Tetrahedron Letters 51 (2010) 6886–6889

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Deoxybenzoins from Stille carbonylative cross-couplings using molybdenum hexacarbonyl

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ARTICLE INFO

Article history:
Received 13 September 2010
Revised 6 October 2010
Accepted 22 October 2010
Available online 30 October 2010

Keywords:
Stille
Molybdenum hexacarbonyl
Deoxybenzoins
Palladium

ABSTRACT

Stille-type carbonylative cross-couplings, employing palladium catalysis and $Mo(CO)_6$ as the carbon monoxide carrier, were used for the preparation of deoxybenzoins. Straightforward transformations were conveniently performed in closed vessels at 100 °C, providing the products in good yields. Benzyl bromides and chlorides were used as coupling partners with aryl and heteroaryl stannanes. This mild three-component carbonylation employs the destabilizing agent DBU to promote smooth release of carbon monoxide from $Mo(CO)_6$, which made this protocol operationally simple and minimized the formation of Stille diarylmethane products.

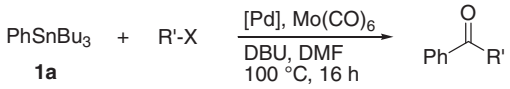
1,2-Diarylated ethanones (deoxybenzoins) are a common motif among approved pharmaceuticals such as the anti-inflammatory Bermoprofen,[1] in oxacarbazepine[2] (anticonvulsant) and in analgesics such as Narceine.[3] Deoxybenzoins are also important building blocks in heterocyclic chemistry (e.g., formation of isoxazoles,[4] pyrazoles,[1] and indoles[5]). The synthesis, via the direct α-arylation of acetophenones has, during the past decade enjoyed a renaissance due to the discovery of the simple two-component coupling between acetophenones and a suitable Ar-X reagent (X is commonly a halogen) under palladium catalysis.[6,7] Classically, this type of reaction is performed using α-halo carbonyl compounds[8] or preformed enolates.[9] Modern methods also include other approaches such as the Negishi coupling of benzyl zinc derivatives to aroyl chlorides.[10]

Previously, our group developed a methodology relying on sequential Heck-arylations of enol ethers to obtain deoxybenzoins after hydrolysis.[11] In addition to a cobalt-catalyzed carbonylation[12] procedure to access symmetrical diarylketones using solid $Co_2(CO)_8$ and microwaves, we have developed a Stille carbonylative cross-coupling method[13] to obtain a variety of unsymmetrical diarylketones. Synthetic advantages of the Stille carbonylation reaction include: the wide functional group tolerance exhibited by organostannanes, thus increasing the number of available building blocks, the three-component[14] nature of this coupling, and additionally, the convenience of non-gaseous substrates.[15–18]

Herein, we present an investigation of the scope and limitation of a Stille carbonylation protocol using vinyl and alkyl halide substrates. Our original protocol using 10 mol % of the palladium catalyst, $PdCl_2(dppf)\cdot CH_2Cl_2$, one equivalent of $Mo(CO)_6$, and 10 mol % of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) in DMF is a very robust protocol for diarylketone synthesis employing aryl triflates and bromides in couplings with various aryl stannanes.[13] Thus, there was a clear incentive to examine additional organohalide moieties, prone to undergo oxidative addition to palladium, in order to further extend the methodology.

Initially, we decided to investigate a set of suitable moieties lacking activated β-hydrogens (Scheme 1).[19] The first attempts using simple vinyl bromide and methyl iodide proved unsuccessful with only a trace amount of carbonylation product formed.

According to LC–MS the organohalides were consumed and benzophenone was formed as the major product. However, employing the styryl substrates, *cis*/*trans*-β-bromostyrene (50:50) and 2-bromoindene produced 72% and 33% yields of carbonylation products, respectively. α-Bromostyrene was productive (~60% yield) but could not be separated from the major side product benzophenone. Substrates such as allyl and cinnamyl bromides furnished less than 10% yields. A plausible explanation is that a π-allyl mechanism is competing with the carbonylative catalytic cycle.[20] It should be noted that, in addition to palladium, molybdenum carbonyls are also known to form π-allyl complexes and may



Scheme 1. Carbonylative coupling of phenyl stannane with different electrophiles (R′ = vinyl, methyl, styryl, allyl; X = Br, and I).

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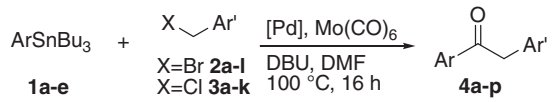
0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.10.115

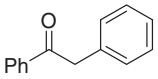
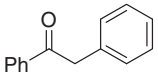
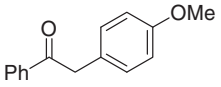
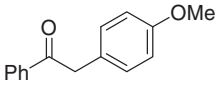
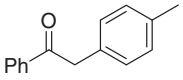
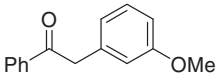
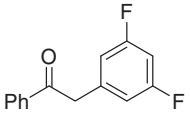
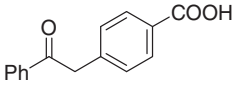
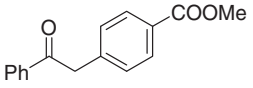
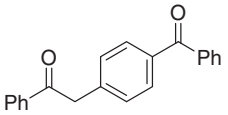
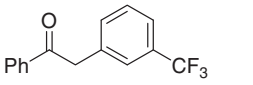
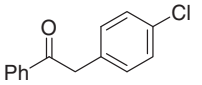


Scheme 2. Carbonylative coupling of arylstannanes with different benzyl halides furnishing deoxybenzoins.

also undergo oxidative addition in rare cases.[21,22] However, the major product formed was yet again benzophenone. Further screening of organohalides led to the benzylic halides, with the prospect of direct assembly of deoxybenzoins. Somewhat expectedly, devoid of high C–X bond energy[23] and diminished π-allyl likelihood, benzyl halides were indeed found to be compatible substrates with our present carbonylation protocol to provide deoxybenzoins in a very versatile and straightforward fashion (Scheme 2).

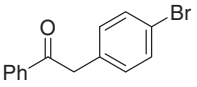
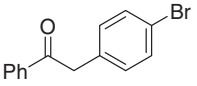
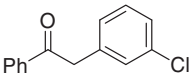
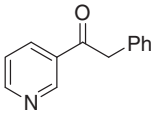
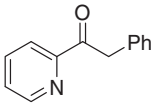
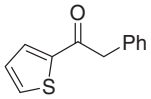
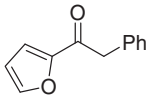
All the reactions in Table 1 were performed in sealed vessels and typically run overnight at 100 °C enabling complete consumption of the benzyl halide. Purification was straightforward following a standard procedure.[24] The effective CO concentration appeared sufficient as no direct Stille coupling product was observed. Coupling of benzyl bromide with phenylstannane delivered deoxybenzoin in an encouraging 72% yield. A small temperature/time investigation using microwave[25] heating indicated lower yields at elevated temperatures (Table 1, entry 1). Benzyl chloride performed slightly better, producing an increased yield (81%) under standard conditions (entry 2). Electron-rich 4-methoxybenzyls reacted smoothly to give satisfactory yields with both the bromide and chloride (entries 3 and 4). The weakly σ-donating 4-methylbenzyl bromide **2c** furnished a slightly higher yield (73%, entry 5). Moving the methoxy-substituent to the *meta* position improved the outcome indicating the weak influence of electronic factors (entry 6). Accordingly, the highest yields from the bromides were obtained using strong electron-withdrawing groups as in entries 7 and 10. As expected, trifluoromethyl substituted benzyl chloride **3i** reacted smoothly (entry 11). Unfortunately, a carboxylate moiety was not compatible with this

Table 1
Carbonylative cross-coupling of organostannanes with different electrophiles[a] producing **4a**–**p** via the reaction depicted in Scheme 2

Entry	R-$SnBu_3$ R		R′-X		Reaction time (h)	Product RCOR′		Isolated yield (%)
1	Ph	**1a**	Benzyl bromide	**2a**	16 0.5 (140 °C)[c] 1 (140 °C)[c] 1 (160 °C)[c]		**4a**	72 53 67 51
2	Ph	**1a**	Benzyl chloride	**3a**	16		**4a**	81
3	Ph	**1a**	4-Methoxybenzyl bromide	**2b**	16		**4b**	53
4	Ph	**1a**	4-Methoxybenzyl chloride	**3b**	16		**4b**	61
5	Ph	**1a**	4-Methylbenzyl bromide	**2c**	16		**4c**	73
6	Ph	**1a**	3-Methoxybenzyl bromide	**2d**	16		**4d**	62
7	Ph	**1a**	3,5-Difluorobenzyl bromide	**2e**	16		**4e**	81
8	Ph	**1a**	(4-Carboxy)benzyl bromide	**2f**	16		**4f**	No product
9	Ph	**1a**	(4-Methoxycarbonyl)benzyl chloride	**3g**	16		**4g**	65
10	Ph	**1a**	(4-Benzoyl)benzyl bromide	**2h**	16		**4h**	76
11	Ph	**1a**	(3-Trifluoromethyl)benzyl chloride	**3i**	16		**4i**	70
12	Ph	**1a**	4-Chlorobenzyl chloride	**3j**	16		**4j**	68[b]

(*continued on next page*)

Table 1 (*continued*)

Entry	R-$SnBu_3$ R		R′-X		Reaction time (h)	Product RCOR′		Isolated yield (%)
13	Ph	**1a**	4-Bromobenzyl bromide	**2k**	16		**4k**	66[b]
14	Ph	**1a**	4-Bromobenzyl chloride	**3k**	16		**4k**	65[b]
15	Ph	**1a**	3-Chlorobenzyl bromide	**2l**	16		**4l**	73[b]
16	3-Pyridyl	**1b**	Benzyl bromide	**2a**	16		**4m**	No product
17	2-Pyridyl	**1c**	Benzyl bromide	**2a**	16		**4n**	No product
18	2-Thienyl	**1d**	Benzyl bromide	**2a**	16		**4o**	54
19	2-Furyl	**1e**	Benzyl bromide	**2a**	16		**4p**	42

[a] The reaction was conducted in closed vessels at 100 °C on a 1 mmol scale (**2a**–**f**, **h**, **k**, **l** or **3a**, **b**, **g**, and **i**–**k**) with 1.4 equiv of **1a**–**e**, 10 mol % $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$, 1 equiv of $Mo(CO)_6$, and 10 mol % DBU in DMF (2 mL).
[b] 1.1 equiv of **1a**.
[c] The reaction vessel was subjected to microwave heating at the specified temperature.

reaction protocol as no product could be isolated (entry 8). This can be attributed to interfering coordination to palladium by the carboxylate. The analogous methyl ester **3g** worked well (entry 9). The chemoselectivity for activation of the C(sp^2)-X and C(sp^3)-X bond was in complete favor of the benzylic halogen as was evident from entries 7 and 12−15.[23,26,27] This is an important finding as halogens are ubiquitous aromatic substituents in many synthetic routes. A slightly smaller excess (1.1 equiv) of arylstannane was used in entries 12–15 to prevent further reaction with the aryl halide product. Overall benzyl chlorides performed slightly better or equally well compared to the corresponding bromides (cf. entries 1–4, 13, and 14).

In contrast to our previous report[13] heteroaromatic stannanes such as the 3- and 2-pyridines **1b** and **1c** were incompatible with this protocol, yielding no products (entries 16 and 17). Competing benzylation of the pyridine nitrogen seems to be the cause as a rapid production of destannylated *N*-benzylpyridinium salt was detected by LC–MS. However, non-nucleophilic heteroaromatics such as thiophene and furan furnished workable yields (entries 18 and 19). Product **4o** can be found as a motif in the antihistamine pharmaceutical ketotifen.

In conclusion, we have successfully developed a convenient and flexible protocol for carbonylative Stille couplings employing a solid CO-source. Benzyl bromides and chlorides showed broad scope producing high yields of products and also allowed couplings with some heteroaromatic stannanes. To the best of our knowledge, this is the first report where a carbonylative Stille cross-coupling is used in the production of deoxybenzoins. A broad array of 1,2-arylated ethanones were produced, in good to high yields, employing a single standard protocol for both benzyl chlorides and bromides. Further investigations are currently ongoing in our laboratory to explore other applications of this protocol.

Acknowledgments

We would like to thank Dr. Luke Odell for critically reviewing this manuscript and the Knut and Alice Wallenberg Foundation for helpful support of this investigation.

Supplementary data

Supplementary data (a detailed experimental procedure and spectra from LC–MS, GC–MS and NMR) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.10.115.

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24. Typical experimental procedure: To a vial (2–5 mL) containing a Teflon coated stirring bar was added benzyl halide (1.0 mmol), aryltributyltin (1.4 mmol), $PdCl_2(dppf)_2{\cdot}CH_2Cl_2$ (81.7 mg, 0.1 mmol), $Mo(CO)_6$ (264 mg, 1.0 mmol), DBU (15 mg, 0.1 mmol), and DMF (2 mL). The vial was then sealed under air, placed in a heating block, and stirred at 100 °C for 16 h. After cooling, the mixture was diluted with CH_2Cl_2 (10 mL) and then washed with 0.1 M NaOH (aq, 10 mL). The organic phase was separated, filtered through Florisil, and concentrated in vacuo. The residue was purified by silica chromatography, eluting with pentane/EtOAc (9:1) to furnish the pure products in the yields specified in Table 1.
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