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Acylation and palladium-mediated couplings of maltol, a biobased γ-pyrone

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ABSTRACT

Maltol triflate **3** undergoes palladium-mediated carbon-carbon bond formation with styrene, boronic acids and alkynes. Benzyl ether **2** can be acylated. The acylation products can be readily converted into furo[3,2-*b*]pyranones.

Maltol (**1**) is a bio-based chemical readily available from tree bark, pine needles and malt [1]. There are numerous preparations of O-alkyl ethers (such as **2**) of maltol and the conversions of these ethers to γ-pyridones are well precedented [2]. Zhu reported innovative thermal transformations of propargyl ethers of maltol into catechols [3]. The metal ion complexation chemistry of maltol has also been widely studied [4] (Fig. 1).

As part of a computational study to identify new bioprivileged molecules (biologically derived platform molecules) [5], Broadbelt and coworkers evaluated a subset of over 29,000 six-carbon compounds from PubChem and refined the large subset to 100 compounds using NetGen, an automated reaction network generation tool [6]. This 100-compound set contained maltol plus a number of lactones, furans, and cyclic ethers. Interestingly, although maltol and 5-hydroxymethylfurfural, a known bioprivileged molecule, are quite different structurally, they are alike in that each of the carbon atoms in both molecules is in a different chemical environment. Herein, we report the evaluation of the organic chemistry of maltol, a potential biobased platform molecule.

We first evaluated the triflate **3**, a compound initially prepared by Lopez [7]. Both Lopez and Yeates reacted **3** with arylstannanes to produce 3-arylpyrones in good yields [7,8]. A related triflate from kojic acid was used in Suzuki-Miyaura reactions [9]. A few chromone triflates have also been generated and reacted with triarylbismuth reagents, aryl boronic acids and arylstannanes [10]. Triflate **3** reacted with three aryl boronic acids to generate pyrones **4**, **5**, and **6** in 82, 69, and 75% yields, respectively, as shown in Scheme 1. The reaction of pyrone **6** with *t*-BuOK provided the 5,6-benzochromone **7**, a known photoactive molecule, in 71% yield [11].

The Sonogashira reaction has not been reported for triflates of γ-pyrones. Using $Pd(PPh_3)_2Cl_2$ as the catalyst, we obtained 3-alkynylpyrones **8**, **9**, and **10** in 88%, 70%, and 57% yields, respectively, as illustrated in Scheme 2. Pyrones **8**, **9**, and **10** are new compounds whose structures were supported by proton ^{1}H NMR, ^{13}C NMR and high-resolution mass spectrometry.

The Heck reaction of maltol derivatives has not been reported. This reaction was sensitive to reaction parameters such as the choice of a catalyst and temperature. Although the reaction of triflate **3** with methyl vinyl ketone failed, the reaction with ethyl acrylate, acrylonitrile, and styrene proceeded well, providing alkenylpyrones **11**–**13** in 40%, 52% and 34% yields, as shown in Scheme 3.

Another fundamental reaction of carbonyl compounds is deprotonation in the presence of strong bases [12]. Deprotonation of γ-pyrones has not been systematically studied [13]. There are only a few isolated examples of aldol reactions employing maltol ethers [14,15]. The reaction of **1** with two equivalents of lithium diisopropylamide (LDA) afforded poor yields of acylation products, presumably due to solubility problems. Fortunately, the reaction of benzyl ether **2** with LiHMDS at −78 °C followed by addition of various acyl halides provided pyrones **14**–**16** in 98%, 95%, and 88% yields, respectively, as depicted in Scheme 4. As expected,

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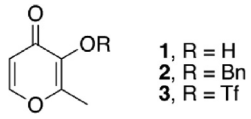
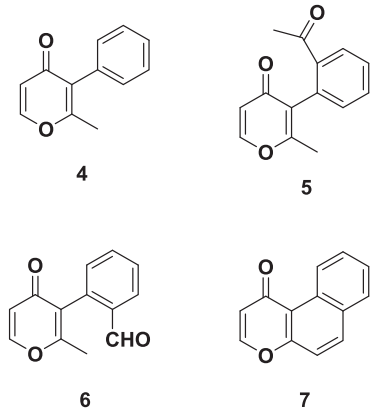
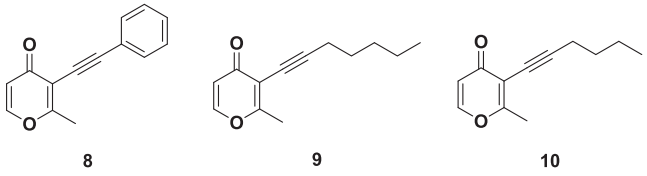


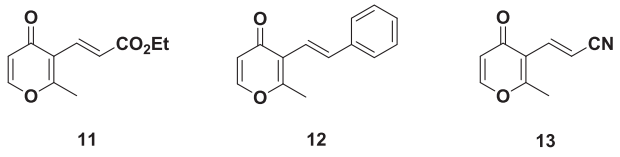
Fig. 1. Maltol and derivatives.



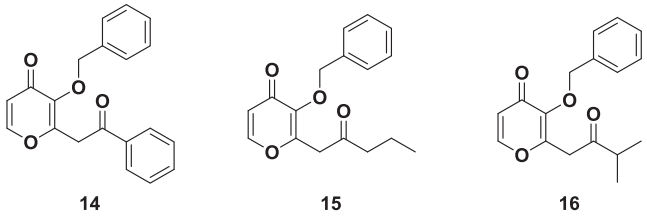
Scheme 1. Products of Suzuki reactions with 3.



Scheme 2. Products of Sonogashira reactions of 3.

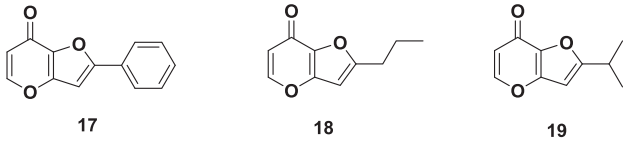


Scheme 3. Products of Heck coupling reactions of 3.



Scheme 4. Products from acylation of 2.

acylation occurred at the γ-position as evidenced by the methylene singlet around 3.5 to 4.2 in the proton NMR.



Scheme 5. Furylpyrone formation.

These acyl pyrones could be converted into 7H-furo[3,2-*b*] pyran-7-ones **17 – 19** in a simple one-pot procedure. Removal of the benzyl protecting group under acidic conditions led to the hydroxy-γ-pyrone which rapidly underwent cyclization and dehydration to produce **17**–**19** in very good yields as shown in Scheme 5. There are only a few isolated reports of the synthesis of this class of pyrones [15]. This is the first synthesis using an acylation-cyclization strategy.

The above reactions reveal that maltol can undergo a number of important carbon-carbon bond forming reactions. This is certain to stimulate interest in maltol. We believe that maltol can be considered to be a bioprivileged molecule.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151591.

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