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AN EFFICIENT SYNTHESIS OF 2-ARYL AND 2-ALKENYL-3-ALKOXY-CYCLOHEXENONES BY A MODIFIED STILLE REACTION

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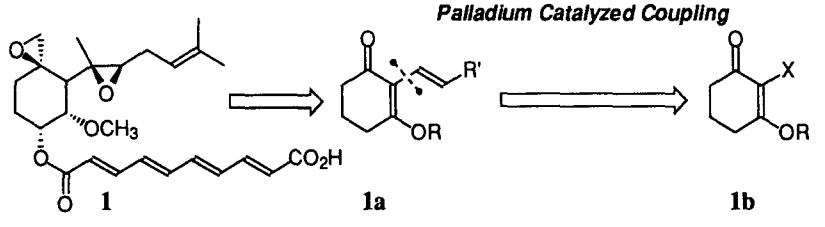
Abstract: A general, direct procedure for the synthesis of 2-aryl and 2-alkenyl-3-alkoxy-cyclohexenones using a modified Stille coupling is described.

In the course of our studies on the design and synthesis of analogs of the angiogenesis inhibitor fumagillin (**1**), we required an expedient method for the preparation of functionalized 2-alkenyl-3-alkoxyenones (**1a**, Scheme 1). Although Blagbrough and Pattenden[1] have reported the preparation of 3-methoxy-2-propenyl-cyclohex-2-enone (**1a**, R=R'=methyl) using a $RhCl_3 \cdot H_2O$ catalyzed isomerization, we desired a milder, more direct route to those substrates. Over the past decade, the palladium catalyzed coupling of aryl and vinyl halides with olefins has emerged as a mild, yet versatile tool in organic synthesis.[2] As a result, it was anticipated that our desired products **1a** could be obtained utilizing one of those protocols starting from precursor **1b**.

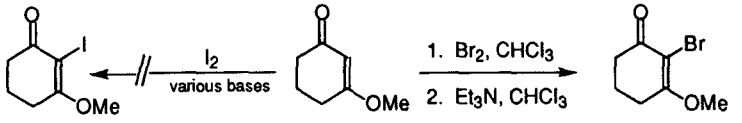
Scheme 1



1 **1a** **1b**

As it is well known that vinyl iodides are superior substrates to the corresponding vinyl bromides for oxidative palladium insertions,[2] we considered the preparation of **2b** using standard protocols (Scheme 2). Unfortunately all attempts to prepare **2b** by iodination of enone **2a** proved unsuccessful. In contrast, the corresponding bromide **2c** was readily synthesized (80%) using a known bromination-elimination sequence.[3]

Scheme 2



2b **2a** **2c**

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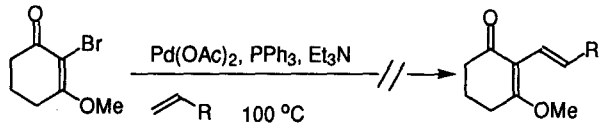
Unlike the Sonogashira,[4] Suzuki,[5] and Stille[6] modifications, the Heck reaction[7] is known to require no unique olefin functionalization. Consequently, we were hopeful that a Heck reaction between vinyl bromide **2c** and simple alkenes would provide the desired alkenyl side chain. Toward that goal, the olefin initially chosen for the coupling was the TBS-ether of allyl alcohol, since the sterically demanding protecting group would magnify terminal regioselectivity.[8] Unfortunately, all efforts to convert bromoenone **2c** to the substituted vinyl derivative **3a** were unsuccessful (Scheme 3). Significant amounts (90-95%) of unreacted **2c** was recovered even after prolonged reaction times. The attempted coupling between vinyl bromide **2c** and methyl acrylate proceeded similarly.

Scheme 3

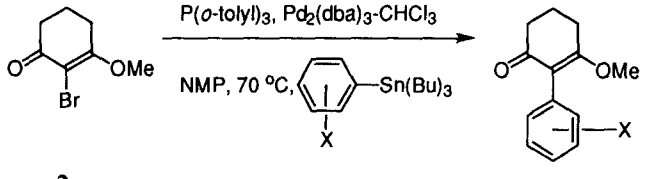


2c

3a R=CH_2OTBS
3b R=CO_2Me

Discouraged by those results, we focused our attention on the preparation of diene **3** utilizing the Stille cross-coupling reaction.[6] Although Johnson and coworkers[9] found that simple α-bromoenones were unreactive coupling partners in the Stille reaction, Nishikawa and Isobe[10] recently reported that α-bromoenones bearing β-alkyl substituents were suitable substrates for coupling with aryl stannanes. That account prompted us to study the system in detail with respect to our α-bromo-β-methoxy enone **2c**. The coupling of vinyl bromide **2c** and tributylphenyltin in the presence of tri-*ortho*-tolylphosphine and the tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct at 70 °C for two hours in *N*-methyl-2-pyrrolidone (NMP) afforded the desired 2-phenyl-3-methoxy-2-cyclohexenone (**4a**) in 75% yield (Scheme 4). The reaction was general for a variety of arylstannanes and provided 2-arylenones (**4b-e**) in good yield (59-78%). To the best of our knowledge, this was the first successful application of the Stille coupling to α-bromo-β-methoxy enones.

Scheme 4

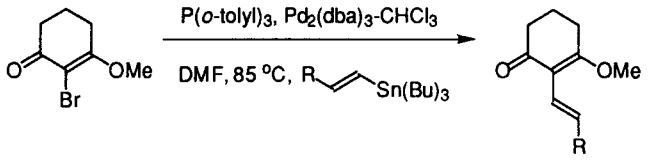


2c

4a X=H (75%)
4b X=*p*-Cl (78%)
4c X=*o*-Cl (70%)
4d X=*p*-OMe (64%)
4e X=*o*-OMe (59%)

Having demonstrated that enone **2c** was a viable substrate for the Stille aryl coupling, we altered our focus to the corresponding coupling with vinyl stannanes.[6] Transfer of the exact conditions used in the arylation to the reaction of **2c** with tributylvinyltin provided the desired vinyl adduct (**5a**) in 30% yield. The yields were optimized (80%) by adjusting the proportion of the palladium catalyst from 2% to 8%, by changing the solvent from NMP to DMF, and by increasing the temperature to 85 °C. This novel methodology was extended successfully to other alkenyl side chains (**5b-e**), further demonstrating the general nature of this modification (Scheme 5).[11]

Scheme 5



2c

5a R=H (80%)
5b R=CH_3 (76%)
5c R=CH_2CH_3 (78%)
5d R=CH_2OTBS (67%)
5e R=CO_2Me (81%)

In conclusion, we have described a mild, highly efficient and convenient method for the synthesis of both 2-aryl and 2-alkenyl-3-alkoxy-cyclohexenones using a modified Stille coupling. Further studies to determine the scope, limitation, and application of this coupling to more complex systems are under investigation.[12]

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11. Representative procedure: **3-methoxy-2-vinyl-2-cyclohexenone (5a).** 2-bromo-3-methoxy-2-cyclohexenone (**2**) (250 mg, 1.22 mmol), tris(dibenzylideneacetone)dipalladium(0)-chloroform adduct (100 mg, 0.098 mmol), and tri-*o*-tolylphosphine (61 mg, 0.2 mmol) were dissolved in DMF (3 mL) and maintained at 23 °C for 30 min under nitrogen. A solution of tri-*n*-butylvinyltin (0.46 g, 1.46 mmol) in DMF (5 mL) was added dropwise via syringe to the light orange solution and the reaction mixture warmed to 85 °C. The resulting solution gradually darkened over 5 h whereupon TLC analysis indicated completion of the reaction. After cooling to room temperature, the reaction mixture was quenched with a cold, saturated $NaHCO_3$ solution and then extracted with ether (3 x 35 mL). The combined organic extracts were washed with H_2O (2 x), brine (2 x), and dried over Na_2SO_4. After concentration under reduced pressure, the crude product was purified by column chromatography (silica gel, ether/hexane 1:2 , 1:1, 1:0) to afford 150 mg (80%) of the product which was homogeneous by TLC analysis. ^1H NMR (250 MHz) δ 6.66-6.56 (dd, 1 H), 5.94-5.87 (dd, 1 H), 5.28-5.23 (dd, 1 H), 3.87 (s, 3 H), 2.67-2.62 (t, 2 H), 2.42-2.31 (m, 2 H), 2.01-1.94 (m, 2 H); ^{13}C NMR (62.7 MHz) 199.4, 178.3, 126.2, 117.7, 102.3, 55.5, 36.9, 25.5, 20.3 ppm. Anal. Calc. for $C_9H_{12}O_2$: C, 71.03%; H, 7.95%; O, 21.03%. Found: C, 71.10%; H, 7.92%; O, 20.98%.

12. While attempting to apply the Heck reaction to our system (Scheme 3), we transferred the successful conditions described in this account to the simple olefin methyl acrylate. None of the desired coupled product was isolated, which suggests that the vinyl stannanes are necessary for coupling with α-bromo-β-methoxy enones.