Tetrahedron Letters 56 (2015) 4392–4396

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Metal-free methodology for the preparation of sterically hindered alkynoylphenols and its application to the synthesis of flavones and aurones

Cassandra Taylor, Yuri Bolshan *

Faculty of Science, University of Ontario Institute of Technology (UOIT), 2000 Simcoe Street North, Oshawa, Ontario L1H7K4, Canada

ARTICLE INFO

Article history:
Received 7 April 2015
Revised 19 May 2015
Accepted 26 May 2015
Available online 30 May 2015

Keywords:
Trifluoroborate salts
Synthetic methodology
Lewis acids
Natural products
Oxygen heterocycles

ABSTRACT

A metal-free synthesis for the preparation of sterically demanding *ortho*-demethylated ynones from mixed anhydrides and potassium alkynyltrifluoroborate salts has been developed. The one-pot reaction proceeds rapidly in the presence of a Lewis acid without the exclusion of air and moisture. This method is advantageous in that it is operationally simple, proceeds under mild conditions, and has a broad substrate scope. 2,6-Dimethoxy substituted anhydrides afford the corresponding mono-demethylated ynone products in good yields. In particular, 2-hydroxy substituted ynone products are valuable synthetic intermediates because their conversion to biologically active natural product scaffolds is straightforward. Flavones were obtained via 6-endo cyclization of the *o*-alkynyoylphenol intermediates under acidic conditions. Cesium carbonate was found to promote rapid 5-exo cyclization to furnish aurone products.

Introduction

Aurones and flavones (Fig. 1) are natural products that have been identified as valuable organic scaffolds due to their range of biological activities.[1] Hydroxyl and methoxy-substituted flavones are ubiquitous in fruits, vegetables, flowers, and barks.[2] Polymethoxyflavones (PMFs) are of particular interest as a result of their biological features including anti-carcinogenic, anti-inflammatory, and anti-atherogenic properties.[2a,3] Additionally, PMFs have been demonstrated to have increased metabolic stability compared to unmethylated analogues.[4] Recently, potent anti-cancer activity of PMFs has been demonstrated.[5] In contrast, aurones are comparatively limited in their natural abundance and as such have been less extensively studied. Aurones are dyes that contribute to the coloration of many fruits, vegetables, and flowers.[6] Additionally, they have been described as phytoalexins, aiding in the defense mechanism of plants against infections.[7] Functionalized aurones have been highlighted as versatile scaffolds for the modulation of proteins linked to multidrug resistance in cancer chemotherapy.[8]

The diverse biological activities exhibited by flavone derivatives have made them of particular synthetic interest. As such, several methods for the synthesis of flavones are available.[9] Flavones are commonly prepared via β-diketone intermediate formed using the base-catalyzed Baker–Venkataraman rearrangement of 2-acetoxyacetophenones.[10] Cyclization of diketone is achieved under harsh conditions such as treatment with concentrated sulfuric acid[11] or microwave irradiation.[12] Alternatively, flavones may be prepared via the oxidative cyclization of substituted 2-hydroxy chalcones, which are obtained by an aldol condensation between an aldehyde and a 2-hydroxyacetophenone.[13] More recently, flavones have been prepared via palladium-catalyzed carbonylative Sonogashira coupling of aryl halides with terminal alkynes.[14]

Aurones are typically synthesized by two main methods: oxidative ring closure of 2′-hydroxychalcones[15] and aluminum oxide catalyzed condensation of benzofuranones with substituted benzaldehydes.[16] Alternatively, aurones can be prepared via gold(I) catalyzed cyclization of *ortho*-(1-hydroxyprop-2-ynyl)phenols[17] or palladium catalyzed carbonylative annulation of 2-bromophenols and terminal alkynes.[14a]

Traditional synthetic methods for the preparation of aurone and flavone scaffolds are typically associated with drawbacks such as arduous multi-step procedures, the need for transition metal catalysts, harsh reaction conditions, and low to moderate yields. An alternative method for the synthesis of both aurones and flavones involves the cyclization of *o*-alkynoylphenol precursors (Scheme 1). Under basic conditions 5-*exo* and 6-*endo* ring cyclization modes are competing pathways.[18] Often, basic conditions promote the 5-*exo* cyclization to form aurone scaffolds, however, this is dependent on the base and conditions applied. While

* Corresponding author. Tel.: +1 (905) 721 8668x5353.
E-mail address: yuri.bolshan@uoit.ca (Y. Bolshan).

http://dx.doi.org/10.1016/j.tetlet.2015.05.097
0040-4039/

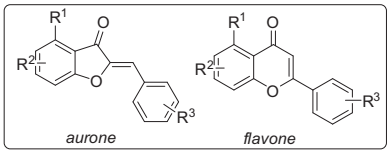


Figure 1. Structure of substituted aurone and flavone.

manipulation of the conditions does affect which major product is formed, accounts in the literature indicate the formation of a mixture of both cyclization products.[18] Silver(I) ion-catalyzed cyclization of *o*-alkynoylphenols results predominantly in the 5-*exo* cyclized aurone product, however, trace amounts of the 6-*endo* product are also formed.[19] A similar outcome has been observed when tributylphosphine was employed as a catalyst.[20] Product mixtures are problematic since separation of structurally similar aurone and flavone products is not trivial. Fortunately, in the course of our investigation we have discovered cesium carbonate to promote the rapid and exclusive 5-*exo* cyclization of *o*-alkynoylphenol compounds in high yields.

It is possible to regioselectively promote the 6-*endo* cyclization of *o*-alkynoylphenols by applying the principles of the Morita–Baylis–Hillman reaction.[21] Flavone synthesis may be achieved via 1,4-addition of a nucleophile to the β-carbon in the ynone system. Intramolecular Michael addition followed by elimination of the nucleophile results in the 6-*endo* cyclized flavone product.[22] Specifically, we have employed a protocol reported by Doi and coworkers, where trifluoromethanesulfonic acid (TfOH) promotes the exclusive 6-*endo* cyclization to produce the desired flavone product.[22a] A straightforward method for the preparation of *o*-alkynoylphenols is particularly appealing given that they may be utilized as a convenient starting material for the efficient synthesis of both aurone and flavone scaffolds.

There are a number of synthetically useful methods for the preparation of ynones.[23] However, efficient methods for the preparation of sterically hindered examples, especially *o*-alkynoylphenols, are scarce. Suzuki–Miyaura carbonylative coupling of sterically hindered aryl iodides with boronic acids has been reported.[24] More recently, carbonylative Negishi coupling of an alkynylzinc reagent to a 2,6-dimethoxy substituted aryl iodide has been demonstrated in modest yields.[25] The use of unstable alkynylboronic acids and alkynylzinc reagents as well as the presence of unwanted direct coupling byproducts reduces the efficiency of these methods. Moreover, selective monodemethylation of an *ortho*-methoxy group is challenging.[25] Alternative methods for the synthesis of *o*-alkynoylphenols involve the addition of metal acetylides to an aldehyde followed by oxidation of the secondary alcohol to a ketone.[22a,d,26] These approaches for the preparation of hindered *o*-alkynoylphenols suffer from low atom economy, multistep procedures, and low yields.

Recently, transition-metal-free reactions of organoboranes have gained considerable attention.[27] Previously, we have developed a straightforward procedure for the preparation of ynones from acyl chlorides and potassium alkynyltrifluoroborate salts (Scheme 2).[28] This convenient, one-pot reaction proceeds rapidly in the presence of boron trichloride without exclusion of air or moisture. Furthermore, alkynyltrifluoroborate salts can be easily prepared from terminal alkynes according to the published procedure.[29] Given the interesting biological properties of aurone and flavone natural products, we sought to develop a method for the preparation of 2-hydroxylated precursors of aurone and flavone scaffolds. Unfortunately, the method highlighted in Scheme 2 is limited by commercial availability of acyl chloride starting materials.

Limited access to good quality sterically hindered benzoyl chloride derivatives led us to seek an alternative method for the preparation of the *o*-alkynoylphenol precursors. Herein, we describe a new method for the preparation of sterically hindered ynones from potassium alkynyltrifluoroborate salts and mixed anhydrides and its application to the synthesis of both natural and unnatural flavone and aurone derivatives.

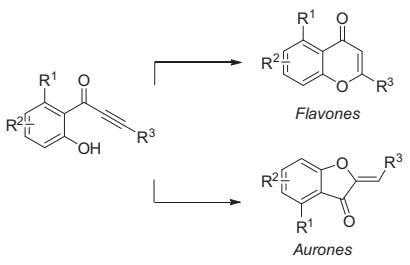
Results and discussion

Due to the limited commercial availability of substituted benzoyl chloride derivatives, our first challenge was to find a way to apply our methodology to the sterically hindered, *ortho* hydroxy substituted benzoic acid **1**. Scheme 3 illustrates initial efforts to convert the carboxylic acid group to an acyl chloride, which could subsequently be converted to an ynone. Direct conversion of the acid to an acyl chloride using thionyl chloride was not successful. Therefore, we sought to protect the acid and hydroxyl functionalities of the starting material. This would allow for subsequent transformation to the desired acyl chloride precursor.

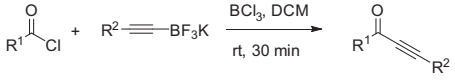
Initially, allyl bromide was used to form a diprotected acid. Subsequent exposure of the protected acid group to sodium hydroxide followed by conversion to an acyl chloride using thionyl chloride was expected to produce a protected benzoyl chloride **3**. Compound **3** could be converted to the desired ynone intermediate (Scheme 3).[28] Unfortunately, conditions for the conversion of **2**–**3** resulted in partial decomposition making isolation of clean product a challenge. Additionally, this method is not ideal as a result of the number of steps required for the preparation of acyl chloride.

As an alternative strategy, we silylated substituted carboxylic acid **1** to allow for the direct conversion of the protected acid to an acyl chloride. Scheme 4 illustrates the transformation of the TBDMS protected intermediate **4** to an acyl chloride using oxalyl chloride,[30] followed by reaction with *para*-methoxy phenylacetylenetrifluoroborate under the reported reaction conditions. In addition to ynone formation, we observed the concurrent demethylation of the *ortho*-methoxy group under the conditions applied. Ynone product **6** was obtained in 16% yield. The low yield of this particular reaction may be attributed to incomplete conversion of **4** to the acyl chloride intermediate as well as steric bulk associated with the silyl protecting group.

The demethylation of an *ortho*-methoxy group under the developed conditions for ynone preparation led us to continue our investigation using 2,4,6-trimethoxy substituted starting materials. First, 2,4,6-trimethoxybenzoic acid was converted to benzoyl chloride **7** using oxalyl chloride. The conversion to **7** was not complete, however, we proceeded with the next step of the synthesis. The boron trichloride-catalyzed reaction with *para*-methoxy



Scheme 1. Cyclization of *o*-alkynoylphenols.



Scheme 2. Straightforward preparation of ynones.