activities have also been reported (Figure 8). For example, Mikolajczak et al. synthesized several cephalotaxine esters for their antitumor activities as in 19 [15]. Boger and Benkovic et al. reported some analogues of 5,8,10-trideazafolate, 20, which can serve as potential inhibitors of GAR Tfase or AICAR Tfase [16]. Pettit et al. also reported SAR studies of synthetic derivatives of a natural product, narciclasine, isolated from *Narcissus sp.* for anti-neoplastic activities as in 21 [17].

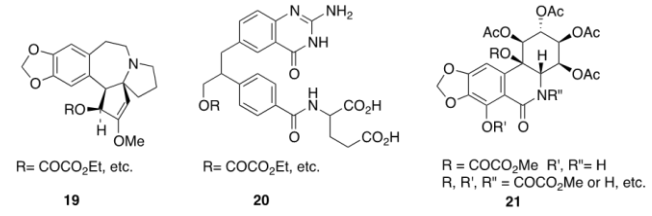

***Figure 8:** Synthesis of some oxalates for SAR studies.*

Because of their structural characteristics, oxalates are prone to radical decarboxylation. This property has been applied to various reactions. For example, Minisci et al. reported silver-catalyzed selective alkoxycarbonylation of heteroaromatic bases, 22, with the use of monomethyl oxalate and monoethyl oxalate in the presence of $S_2O_8^-$ under simple two-phase conditions (Figure 9) [18].

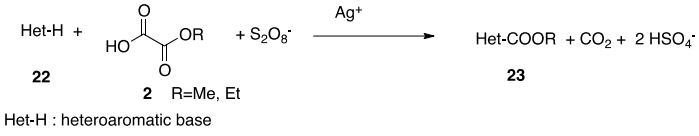

***Figure 9**: Selective alkoxycarbonylation of heteroaromatic bases reported by Minisci et al.*

Barton and Crich reported deoxygenation of tertiary alcohols with the use of derivatives of half-esters of oxalates (Figure 10) [19-20]. The reaction selectively occurs with tertiary alcohols, producing the corresponding hydrocarbons in good yields, allowing cleavage of rather strong C(sp3)-O bonds.

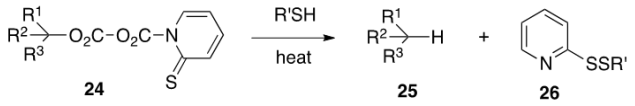

***Figure 10**: Deoxygenation of tertiary alcohols reported by Barton and Crich.*

Inspired by their pioneering work, Overman and MacMillan et al. applied oxalate half-ester salts to deoxygenation of tertiary and secondary alcohols in the presence of photoredox catalysts [21-22]. Such deoxygenation reactions can also be followed by coupling reactions with aryl halides or by addition reactions to Michael acceptors. Overman et al. reported more stable *N*-phthalimidoyl oxalates, 27, allowing similar decarboxylation catalyzed by visible-light photoredox [23-25]. This reaction further leads to the construction of 1,4-dicarbonyl structural units followed by the conjugate additions to various Michael acceptors (Figure 11). The stereoselectivities for the formation of the new quaternary stereocenter can also be high (>20:1) when the precursors are chiral. Such strategies have been applied to synthesis of various complex natural products with quaternary centers, such as Chelovidene A, 29, Dendrillolode C, 30, and Chelovidene B, 31 [26]. They also extended this study to the generation of the methoxycarbonyl radical and subsequent coupling reactions with various alkenes [27]. Similarly, Fu et al. applied these *N*-phthalimidoyl oxalates, 27, to visible-light mediated deoxygenation reactions of *tert*-alcohols and the subsequent coupling reactions with various alkynes [28].

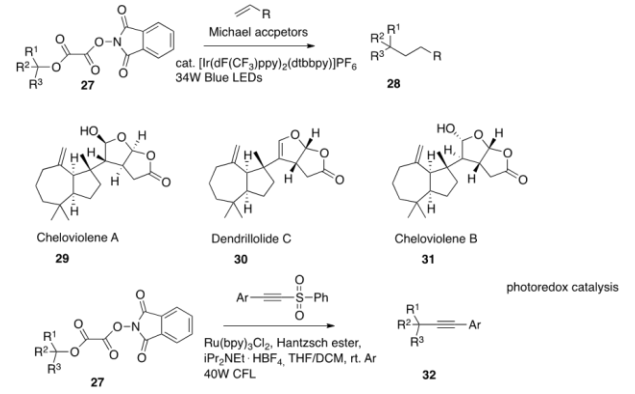

***Figure 11**: Deoxygenation and subsequent Michael addition reported by Overman et al.*

Gong et al. also reported that oxalates from *tert*-alcohols, 33, undergo coupling reactions with various sources such as Michael reactors, TEMPO, and aromatic compounds via C-O bond fragmentation, allowing formation of new quaternary carbon centers (Figure 12) [29].

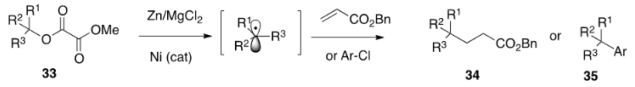

***Figure 12:** Coupling reactions reported by Gong et al.*

Opatz et al. utilized oxalate half-esters for deoxygenative photoredox coupling reactions of alcohols from the oxalate with aromatic nitriles under transition metal-free conditions (Figure 13) [30]. They demonstrated that similar coupling reactions are also possible with carboxylic acids.

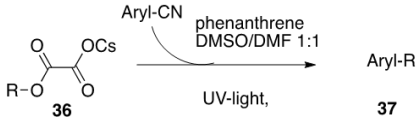

***Figure 13:** Transition metal-free coupling reported by Opatz et al.*

Reiser et al. has reported that ethyl oxalates of 1,2-diols or β-amino alcohols undergo similar visible-light-mediated deoxygenation, further leading to synthesis of various chiral tetrahydrofurans or pyrrolidines (Figure 14) [31].

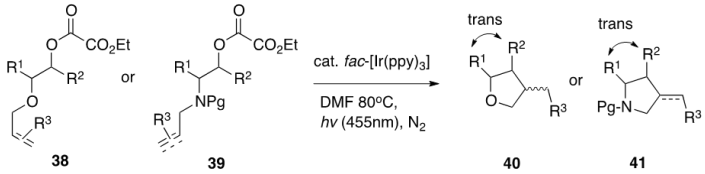

***Figure 14**: Visible-light-mediated deoxygeneration reported by Reiser et al.*

Reisman et al. furthered the radical deoxygenation reaction of alcohols with the use of half-esters of cesium oxalates, and reported deoxychlorination with ethyl 2,2,2-trichloroacetate (ETCA), 43, an Ir-catalyst, and blue LED [32]. Their method appears to be superior to traditional reagents such as thionyl chloride and triphenyl phosphine/CCl_4, allowing the deoxychlorination to occur on the secondary alcohols as well (Figure 15). They also showed that deoxybromination with diethyl bromomalonate and deoxyfluorination with Selectfluor are possible under essentially the same conditions.

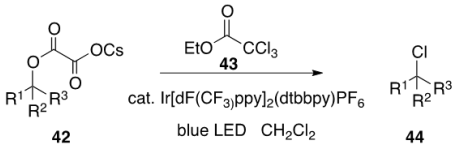

***Figure 15:** Deoxychlorination reported by Reisman et al.*

Interestingly, an oxalate half-ester was utilized for formation of crystalline in the process of the synthesis of cathepsin S inhibitor (Figure 16) [33]. After numerous trials, the authors accidentally found that monoethyl oxalate forms a stable crystalline white solid with a purity of 96% for purification of an important intermediate, 45, and confirmed the structure by X-ray crystal analysis.

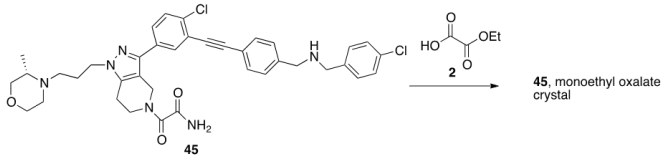

***Figure 16:** Crystallization of Intermediate for cathepsin S inhibitor.*

Oxalate half-esters have also been applied to preparation of esterified starch with new properties. Zhang et al. reported that starch oxalate half-esters with different degrees of substitution can be prepared depending on the quantities of oxalic acid added in the reaction (Figure 17) [34]. They demonstrated that the average viscometric molecular weight, crystallization and thermal stability vary according to the degree of substitution, suggesting a potential use of oxalic acid-modified starches as bread softening agents and starch gelation inhibitors.

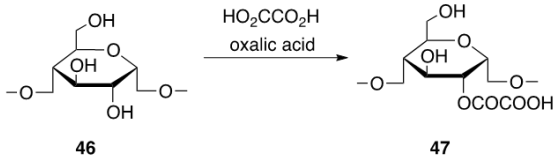

Figure 17: *Starch oxalate half-ester reported by Zhang et al.*

Oxalate half-esters are the simplest half-esters with no chiral center in the parent chain, and therefore their applicability may be tend to be overlooked. However, with this structural characteristic, they exert reactivities that other half-esters do not have as exemplified here. Future studies for their efficient and economical production will be of significance for the synthetic organic chemistry community.

Acknowledgements:

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