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Synthesis of chalcones *via* domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction

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ABSTRACT

A new method has been developed for the cross-coupling of aryl halides with *β*-chloroalkyl aryl ketones and their ester and amide analogs through a domino dehydrochlorination/Pd(OAc)$_2$-catalyzed Heck reaction sequence. The enone intermediates generated *in situ* reduced the occurrence of side reactions and therefore enhanced the efficiency of the reaction. This reaction exhibited good tolerance to various functional groups on both substrates and provides rapid access to a wide range of chalcone derivatives.

1. Introduction

Chalcones are an important class of biologically active compounds (Scheme 1) [1,2], which have been reported to exhibit a wide range of pharmacological properties, including anticancer, anti-inflammatory, antioxidant, antimicrobial, and antiallergic activity [3]. Compounds belonging to this structural class are also recognized as important intermediates for the synthesis of heterocyclic systems [4–6] and functional materials [7,8]. Chalcones are generally synthesized using a Claisen-Schmidt condensation [9]. However, the overall efficiency and functional group tolerance of this reaction are usually poor because of its requirement for strongly basic conditions. To overcome these limitations, several transition-mental-catalyzed cross-coupling reactions have been developed for the synthesis of chalcones, which can be conducted under relatively mild conditions [10–13].

The Pd-catalyzed Heck reaction is one of the most powerful methods for the arylation and vinylation of alkenes [14]. Although chalcones can be generated directly by the Heck-type cross-coupling of aryl halides with aryl vinyl ketones, there have been very few examples of this reaction in the literature [15,16]. The main reason for the lack of publications in this area can be attributed to the poor stability of most aryl vinyl ketones (enones), which can decompose upon exposure to heat, light and oxygen during their preparation and storage. Multi-step procedures are therefore often required for the preparation of *α,β*-unsaturated carbonyl compounds starting from the corresponding saturated carbonyl compounds [17,18]. For the synthesis of chalcones using enones as substrates, it is envisaged that a domino reaction sequence involving the *in-situ* generation of an enone followed by its cross-coupling with an aryl halide would provide facile access to a broad range of chalcones. The Pd-catalyzed cross-coupling reactions of propiophenones with aryl carboxylic acids [19] and (hetero)arenes [20] have been reported to afford chalcon-

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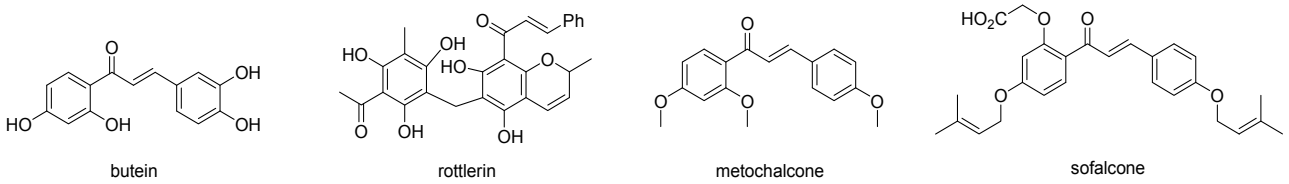

Scheme 1. Examples of bioactive chalcones.

es via the *in-situ* generation of the corresponding enones. The decarboxylative arylation of benzoylacrylic acids has also been reported to provide access to chalcones in a similar manner [21]. Although these methods represent useful strategies for the synthesis of chalcones, their overall utility has been limited by their general requirement for high loadings of the catalysts and oxidants under relatively harsh conditions. We recently found that *β*-chloroalkyl aryl ketones and their ester and amide analogs could be used as precursors to *α,β*-unsaturated carbonyls in the Rh(I)-catalyzed conjugate addition by arylboronic acids [22], as well as the Pd-catalyzed, Cu-mediated synthesis of carbazoles [23]. As part of our ongoing research into the development of new domino reactions [24], we envisioned that *in-situ* generated enones could be employed in a Heck-type cross-coupling reaction under mild conditions without the addition of an oxidant. Herein, we report the development of a new method for the synthesis of chalcones by Pd-catalyzed formal sp^2 C-X (X = I, Br) / sp^3 C-Cl cross-coupling of aryl halides with *β*-chloroalkyl aryl ketones, and their ester and amide analogs.

2. Experimental

General considerations. All the aryl halides were purchased from commercial suppliers and used as provided without further purification. The *β*-chloroalkyl carbonyl compounds were either purchased from commercial suppliers or prepared according to the literature procedures [22]. Compounds **3a**–**3c** [21], **3d** [25], **3e** and **3f** [21], **3g** [26], **3h** [21], **3i** [25], **3j** [21], **3k** [27], **3l** [27], **3m** [21], **3n** [28], **5a** and **5b** [10], **5c** [29], **5d** [30], **5e** [31], **5f** and **5g** [10], **5h** and **5i** [25], **5j** [32], **5k** [33], **5l** [34], and **5m** and **5n** [35] are known compounds and the spectroscopic features of the materials synthesized in current study were found to be in good agreement with those reported in the literature. All of the solvents used in the current study were freshly distilled prior to use. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer (Bruker, German) and all the chemical shift values were measured relative to tetramethylsilane (TMS; δ_{TMS} = 0.00) or the residual chloroform peak of $CDCl_3$ [δ(^{1}H) = 7.26; δ(^{13}C) = 77.16].

General procedure for the synthesis of chalcones – synthesis of chalcone **3a**. A mixture of $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), PPh_3 (11.2 mg, 0.04 mmol), iodobenzene (**1a**) (82 mg, 0.4 mmol), 3-chloropropiophenone (**2a**) (87 mg, 0.5 mmol), and K_2CO_3 (166 mg, 1.2 mmol) in DMF (2.5 mL) was stirred under a N_2 atmosphere at room temperature for 10 min, and then heated at 90 °C for 16 h. The reaction was then cooled to ambient temperature and diluted with CH_2Cl_2 (10 mL) before being filtered through a short pad of silica gel. The silica pad was rinsed with DCM (5 mL), and the combined filtrates were washed with brine (15 mL), dried over anhydrous Na_2SO_4. The solvent was then removed under reduced pressure to give the crude product as a residue, which was purified by silica gel column chromatography eluting with a mixture of petroleum ether (60–90 °C)/EtOAc (v/v = 30:1).

(*E*)-Chalcone (3a) [21]. Yield 90%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.11 (d, *J* = 7.3 Hz, 2H, aromatic CH), 7.90 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.72 (dd, *J* = 6.3, 2.8 Hz, 2H, aromatic CH), 7.69–7.55 (m, 4H, aromatic CH and CH=C*H*COPh), 7.52–7.46 (m, 3H, aromatic CH).

(*E*)-1-Phenyl-3-(*p*-tolyl)prop-2-en-1-one (3b) [21]. Yield 83%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07–7.99 (m, 2H, aromatic CH), 7.80 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.61–7.46 (m, 6H, aromatic CH and CH=C*H*COPh), 7.24 (t, *J* = X Hz, 2H, aromatic CH), 2.40 (s, 3H, CH_3).

(*E*)-1-phenyl-3-(*m*-tolyl)prop-2-en-1-one (3c) [21]. Yield 84%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (d, *J* = 7.4 Hz, 2H, aromatic CH), 7.85 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.58 (m, 4H, aromatic CH and CH=C*H*COPh), 7.49 (d, *J* = 6.0 Hz, 2H, aromatic CH), 7.35 (t, 1H, aromatic CH), 7.28 (t, 1H, aromatic CH), 2.44 (s, 3H, CH_3).

(*E*)-1-Phenyl-3-(*o*-tolyl)prop-2-en-1-one (3d) [25]. Yield 87%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 15.6 Hz, 1H, C*H*=CHCOPh), 8.08 (m, 2H, aromatic CH), 7.75 (d, *J* = 7.4 Hz, 1H, aromatic CH), 7.63 (t, *J* = X Hz, 1H, aromatic CH), 7.53 (m, 3H, aromatic CH and CH=C*H*COPh), 7.35 (t, 1H, aromatic CH), 7.28 (m, 2H, aromatic CH), 2.52 (s, 3H, CH_3).

(*E*)-3-(4-Methoxyphenyl)-1-phenylprop-2-en-1-one (3e) [21]. Yield 85%, white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.01 (d, *J* = 8.1 Hz, 2H, aromatic CH), 7.79 (d, *J* = 15.6 Hz, 1H, C*H*=CHCOPh), 7.59 (m, 3H, aromatic CH), 7.50 (t, *J* = X Hz, 2H, aromatic CH), 7.42 (d, *J* = 15.6 Hz, 1H, CH=C*H*COPh), 6.94 (d, *J* = 8.5 Hz, 2H, aromatic CH), 3.86 (s, 3H, OCH_3).

(*E*)-3-(4-Chlorophenyl)-1-phenylprop-2-en-1-one (3f) [21]. Yield 86%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00 (m, 2H, aromatic CH), 7.74 (d, *J* = 15.7 Hz, 1H, C*H*=CHCOPh), 7.57 (m, 3H, aromatic CH), 7.49 (m, 3H, aromatic CH and CH=C*H*COPh), 7.37 (d, *J* = 8.5 Hz, 2H, aromatic CH).

(*E*)-3-(2-Chlorophenyl)-1-phenylprop-2-en-1-one (3g) [26]. Yield 81%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 15.8 Hz, 1H, C*H*=CHCOPh), 8.02 (d, *J* = 7.2 Hz, 2H, aromatic CH), 7.75 (dd, *J* = 7.0, 2.4 Hz, 1H, aromatic CH), 7.59 (t, *J* = X Hz, 1H, aromatic CH), 7.50 (m, 3H, aromatic CH and CH=C*H*COPh), 7.43 (m, 1H, aromatic CH), 7.32 (m, 2H, aromatic CH).

(*E*)-3-(4-fluorophenyl)-1-phenylprop-2-en-1-one (3h) [21]. Yield 91%, pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ