SYNTHESIS AND THERAPEUTIC APPLICATIONS OF CHALCONES

Reported by Adon Kwong May 4th, 2021

INTRODUCTION

Chalcones are privileged structures that exhibit a broad array of biological activities. Chalcones consist of two aromatic rings linked by an α,β-unsaturated ketone to form its common 1,3-diaryl-2-propen-1-one scaffold. This structurally simple yet reactive core allows transformations and derivatization that are often the key to therapeutic activity. However, although chalcones have been applied therapeutically through use of plants and herbs for thousands of years, many of the mechanisms of action are still not fully understood. As a result, chalcones and their derivatives have attracted great interest in recent years as a potential scaffold in drug discovery.[1]

RECENT ADVANCES IN SYNTHESIS

Owing to their simple structure, chalcones are easily prepared by numerous well-studied reactions (Figure 1). The most commonly employed method is the condensation of substituted benzaldehydes and aryl methyl ketones, also known as the Claisen-Schmidt reaction.[1] However, because of the varying yields and occasional difficulty in purification, other well-known methods have been explored and applied to synthesizing chalcones. For example, the ketone and olefin moieties allow for cross-coupling and olefin metathesis reactions such as the Suzuki reaction[2], Heck reaction[3], Wittig reaction[4], and Julia-Kocienski reactions[5] to be applied to chalcone synthesis with moderate to excellent yields. These alternatives boast shorter reaction times and ease of purification.[2] Despite this, the base-catalyzed Claisen-Schmidt reaction is still currently the most utilized method of synthesizing chalcones due to its simplicity.

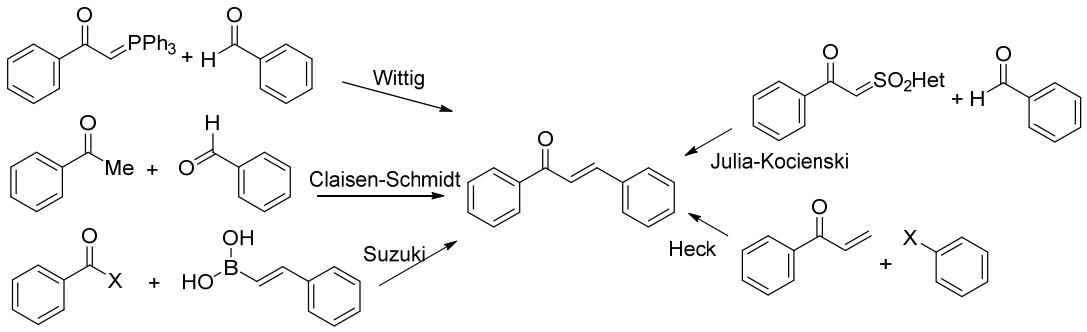
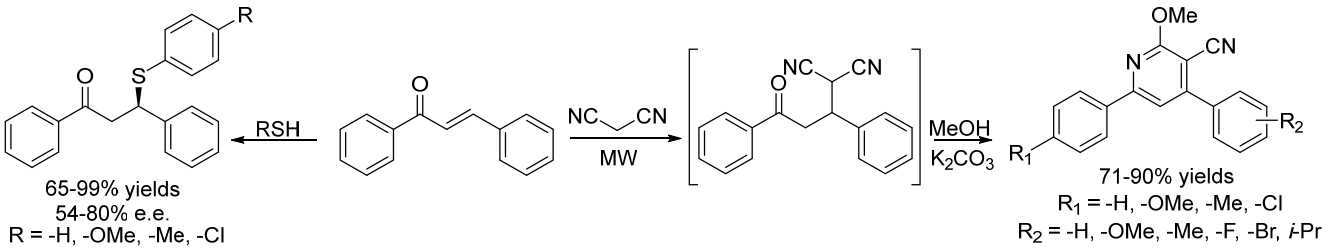


Figure 1. Methods in the Synthesis of Chalcones

THERAPEUTICALLY SIGNIFICANT APPLICATIONS

Because chalcones contain the enone moiety, there is a variety of transformations that are of interest in medicinal chemistry. Enantioselective conjugate addition is one such transformation that creates adducts for further functionalization. Michael additions[6], thiol additions[7], and cyclizations[8,9] are of great interest to medicinal chemists as efficient methods to creating interesting adducts as intermediates for therapeutically relevant molecules (Scheme 1).

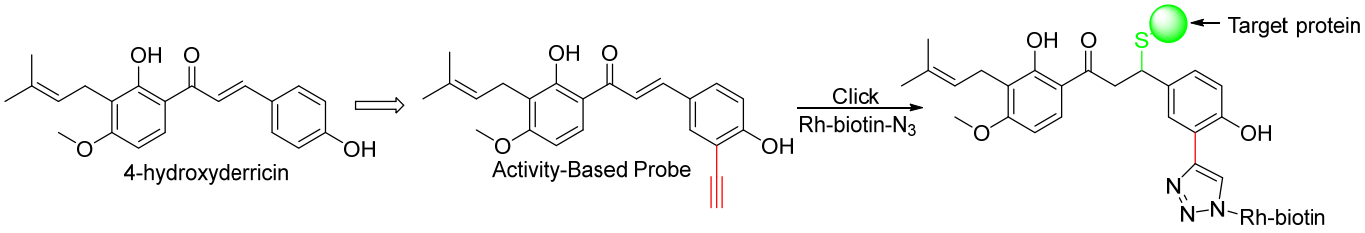
Scheme 1. Synthetic Applications of Chalcones



CHALCONES AS THERAPEUTICS

Because chalcones can bind to a variety of proteins, it is often difficult to pinpoint where and by what mechanism chalcones exhibit therapeutic activity, but scientists continue to explore strategies of approaching target identification. For example, Ducki and coworkers have employed *in silico* methods to predict structural features to increase the potency of chalcones with anticancer activity.[10] Furthermore, the emerging use of activity-based protein profiling on chalcones has shown promise. Seiber and coworkers developed an alkyne-including analogue of antibiotic 4-hydroxyderricin to be used as a probe and bind to the active site of a pathogen (Scheme 2). The alkyne moiety reacts with a molecular tag through click chemistry and the bound proteins are enriched and isolated. By this method, it was found that 4-hydroxyderricin inhibits the catalytic activity of seryl-tRNA synthetase, although further binding details are unclear.[11] Similar methods have also been used to identify structure-activity relationships using a survey of chalcones with photoactivatable functional groups and an alkyne for click chemistry.[12]

Scheme 2. 4-Hydroxyderricin Used in Activity-Based Protein Profiling



REFERENCES

(1) Sivakumar, P. M.; Priya, S.; Doble, M. *Chem. Biol. Drug Des.* **2009**, *73* (4), 403–415. (2) Eddarir, S.; Cotelle, N.; Bakkour, Y.; Rolando, C. *Tetrahedron Lett.* **2003**, *44* (28), 5359–5363. (3) Bianco, A.; Cavarischia, C.; Farina, A.; Guiso, M.; Marra, C. *Tetrahedron Lett.* **2003**, *44* (51), 9107–9109. (4) Xu, C.; Chen, G.; Huang, X. *Org. Prep. Proced. Int.* **1995**, *27* (5), 559–561. (5) Kumar, A.; Sharma, S.; Tripathi, V. D.; Srivastava, S. *Tetrahedron* **2010**, *66* (48), 9445–9449. (6) Yang, W.; Jia, Y.; Du, D.-M. *Org. Biomol. Chem.* **2012**, *10* (2), 332–338. (7) Skarżewski, J.; Zielińska-Błajet, M.; Turowska-Tyrk, I. *Tetrahedron Asymmetry* **2001**, *12* (13), 1923–1928. (8) Feng, H.; Li, Y.; Van der Eycken, E. V.; Peng, Y.; Song, G. *Tetrahedron Lett.* **2012**, *53* (9), 1160–1162. (9) Panda, S. S.; Chowdary, P. V. R. Synthesis of Novel *Indian J. Pharm. Sci.* **2008**, *70* (2), 208–215. (10) Ducki, S.; Rennison, D.; Woo, M.; Kendall, A.; Chabert, J. F. D.; McGown, A. T.; Lawrence, N. J. *Bioorg. Med. Chem.* **2009**, *17* (22), 7698–7710. (11) Battenberg, O. A.; Yang, Y.; Verhelst, S. H. L.; Sieber, S. A. *Mol. Biosyst.* **2013**, *9* (3), 343–351. (12) Zhou, B.; Yu, X.; Zhuang, C.; Villalta, P.; Lin, Y.; Lu, J.; Xing, C. *ChemMedChem* **2016**, *11* (13), 1436–1445.