Palladium-Catalyzed Reaction of Arenediazonium Tetrafluoroborates with Methyl 4-Hydroxy-2-butenoate: An Approach to 4-Aryl Butenolides and an Expeditious Synthesis of Rubrolide E

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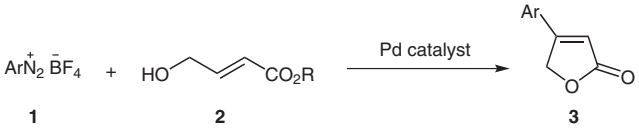
Abstract: The palladium-catalyzed reaction of arenediazonium tetrafluoroborates with methyl 4-hydroxy-2-butenoate in MeOH under mild conditions gives 4-arylbutenolides usually in good to high yields through a domino vinylic substitution/cyclization process. The reaction tolerates a variety of useful substituents including the whole range of halogen substituents, nitro, ether, cyano, keto, and ester groups and can be performed as a one-pot process generating the arenediazonium salt in situ. By using this method, the marine antibiotic rubrolide E has been synthesized via an expeditious and efficient sequential protocol that omits the isolation of the butenolide intermediate (two operative steps, 52% overall yield).

Key words: diazonium salts, Heck reaction, cyclization, butenolides, rubrolides

Because of their availability from inexpensive anilines, higher reactivity, utilization under aerobic and phosphine-free conditions in the absence of added bases, arenediazonium salts are an attractive alternative to aryl halides or triflates in Heck reactions.[1,2–5] Most of the applications described have been based on the palladium-catalyzed reaction of arenediazonium salts with monosubstituted olefins.[2] A variety of cyclic olefinic systems have also been investigated.[3] Very little, however, has been done with acyclic disubstituted olefins. Acyclic 1,1-disubstituted olefins have been used to prepare α-benzyl-β-keto esters[4] and (*E*)-dimethyl 2-benzylidensuccinates,[3e] the reactivity of acyclic β-substituted and α,β-disubstituted acrylates has been investigated by Correia et al.,[3e] and (*E*)-4,4,4-trifluoro-1-phenyl-2-buten-1-one has been converted into the corresponding α-arylated derivatives.[5]

Our interest in the palladium chemistry of arenediazonium salts[3n,6] prompted us to investigate whether their reaction with 1,2-disubstituted olefins bearing a nucleophile at one olefinic terminus and an electrophile at the other one might lead to the de novo construction of functionalized cyclic derivatives through a domino Heck reaction–cyclization process. In particular, we decided to explore the palladium-catalyzed reaction of arenediazonium salts with readily available alkyl 4-hydroxy-2-butenoate[7] (**2**) to develop a new route to the 4-arylbutenolide [or 4-aryl-2(5*H*)-furanone] skeleton **3** (Scheme 1), a structural unit that characterizes a large number of biologically important compounds.[8] Herein we report the results of this study.



Scheme 1

We initiated our study by subjecting **2a** (R = Et) to 2 equivalents of 4-methoxydiazobenzene tetrafluoroborate (**1a**), a model of electron-rich arenediazonium salts, in the presence of 5 mol% of $Pd(OAc)_2$ in EtOH at 40 °C for 8 hours. The expected butenolide product **3a** was isolated in 50% yield along with a 19% yield of the acyclic derivative **4a**, most probably because of the low regioselectivity of the carbopalladation step under these conditions (Table 1, entry 1). The starting arenediazonium salt **1a** was recovered in 14% yield. We then switched to the methyl ester **2b** (R = Me) in MeOH and found that **3a** could be isolated in a 63% yield after 5.5 hours and that a higher regioselectivity in the carbopalladation step could be attained (**4a** was isolated only in 6% yield; Table 1, entry 2). The reason of the higher regioselectivity observed under these conditions was not investigated. Optimization experiments were then carried out. These investigations revealed that the best result in terms of yield and excess of **1a** could be obtained using 2 equivalents of **1a** in MeOH at room temperature (Table 1, entry 3). Increasing the excess of **1a** led only to moderately higher yields of the butenolide derivative (Table 1, compare entries 4 and 5 with entries 2 and 3, respectively) and using solvents such as THF and MeCN met with failure (Table 1, entries 6 and 7). Using 4-methoxycarbonyldiazobenzene tetrafluoroborate (**1b**) under the same conditions (2 equiv of arenediazonium salt in MeOH), a model of electron-poor arenediazonium salts, gave high yields of **3b** both at 40 °C (Table 1, entries 8) and at room temperature (Table 1, entry 9). A lower yield of **3b** was obtained increasing the excess of **1b** (Table 1, entry 10).

Using 1 equivalent of **2b**, 2 equivalents of the arenediazonium salt in MeOH at room temperature or 40 °C, we next explored the scope and generality of the process.[9]

As shown in Table 2, the reaction tolerates a variety of useful substituents including the whole range of halogen substituents, nitro, ether, cyano, keto, and ester groups.

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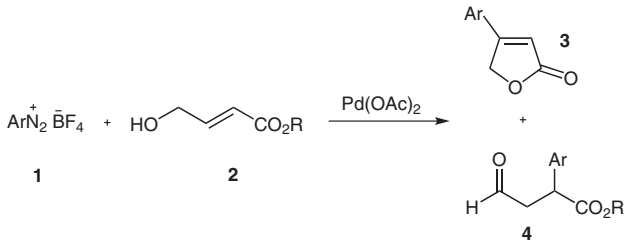
Table 1 Optimization of the Reaction Conditions[a]



Entry	**1** Ar (equiv)		**2** R		Solvent	Temp (°C)	Time (h)	Yield of **3** (%)[b]		Yield of **4** (%)[b]	
1	4-$MeOC_6H_4$ (2)	**1a**	Et	**2a**	EtOH	40	8	50[c]	**3a**	19	**4a**
2	4-$MeOC_6H_4$ (2)	**1a**	Me	**2b**	MeOH	40	5.5	63	**3a**	6	**4a**
3	4-$MeOC_6H_4$ (2)	**1a**	Me	**2b**	MeOH	r.t.	24	73	**3a**	3	**4a**
4	4-$MeOC_6H_4$ (3)	**1a**	Me	**2b**	MeOH	40	6	74	**3a**	5	**4a**
5	4-$MeOC_6H_4$ (3)	**1a**	Me	**2b**	MeOH	r.t.	16	79	**3a**	6	**4a**
6	4-$MeOC_6H_4$ (3)	**1a**	Me	**2b**	THF	40	7	–	–	–	–
7	4-$MeOC_6H_4$ (3)	**1a**	Me	**2b**	MeCN	r.t.	6	–	–	–	–
8	4-$MeO_2CC_6H_4$ (2)	**1b**	Me	**2b**	MeOH	40	4	77	**3b**	–	–
9	4-$MeO_2CC_6H_4$ (2)	**1b**	Me	**2b**	MeOH	r.t.	24	79	**3b**	–	–
10	4-$MeO_2CC_6H_4$ (3)	**1b**	Me	**2b**	MeOH	r.t.	24	74	**3b**	–	–

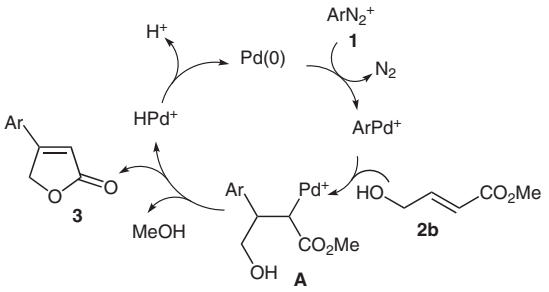
[a] Reactions were carried out on a 0.5 mmol scale in 5 mL of solvent.
[b] Yields are given for isolated products.
[c] Compound **2a** was recovered in 14% yield.

Arenediazonium salts containing *ortho* substituents such as chloro, methoxy, and methyl groups also give the corresponding butenolide products in good to high yields (Table 2, entries 8, 14–17).

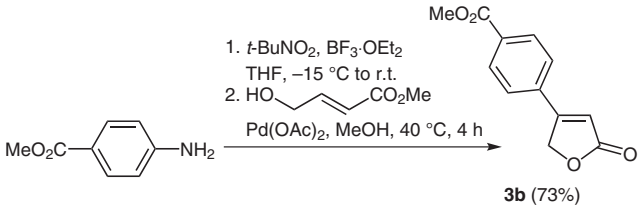
A plausible catalytic cycle for this reaction is shown in Scheme 2. The arylpalladium complex, formed in situ via the reaction of the arenediazonium salt with Pd(0), reacts with methyl 4-hydroxy-2-butenoate to give regioselectively the carbopalladation adduct **A**. Subsequent *syn*-β-elimination of HPd species and cyclization, not necessarily in that order, afford the butenolide product.

The reaction was also performed generating the arenediazonium salt in situ.[13] This protocol was attempted with 4-carbomethoxylaniline and **2b** (Scheme 3).[14] The best result was obtained by adding MeOH, $Pd(OAc)_2$, and **2b** to the crude mixture resulting from the preparation of 4-carbomethoxybenzenediazonium tetrafluoroborate concentrated under reduced pressure.

By using this method, we developed an expeditious approach to the synthesis of rubrolide E, a naturally occurring butenolide derivative belonging to rubrolides, a family of biologically active marine ascidian metabolites isolated from tunicate *Ritterella rubra*[10] and *Synoicum blochmanni*.[11] Because of their antibiotic and cytotoxic activities, the synthesis of these compounds is a subject of great current interest.[12] We prepared rubrolide E as follows: the Knoevenagel condensation product **5** was obtained in 55% yield through a one-pot process by adding piperidine and 4-anisaldehyde to the crude mixture derived from the reaction of **1a** with methyl 4-hydroxy-2-butenoate; subsequent treatment of **5** with BBr_3 gave rubrolide E in 52% overall isolated yield (Scheme 4). In a recent synthesis from *N*-phenylmaleimide rubrolide E was obtained in 32% overall yield in five steps.[12e]



Scheme 2

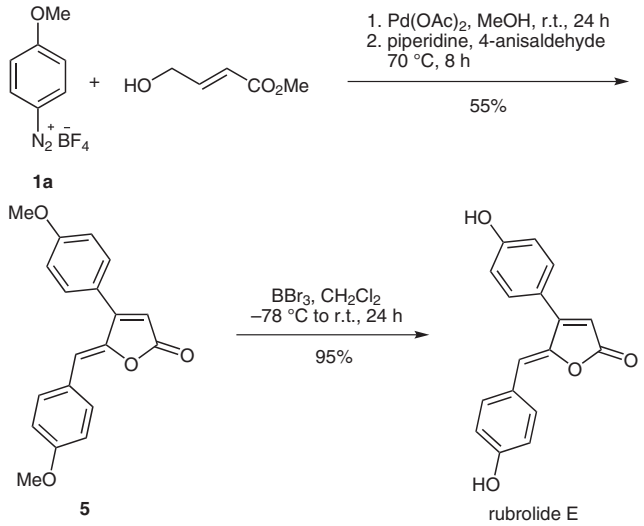


Scheme 3

Table 2 Synthesis of 4-Arylbutenolides **3** from Arenediazonium Tetrafluoroborates **1** and Methyl 4-Hydroxy-2-butenoate **2b**[a]

Entry	**1** Ar	Time (°C)	Time (h)	Yield of **3** (%)[b]	
1	4-$MeOC_6H_4$	r.t.	24	**3a**	73
2	4-$MeO_2CC_6H_4$	r.t.	24	**3b**	79
3	4-$MeCOC_6H_4$	40	6	**3c**	67
4	4-$O_2NC_6H_4$	r.t.	24	**3d**	87[c]
5	4-MeC_6H_4	40	24	**3e**	71
6	3-$F_3CC_6H_4$	40	5	**3f**	73
7	4-NCC_6H_4	40	24	**3g**	54
8	2-ClC_6H_4	40	7	**3h**	72
9	4-IC_6H_4	40	8.5	**3i**	62
10	4-ClC_6H_4	40	6	**3j**	81
11	4-FC_6H_4	40	3	**3k**	67
12	4-BrC_6H_4	r.t.	12	**3l**	86
13	Ph	r.t.	24	**3m**	91[d]
14	2-$MeOC_6H_4$	40	22	**3n**	67
15	2,4-$Me_2C_6H_3$	r.t.	24	**3o**	87[e]
16	2-Me-4-$MeOC_6H_3$	40	16	**3p**	75
17	2-Me-4-FC_6H_3	r.t.	24	**3q**	81

[a] Reactions have been carried out on a 0.5 mmol scale using 1 equiv of **2b**, 2 equiv of **1** in 5 mL of anhyd MeOH.
[b] Yields are given for isolated products.
[c] A 55% yield at 40 °C (3.5 h).
[d] A 62% yield at 40 °C (24 h).
[e] A 51% yield at 40 °C (6 h).



Scheme 4

In conclusion, we have shown that arenediazonium tetrafluoroborates react with readily available methyl 4-hydroxy-2-butenoate in the presence of catalytic amounts of $Pd(OAc)_2$ in methanol under mild conditions to give 4-arylbutenolides usually in good to high yields. The reaction tolerates a variety of useful substituents including the whole range of halogen substituents, nitro, ether, cyano, keto, and ester groups and can be performed as a one-pot process generating the arenediazonium salt in situ. The *ortho* substituents such as methoxy, methyl, and chloro are also tolerated. By using this method, the rubrolide skeleton can be constructed via an efficient two-step protocol omitting the isolation of butenolide intermediates.

Acknowledgment

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(9) **Typical Procedure for the Preparation of Butenolides (3)**
To a stirred solution of **2b** (58.0 mg, 0.50 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) in anhyd MeOH (5.0 mL), **1b** (250.0 mg, 1.0 mmol) was added at r.t. under argon. The reaction mixture was warmed at 40 °C and stirred at that temperature for 4 h (the reactor was protected from light with aluminum film). After cooling, the reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 [*n*-hexane–EtOAc, 60:40] to afford 83.9 mg of **3b** (77% yield); mp: 192–194 °C. IR (KBr): 1745, 1710, 1280 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 8.4 Hz, 2 H), 7.60 (d, *J* = 8.4 Hz, 2 H), 6.21 (t, *J* = 1.6 Hz, 2 H), 5.16 (d, *J* = 1.6 Hz, 2 H), 3.97 (s, 3 H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 173.2, 166.0, 162.5, 133.6, 132.9, 130.5, 126.5, 115.3, 70.9, 52.6. MS: *m/z* (%) = 216 (8) [M^+], 75 (42), 59 (100).

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(14) **One-Pot Procedure for the Preparation of Butenolides (3) from Anilines**
A solution of $BF_3{\cdot}OEt_2$ (140 μL, 1.1 mmol) in anhyd THF (1 mL) was cooled at –15 °C, and 4-carbomethoxylaniline (151.2 mg, 1 mmol) was added. Then, *tert*-butyl nitrite (160 μL, 1.3 mmol) in 1 mL of the same solvent was added dropwise to the rapidly stirred solution over a 10 min period. After that, the reaction temperature was maintained at –15 °C for 10 min, allowed to warm to 5 °C (ice-water bath) over a 20 min period, warmed to r.t., and stirred at the same temperature till the disappearance of the starting aniline. The reaction mixture was subsequently concentrated under reduced pressure and diluted with anhyd MeOH (5 mL). Then, **2b** (58.0 mg, 0.50 mmol) and $Pd(OAc)_2$ (5.6 mg, 0.025 mmol) were added, the reaction mixture was warmed at 40 °C, and stirred at that temperature for 4 h (the reactor was protected from light with aluminum film). After cooling, the reaction mixture was diluted with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on SiO_2 [*n*-hexane–EtOAc, 60:40] to afford 80.0 mg of **3b** (73% yield).