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Double Heck reaction of bridged *o*,*o*′-dibromobiaryls with ethyl acrylate

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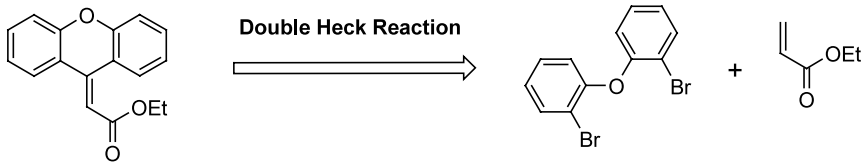
Abstract—An inter- followed by an intramolecular double Heck reaction of bridged *o*,*o*′-dibromobiaryls with ethyl acrylate is described. The nature of the bridging atom/group determined the outcome of the reaction. This double Heck reaction strategy afforded a safe and convenient synthesis of 9-(ethoxycarbonylmethylene)-9*H*-xanthene and a novel route to 9 and/or 10-substituted anthracene derivatives. © 2002 Elsevier Science Ltd. All rights reserved.

9-(Ethoxycarbonylmethylene)-9*H*-xanthene (**1**) serves as an important intermediate in the synthesis of biologically important molecules. Preparation of **1** by a reaction of 9*H*-xanthene-9-thione with ethyl diazoacetate at 60°C was reported in 51% yield.[1] The known explosive nature of ethyl diazoacetate at elevated temperature presented safety concerns and made this method impractical for a large scale. Thus, our goal was to develop a safer synthesis of **1**. Another look at the structure of **1** revealed a new approach to this molecule that involved an inter- followed by an intramolecular Heck reaction of 2-bromophenyl ether (**2a**) with ethyl acrylate (Scheme 1).

We had previously reported an intermolecular double Heck reaction with cyclopentene.[2] A domino process involving an inter- followed by an intramolecular Heck reaction between (*Z*)-(2-bromoethenyl)bromobenzene and a hexahydro-1*H*-indene derivative is also reported.[3] However, the intermediate of the intermolecular Heck reaction had to be isolated and different reaction conditions had to be used for the intramolecular Heck reaction. We reasoned that two consecutive Heck reactions, inter- followed by intramolecular, could be carried out in one-pot under the same reaction conditions. This paper describes our results on this approach.

It is well known that the Heck reaction often requires specific conditions for different substrates.[4] Thus, we investigated this reaction under a variety of conditions, and the results are listed in Table 1. The reaction of 2-bromophenyl ether (**2a**) with ethyl acrylate under standard Heck reaction conditions using palladium acetate, triphenylphosphine, and triethylamine in refluxing acetonitrile (entry 1, Table 1), disappointingly, gave no desired product **1**. Interestingly, eliminating the phosphine ligand and changing the solvent to 1-methyl-2-pyrrolidinone (NMP), the reaction of **2a** with ethyl acrylate in the presence of triethylamine (5 equiv.) and tetra-*n*-butyl ammonium bromide (1 equiv.) afforded a mixture of the desired product **1** and its reduced deriva-



1 **2a**

Scheme 1.

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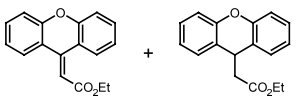
Table 1. Double Heck reaction of 2-bromophenyl ether (**2a**) with ethyl acrylate (1.2 equiv.)[10]

Entry	Conditions	Product(s)	Isolated Yield (%)
1	$Pd(OAc)_2$ (2.5 mol%), Et_3N (5 equiv), Ph_3P (7.5 mol%), CH_3CN, reflux, 16 h	No reaction	-
2	$Pd(OAc)_2$ (2.5 mol%), Et_3N (5 equiv), n-Bu_4NBr (1 equiv), NMP, 115 °C, 12 h	 **1** **3** (7.2 : 2.8)	42
3	$Pd(OAc)_2$ (2.5 mol%), KOAc (5 equiv), n-Bu_4NBr (1 equiv), NMP, 115 °C, 16 h	**1**	67
4	$Pd(OAc)_2$ (2.5 mol%), NaOAc (5 equiv), *n*-Bu_4NBr (1 equiv), NMP, 120 °C, 16 h	**1**	76
5	$Pd(OAc)_2$ (2.5 mol%), KOAc (5 equiv), n-Bu_4NBr (1 equiv), DMF, 115 °C, 12 h	Complicated mixture	Not isolated
6	Herrmann's palladacycle (2.0 mol%), NaOAc (5 equiv), *n*-Bu_4NBr (1 equiv), NMP, 140 °C, 16 h	**1**	65

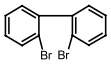
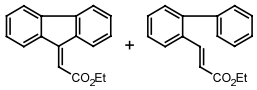
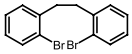
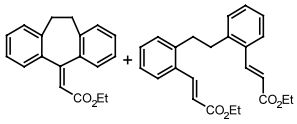
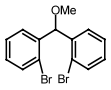
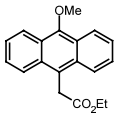
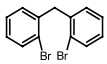
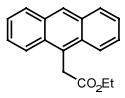
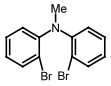
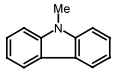
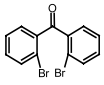
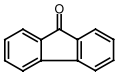
tive **3** in a 7.2:2.8 ratio (entry 2), from which **1** was isolated in 42% yield. The formation of the reduced product **3** was unusual in that such a reduction has not been previously reported in the Heck reaction. Allowing the reaction to proceed for a longer period did not increase the formation of **3**. Also, pure **1** did not undergo reduction when it was subjected to identical conditions. Suspecting that triethylamine may be the cause of the formation of reduced product **3**, we decided to change the base to well-known bases for this reaction: potassium acetate or sodium acetate. The desired product **1** was obtained in 67% yield with potassium acetate as the base (entry 3) and in 76% yield with sodium acetate (entry 4). The reduced by-product **3** was formed in only trace amounts in both cases. Surprisingly, the use of DMF as the solvent (entry 5) gave a complicated mixture, suggesting that NMP is the best solvent for this reaction. Use of Herrmann's palladacycle *trans*-di(μ-acetato)bis[*o*-(di-*o*-tolylphophino)-benzyl]dipalladium(II)[5] afforded **1** in 65% yield. Thus, the best conditions for an inter- followed by intramolecular double Heck reaction of **2a** with ethyl acrylate involved palladium acetate, sodium acetate in the presence of tetra-*n*-butylammonium bromide in NMP at 120°C (entry 4).

To test the general synthetic utility, we next studied the double Heck reaction of a variety of bridged *o*,*o*′-dibromo biaryls (**2b**–**2g**) with ethyl acrylate. The results are summarized in Table 2. Reaction of 2,2′-dibromobiphenyl **2b** with ethyl acrylate (entry 1) under the above established conditions for **2a** afforded a 8.7:1.3 mixture of the desired double Heck product **4** and the acyclic debrominated Heck product **5**. The desired product **4** was isolated in 71% yield from this mixture. Such a reduction of aryl halides, as the formation of **5**, has been reported in the literature.[6] When the linker was an ethylene group, as in dibromo compound **2c**, the desired product **6** was produced in only 49% yield (entry 2). A by-product **7** was generated in significant amounts by a double intermolecular Heck reaction. In this case, however, use of Herrmann's palladacycle afforded the desired **6** in higher yield (71%, entry 3). Interestingly, the reaction of **2d** and **2e**, with methoxymethylene and methylene groups as linkers, afforded anthracene derivatives **8** and **9**, respectively (entries 4 and 5) in excellent yields, representing a novel route to this class of compounds. The expected double Heck reaction product (**A**) aromatized spontaneously to the anthracene skeleton (Scheme 2). This novel method would allow an easy access to 9 and/or 10-substituted anthracene derivatives.

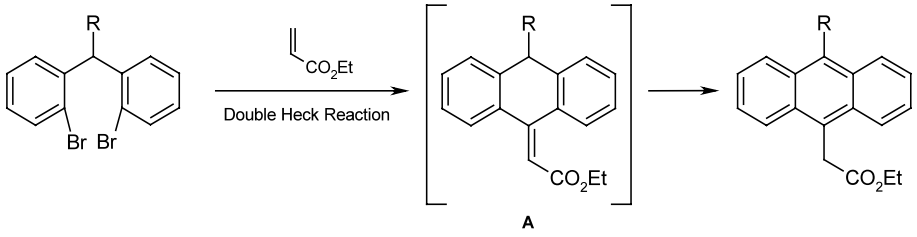
No double Heck reaction was observed when the linker was an *N*-methyl (**2f**)[7] or a carbonyl group (**2g**).[8] Instead, the dibromides underwent an intramolecular homocoupling reaction to afford compounds **10** and **11**, respectively (entries 6 and 7), in excellent yields. Palladium-catalyzed intermolecular homocoupling of aryl halides has been reported.[9]

Thus, the nature of the bridging atom/group in *o*,*o*′-dibromobiaryls (**2a**–**2g**) determined the outcome of the Heck reaction. The inter- followed by an intramolecular double Heck reaction was favored when the bridge was a hydrocarbon chain, an oxygen atom, or no bridging atom; the intramolecular homocoupling of the substrate was favored when the bridge was a carbonyl or an *N*-methyl group.

Table 2. Double Heck reaction of bridged *o*,*o*′-dibromobiaryls[10]

Entry	Substrate	Temp. (°C)	Time (h)	Product(s)	Isolated Yield (%)
1	 **2b**	120	6	 **4** (8.7 : 1.3) **5**	71
2	 **2c**	140	16	 **6** (6.5 : 3.5) **7**	49
3*	**2c**	140	24	**6** + **7** (8.0 : 2.0)	71
4	 **2d**	120	12	 **8**	80
5	 **2e**	120	20	 **9**	75
6	 **2f**	140	48	 **10**	85
7	 **2g**	140	12	 **11**	91

Reaction conditions: Substrate (1 equiv), ethyl acrylate (1.3 equiv for entries 1 and 3; 1.0 equiv for entries 2 and 6, 1.2 equiv for entries 4, 5, and 7), $Pd(OAc)_2$ (2.5 mol%), *n*-Bu_4NBr (1 equiv), NaOAc (5 equiv), NMP. * Herrmann's palladacycle (2.0 mol%), Substrate (1 equiv), ethyl acrylate (1.3 equiv), $Pd(OAc)_2$ (2.5 mol%), *n*-Bu_4NBr (1 equiv), NaOAc (5 equiv), NMP.



Scheme 2.

In summary, an inter- followed by an intramolecular double Heck reaction of bridged *o*,*o*′-dibromobiaryls with ethyl acrylate is described. The nature of the bridging atom/group determined the outcome of the reaction. This double Heck reaction strategy afforded a safe and convenient synthesis of 9-(ethoxycarbonylmethylene)-9*H*-xanthene and a novel route to 9 and/or 10-substituted anthracene derivatives.

Acknowledgements

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10. **Typical procedure**: A mixture of *o*-bromophenyl ether (500 mg, 1.52 mmol), $Pd(OAc)_2$ (8.6 mg, 0.038 mmol), tetrabutylammonium bromide (491 mg, 1.52 mmol), sodium acetate (625 mg, 7.62 mmol), ethyl acrylate (183 mg, 1.83 mmol) and 1-methyl-2-pyrrolidinone (5 mL) was flushed with nitrogen for 15 s, and the mixture was heated to 140°C over a period of 20 min. The reaction mixture was stirred at this temperature for an additional 12 h, cooled to 25°C, and *t*-butyl methyl ether (10 mL) was added. The mixture was washed with water (10 mL), and the organic layer was concentrated under reduced pressure to afford a residue which was purified by silica gel chromatography using heptane/EtOAc (20:1 to 5:1) as the eluant to furnish the desired product **1** (310 mg, 76% yield). The exact conditions for other substrates (**2b**–**2g**) are listed in Table 2, but the procedure was essentially the same.

Data for selected compounds: **1**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (dd, 1H, $J=8.0$ Hz, 1.5 Hz), 7.65 (dd, 1H, $J=8.0$ Hz, 1.5 Hz), 7.43–7.33 (m, 2H), 7.23–7.15 (m, 4H), 6.18 (s, 1H), 4.23 (q, 2H, $J=7.2$ Hz), 1.3 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.9, 152.2, 151.4, 139.4, 131.2, 130.5, 129.8, 123.9, 123.7, 122.7, 122.5, 119.0, 117.1, 116.8, 110.4, 60.3, 14.3; MS (ESI): m/z 267.1 (MH$^+$). **6**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.30–6.97 (m, 8H), 6.20 (s, 1H), 4.01 (q, 2H, $J=7.0$ Hz), 3.2–2.8 (m, 4H), 1.06 (t, 3H, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 159.4, 140.0, 138.3, 137.9, 129.1, 128.9, 128.4, 128.3, 128.2, 126.8, 126.2, 120.9, 60.5, 34.1, 32.3, 14.6; MS (ESI): m/z 279.0 (MH$^+$). **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.36–8.26 (m, 4H), 7.56–7.46 (m, 4H), 4.56 (s, 2H), 4.12 (q, 2H, $J=7.2$ Hz), 4.11 (s, 3H), 1.19 (t, 3H, $J=7.2$ Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.5, 152.4, 131.3, 126.3, 124.8, 124.7, 124.4, 122.9, 122.1, 63.3, 61.0, 33.9, 14.2; MS (ESI): m/z 295.1 (MH$^+$). **9**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.37 (s, 1H), 8.28–8.25 (m, 2H), 7.98–7.95 (m, 2H), 7.52–7.43 (m, 4H), 4.59 (s, 2H), 4.10 (q, 2H, $J=7.1$ Hz), 1.16 (t, 3H, $J=7.1$); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.8, 132.0, 131.0, 129.6, 127.8, 126.6, 126.5, 125.3, 124.8, 61.5, 34.5, 14.6; MS (EI): m/z 264.1 (M^+). **10**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.07 (d, 2H, $J=7.7$ Hz), 7.48–7.42 (m, 2H), 7.35 (d, 4H, $J=8.1$ Hz), 7.24–7.22 (m, 2H), 3.79 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.0, 125.6, 122.7, 120.3, 118.8, 108.4, 29.0; MS (ESI): m/z 182.1 (MH$^+$).