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Synthesis of novel heterocyclic acetyl coenzyme-A carboxylase inhibitors via a Claisen rearrangement

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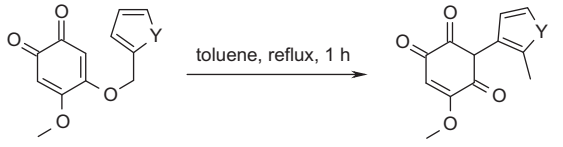
ABSTRACT

The synthesis of functionalized heteroaromatic compounds is of high importance in the discovery of novel herbicides. In this Letter is reported the synthesis of a series of 2-heteroaromatic-1,3-diones utilizing a Claisen rearrangement to form a key carbon–carbon bond. The paper focuses on the scope and diversity of the molecules synthesized via this route.

With the increasing world population, agricultural yields will have to improve to satisfy the rising demand for food. Innovative solutions are required in the field of chemical crop protection to match this ever-greater demand for high crop yields. One such innovative solution in cereals is Syngenta's newly launched herbicide, Pinoxaden **1** (Fig. 1). This active ingredient is actually a pro-herbicide, being cleaved in planta to Pinoxaden acid **2** (Fig. 1), which exerts its biological activity by inhibition of acetyl coenzyme-A carboxylase (ACCase, EC 6.4.1.2).[1,2]

Pinoxaden acid **2** belongs to the aryl-keto-enol family of ACCase inhibitors (Fig. 1, **3**). To further explore this area, we were



Scheme 1.

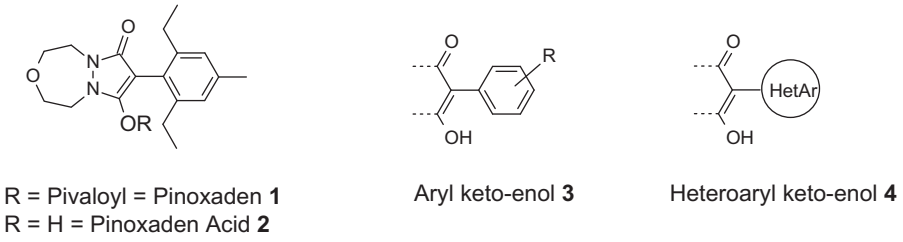


Figure 1. Examples of aryl and heteroaryl keto-enol scafolds.

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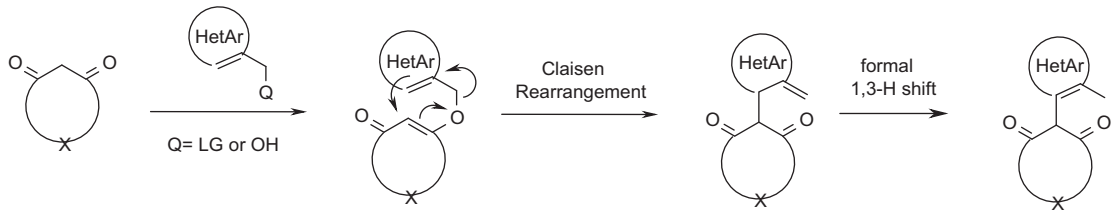
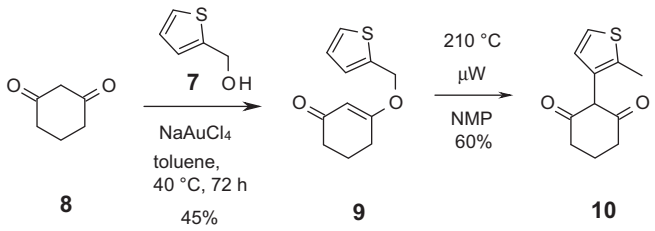


Scheme 2.



Scheme 3.

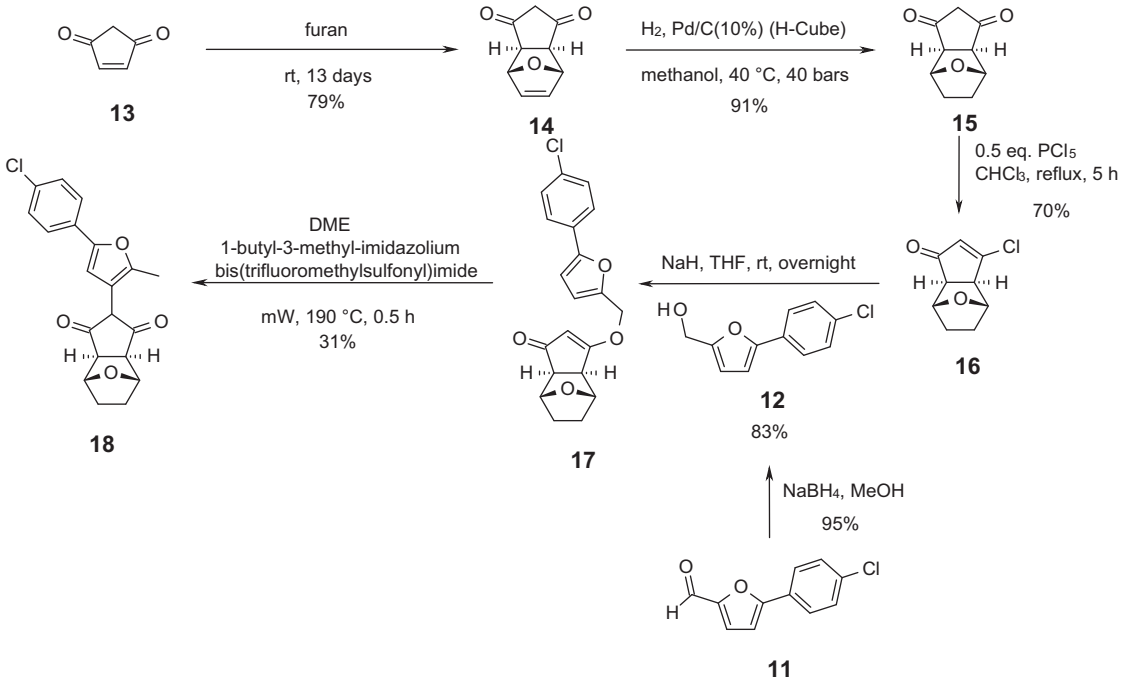
interested in investigating the corresponding heteroaryl keto-enol compounds (Fig. 1, **4**). Some examples of these types of molecules have been described in the literature: For example, Union Carbide has patented pyrazinyl-1,3-cycloalkane dione with herbicidal activity and Bayer CropScience more recently reported the preparation of 2-thiazolylcyclopentane-1,3-diones and 2-thiazolylcyclohexane-1,3-diones as pesticides, herbicides, and fungicides.[3,4] Nevertheless, the heteroaryl keto-enol scaffolds **4** have been much less investigated than their aryl counterparts mainly due to the fact that there is no general synthesis to such molecules. Surveying the literature, a paper from the group of Michel Maumy caught our attention.[5] The authors reported the effective Claisen rearrangement of furfuryloxy- and (2-thienyl)methyloxy-*o*-benzoquinones (**5a** and **5b**, resepectively) to yield **6a** and **6b** (Scheme 1).[6]

We envisaged that we could extend this type of transformation to provide a general synthesis of heteroaryl keto-enols. The concept involves O-alkylation of a 1,3-dione system and subsequent Claisen rearrangement to migrate the heteroaromatic from the O–C bond to create a new C–C bond (Scheme 2) upon which a formal 1,3-H shift provides the desired 2-aryl-keto-enol.

Proof of concept was investigated using the simple model system 3-(thiophen-2-ylmethoxy)-cyclohex-2-enone **9** (Scheme 3). The initial thermal acidic conditions to form the enol ether intermediate **9** from **7** and **8** were unsuccessful, but moderate conversion could be obtained with gold catalysis, using conditions adapted from the work of Acardi [2.5% $NaAuCl_4$, toluene, 40 °C, 72 h, 45%].[7] The key Claisen rearrangement of **9** proceeded smoothly but required high temperatures due to a large activation energy barrier resulting from the loss of aromaticity in the transition state.[8]

Having achieved proof of concept, the chemical scope of this transformation was investigated with respect to the heterocycle and the 1,3-diones.

The furan derivate **12** (Scheme 4) was prepared by sodium borohydride reduction of commercially available 5-(4-chlorophenyl)furfural **11**. The resultant sodium alcoholate of **12** generated with sodium hydride was then used as a nucleophile to react with the 3-chlorocyclopent-2-en-1-one **16** which, in turn, was synthesized as shown in Scheme 4.[9] Microwave assisted Claisen rearrangement of **17** in dimethoxyethane containing a drop of



Scheme 4.