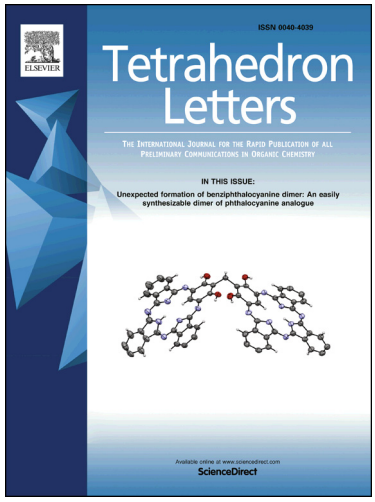

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Palladium-Catalyzed Hydrodehalogenation of Butenolides: An Efficient and Sustainable Access to β-Arylbutenolides

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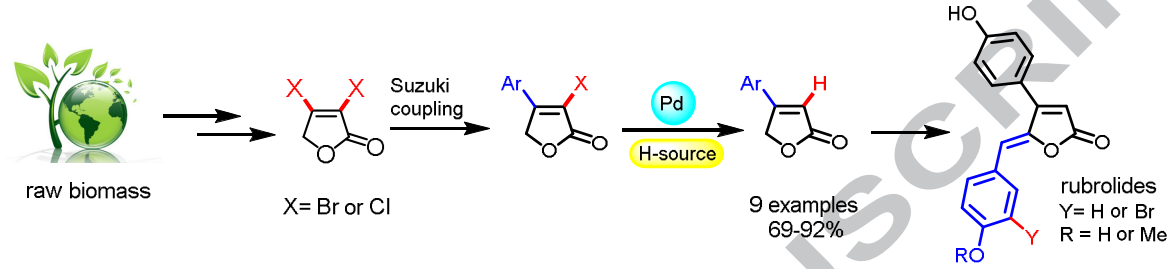

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Palladium-Catalyzed Hydrodehalogenation of Butenolides: An Efficient and Sustainable Access to β-Arylbutenolides

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ABSTRACT

Several α-unsubstituted β-arylbutenolides have been prepared in 69-92% yield by reductive dehalogenation of α-halo-β-arylbutenolides. The latter were assembled in a single-step from α,β-dihalobutenolides, which are accessible on a large-scale from biomass-derived furfural. Our dehalogenation protocol is illustrated by a new synthesis of the marine antibiotics rubrolide E and F, and 3"-bromorubrolide F.

1. Introduction

The α-unsubstituted β-arylbutenolide unit is found in several natural[1] and unnatural products[2] endowed with significant biological activities. For instance, the synthetic drug benfurodil (Eucilat®, **1**) is used in the treatment of congestive heart failure[2a] while β-(2,5-dihydroxyphenyl) butenolide (**2**),[2c] a synthetic analogue of the natural product amisnolide (**3**),[1c] displays antitumor activity comparable to that of Adriamycin®.[2c]

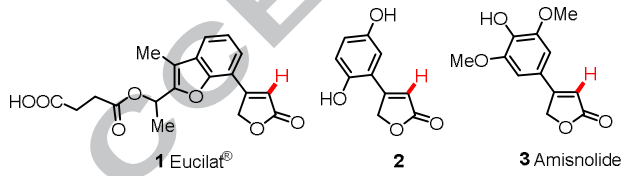
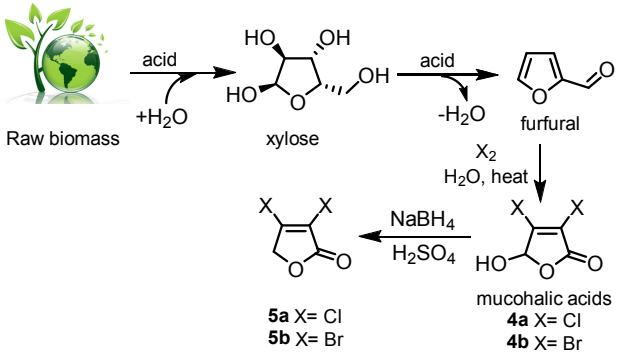


Figure 1. Synthetic and natural β-arylbutenolides

Given the medicinal value and demonstrated utility of β-arylbutenolides as synthetic intermediates, a number of methods for their preparation have been developed.[3-6] Among the most versatile are those involving transition metal catalyzed cross-coupling of tetronic acid derivatives.[4a,5] In this regard, inexpensive mucohalic acids **4a-b** (ca. 0.20–1 US$/gram) represent an attractive starting point as they are readily available on a large scale from furfural,[7] obtained from raw biomass via acid-catalyzed dehydration of xylose[8] (Scheme 1). Addition of chlorine or bromine to furfural affords the corresponding mucohalic acids[7] that can be used in the synthesis of medicinally relevant compounds.[9] For example, replacement of the hydroxyl group in mucochloric acid **4a** by amines provided a series of γ–amino derivatives displaying activity against *Trypanosoma cruzi*.[10] On the other hand, **4a-b** can be easily reduced with sodium borohydride in the presence of sulfuric acid to afford α,β-dihalobutenolides **5a-b** in high yields.[11] These butenolides are also versatile, stable building blocks frequently employed in site-selective cross-coupling reactions leading to α-halo-β-aryl/alkyl butenolides. The latter have served as intermediates in the synthesis of a variety of bioactive compounds,[12] including the well-known COX-2 inhibitor rofecoxib (Vioxx®).[12a,d]



Scheme 1. Sustainable access to α,β-dihalobutenolides from biomass

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Given the ready availability α-halo-β-arylbutenolides from **5a**-**b**,[12] access to their α-unsubstituted counterparts would simply entail removal of the superfluous halogen.

Although many methods are available for the dehalogenation of aromatic halides,[13] few have been shown to be applicable to α or β-halobutenolides.[12a,14,15] Further, only two α-halo-β-arylbutenolides have been dehalogenated thus far, notably by Rossi.[12a] Both of them bear an α-bromo substituent. Their dehalogenation was carried out using either an excess of activated zinc powder (4 equiv) or $Pd(OAc)_2/PPh_3$ (3 mol% each) in the presence of $HCOOH/Et_3N$, affording the desired products in yields of 74% and 41%, respectively.[12a]

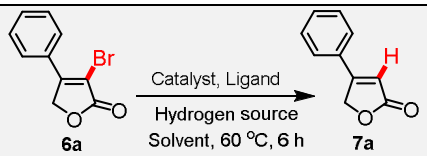
Reported herein is a broader investigation of the latter process along with the development of a new procedure, applicable to a range of α-bromo and chloro-β-arylbutenolides. In addition, we describe an application of this chemistry to the synthesis of three rubrolide antibiotics, notably rubrolides E, F and 3"-bromorubrolide F.[16]

2. Results and discussion

The quest to find optimal conditions for effecting Pd-catalyzed hydrodehalogenation of α-halo-β-arylbutenolides began with **6a** as a model substrate. This compound was prepared in 76% yield by Suzuki-Miyaura coupling of α,β-dibromobutenolide **5b** with phenylboronic acid using a literature procedure.[12k] Bromobutenolide **6a** was then subjected to reduction using different catalysts, ligands, amines/hydrogen sources and solvents, as outlined in Table 1.

At first, we tried the reaction conditions reported by Rossi[12a] and found that the dehalogenated product **7a** was obtained in only 29% yield (Table 1, entry 1). Next, we investigated the effect of the palladium salt (Table 1, entries 2–5). The use of $Pd(PPh_3)_4$ or $PdCl_2(PPh_3)_2$ in the presence or absence of formic acid resulted in low product yields (21-26%, entries 2-3). However, switching to other Pd-salts, such as $Pd(PhCN)_2Cl_2$ or $Pd(MeCN)_2Cl_2$, led to a substantial improvement in yield (58-59%, entries 4-5). A control experiment further revealed that the use of a mixture of an equimolar amount of formic acid and triethylamine resulted in a better yield than the use triethylamine alone as a hydrogen source (entry 5 *vs* 6). Replacing triphenylphosphine by other ligands (cf. triphenylarsine or dppf) did not improve yields (entries 7–8). Likewise, Hünig's base and triethylamine gave comparable yields (entry 5 *vs* 9). In terms of solvent, acetonitrile turned out to be the best choice, with DMF coming a close second (entries 9–14). Ultimately, it was found that the yield of **7a** could be significantly improved (81%) by using a combination of palladium salts, notably equimolar quantities of $Pd(OAc)_2$ and $Pd(MeCN)_2Cl_2$, along with Hünig's base and formic acid in acetonitrile (entry 15). Given the elusive nature of the catalytic species involved in such processes,[17] it is difficult to account for the enhanced performance of this particular procedure. That said, control experiments have shown that when either of the two palladium salts is used alone, the yield of **7a** is substantially lower (Table 1, entry 15 *vs* entries 10 and 16).

Table 1. Optimization of the Reductive Dehalogenation of **6a**



Entry	Catalyst[a]	Ligand[b]	Hydrogen Source[c]	Solvent	Yield[f] (%)
1	$Pd(OAc)_2$	PPh_3	Et_3N[d]	DMF	29
2	$Pd(PPh_3)_4$	-	Et_3N[d]	DMF	21
3	$PdCl_2(PPh_3)_2$	-	Et_3N	DMF	26
4	$Pd(PhCN)_2Cl_2$	PPh_3	Et_3N[d]	DMF	58
5	$Pd(MeCN)_2Cl_2$	PPh_3	Et_3N[d]	DMF	59
6	$Pd(MeCN)_2Cl_2$	PPh_3	Et_3N	DMF	47
7	$Pd(MeCN)_2Cl_2$	$AsPh_3$	Et_3N[d]	DMF	31
8	$Pd(MeCN)_2Cl_2$	dppf	Et_3N	DMF	22
9	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	DMF	61
10	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	MeCN	64
11	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	Toluene	56
12	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	DCM	33
13	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	DMSO	58
14	$Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	Dioxane	47
15[e]	$Pd(OAc)_2$/ $Pd(MeCN)_2Cl_2$	PPh_3	DIPEA[d]	MeCN	81
16	$Pd(OAc)_2$	PPh_3	DIPEA[d]	MeCN	46

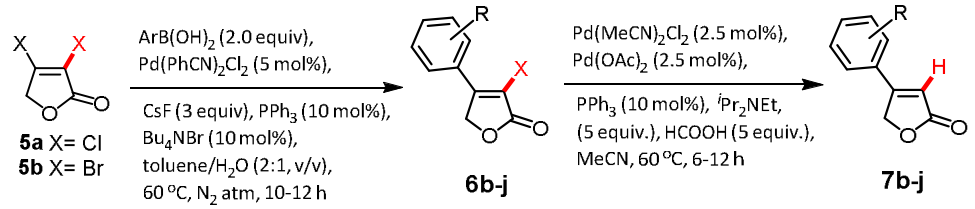
[a] Catalyst (5.0 mol%); [b] Ligand (10.0 mol%); [c] Hydrogen source/base (5.0 equiv.); [d] Mixture of equimolar amount of HCOOH and base (5.0 equiv. each); [e] Each catalyst was used in 2.5 mol%; [f] Isolated yield after purification by column chromatography; no other compound(s) could be isolated or identified from the crude reaction mixture.

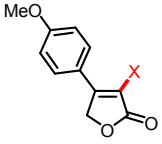
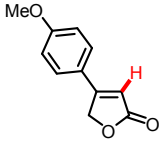
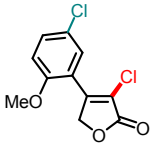
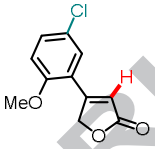
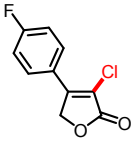
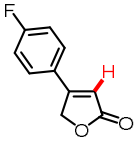
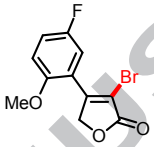
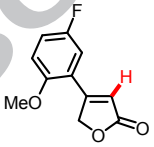
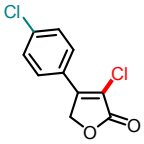
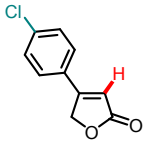
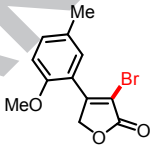
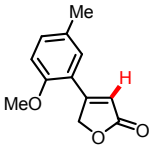
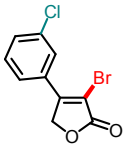
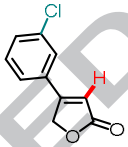
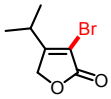
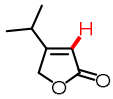
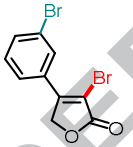
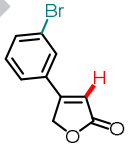
Having uncovered an efficient procedure for converting **6a** to **7a**, the next task was to investigate the substrate scope. To this end, a range of α-halo-β-arylbutenolides were prepared in good yields by Suzuki cross-coupling[12k] (Table 2, entries 1-8, 67-89%). For the sake of comparison, we also included in our study a known α-halo-β-alkylbutenolide (**6j**), synthesized from **5b** by cuprate addition-ellimination,[18] as well as the starting α,β-dihalobutenolides **5a**-**b** (entries 9-10).

As seen from the results, our dehalogenation protocol worked well with all α-halo-β-arylbutenolides tried (Table 2, entries 1-8, 69-92%). However, the highest yields were obtained with substrates bearing an α-bromo substituent (cf. entry 1, **6b** *vs* **6b'**). Importantly, the butenolide halogen could be selectively removed in substrates equipped with a chloro or bromoaryl moiety (entries 3-6). Moreover, the nature of the aromatic substituent(s) had little impact to the yield of **7** (entries 1-8).

In contrast, replacement of the aryl substituent by an alkyl of similar steric bulk (cf. isopropyl) led to a modest yield of dehalogenated product **7j** (47%, entry 9). Further, attempts at removing the β-halogen from dihalobutenolides **5a**-**b** led to complex product mixtures containing only traces of the completely dehalogenated butenolide **5** (entry 10).

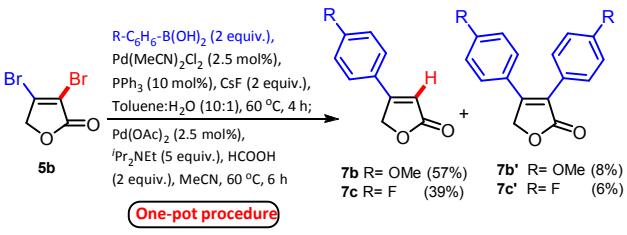
Table 2. Substrate scope.



Entry	Yield of 6 (%)[a]	Yield of 7 (%)[a]	Entry	Yield of 6 (%)[a]	Yield of 7 (%)[a]
1	 **6b** X= Br (89%) **6b'** X= Cl (76%)	 **7b** (from **6b**, 92%) (from **6b'**, 76%)	6	 **6g** (74%)	 **7g** (69%)
2	 **6c** (78%)	 **7c** (71%)	7	 **6h** (67%)	 **7h** (86%)
3	 **6d** (79%)	 **7d** (73%)	8	 **6i** (72%)	 **7i** (90%)
4	 **6e** (86%)	 **7e** (82%)	9	 **6j** (93%)[b]	 **7j** (47%)
5	 **6f** (89%)	 **7f** (73%)	10[c]	 **5a** X= Cl **5b** X= Br	 **5** (from **5a** <1%) (from **5b** <3%)

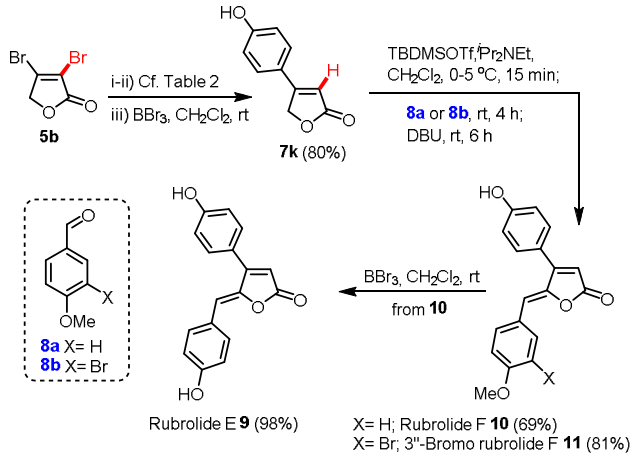
[a] All yields refer to isolated products after purification by column chromatography. [b] **6j** was prepared by cuprate addition-ellimination (ref. 18). [c] In both cases (**5a/5b**) decomposition of starting material was observed and no monohalogenated compound was detected by GC-MS analysis of the crude reaction mixture.

Next, we briefly explored the possibility of performing the Suzuki cross-coupling/dehalogenation sequence in one-pot fashion (Scheme 2). However, these efforts turned out to be only partially successful. Although we were able to generate **7b** or **7c** directly from dibromobutenolide **5b**, the formation of several side-products, including triphenylphosphine oxide and the corresponding α,β-diarylbutenolides (cf. **7b'** or **7c'**) made purification difficult. Thus, **7b** could be isolated in a fairly modest 57% yield when compared to that previously obtained by the 2-step route (cf. 82% overall, entry 1, Table 2).



Scheme 2. One-pot Suzuki coupling and reductive dehalogenation.

At this point, we turned our attention to the synthesis of the marine antibiotics rubrolide E, F and 3''-bromorubrolide F (**9**-**11**, Scheme 3). Besides antimicrobial activities,[16] compounds **9**-**11** were recently shown to inhibit NO production, at concentrations of 10.53, 8.53 and 11.91 μmol/L, respectively.[4f] The simplest member of the family, rubrolide E **9** has been synthesized on numerous occasions in the past.[4a-f] However, there is only one synthesis of rubrolides **10**-**11**, reported in early 2017 by Jun and co-workers.[4f] Jun's route begins from *p*-methoxyacetophenone and involves Wittig-Horner olefination and tandem SeO_2 oxidation/lactonization as key steps.[4f] A deprotection-reprotection-deprtotection cycle was required to reach **10**-**11**.[4f] Our approach is substantially different, utilizing **7k** as a common precursor to all three targeted rubrolides (Scheme 3).



Scheme 3. Synthesis of rubrolides F & E and 3''-bromorubrolide F

Thus, submission of dibromobutenolide **5b** to Suzuki cross-coupling, followed by dehalogenation and methyl ether cleavage afforded **7k** in 80% yield (3 steps). Next, one-pot vinylogous aldol condensation[4a] of **7k** with 4-methoxybenzaldehyde (**8a**) directly provided rubrolide F (**10**, 69%). Likewise, using 3-bromo-4-methoxybenzaldehyde (**8b**) instead of **8a,** 3''-bromorubrolide F (**11**) was obtained in 81% yield. Finally, treatment of rubrolide F with boron tribromide uneventfully led to rubrolide E (**9**).

In conclusion, a new and efficient catalytic method for accomplishing hydrodehalogenation of α-halo-β-arylbutenolides was developed. The procedure is operationally simple and scalable, enabling low-cost access to a variety of α-unsubstituted β-arylbutenolides from sustainable, furfural-derived α,β-dibromo and dichlorobutenolides. Using this methodology, the marine antibiotics rubrolide E, F, and 3''-bromorubrolide F, were synthesized in 4-5 steps and overall yields of 54-65 % .

Acknowledgments

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Supplementary Material

Supplementary data (detailed experimental procedures, compounds characterization data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds) associated with this article can be found, in the online version.

References and notes

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Highlights

- ✓ An efficient reductive dehalogenation of α-halo-β-arylbutenolides was developed
- ✓ A protecting group free synthesis of rubrolides E and F is described
- ✓ β-arylbutenolides were obtained by one-pot process from α,β-dihalobutenolides
- ✓ A regioselective dehalogenation of α-halo-β-arylfuran-2(*5H*)-ones was developed