Tetrahedron Letters 52 (2011) 3861–3864

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Facile synthesis of symmetrical 3,3-diarylacrylates by a Heck-Matsuda reaction: an expedient route to biologically active indanones

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ARTICLE INFO

Article history:
Received 12 April 2011
Revised 6 May 2011
Accepted 9 May 2011
Available online 19 May 2011

Keywords:
Arenediazonium tetrafluoroborates
Heck-Matsuda
Arylation
3,3-Diarylacrylates
Palladium
Indanones

ABSTRACT

A simple and straightforward synthesis of symmetrical 3,3-diarylacrylates based on a Heck-Matsuda reaction of arenediazonium salts bearing electron-donating groups with methylacrylates is described. The reaction employs $Pd(OAc)_2$ as catalyst and goes to completion within 1 h affording the corresponding unsaturated diaryl esters in good to high yields. This method permitted the expeditious and efficient synthesis of the anticancer 3-arylindanone **5** in two operative steps in 43% overall yield.

1. Introduction

Diaryl substituted carbon centers where both aryl units are identical is a ubiquitous structural motif. For example, this moiety can be found in numerous natural products, such as the Peperomin's,[1a] Verimol-F,[1b] Kadangustin-J,[1c] Henricine-B,[1d] Metaseol,[1e] Daphneresinol,[1f] and Tatarinoid-C[1g] (Fig. 1).

β,β-Diarylacrylates are useful building blocks in organic synthesis as well.[2] They can be used for the synthesis of a wide variety of compounds of high value as they can be readily converted into enals or allylic alcohols. Symmetrical β,β-diarylacrylates bearing electron withdrawing groups can be easily prepared from the corresponding benzophenone and phosphonium ylide in high yield.[3a,3b] However, when the requisite ketone is substituted with electron donating groups, the carbonyl is rendered less electrophilic. Typical olefination reactions, such as the Horner–Wadsworth–Emmons (HWE) reactions are then considerably slower, usually requiring strong bases and refluxing conditions to provide synthetically useful yields (Scheme 1).[3b]

Therefore, milder and straightforward methods that are complementary to the HWE reaction for the preparation of symmetrical β,β-diarylacrylates are highly desirable. Such methodologies would be particularly attractive for the synthesis of β,β-diarylacrylates carrying aromatic rings containing several electron-donating groups, a conspicuous structural motif in many bioactive compounds (see Fig. 1). The Heck-Matsuda (HM) reaction involves the Pd-catalysed coupling of arenediazonium salts to olefins and has been known for some time to proceed smoothly with alkyl acrylates affording the corresponding cinnamate esters in high yields.[4,5] Alkyl acrylates were evaluated as substrates for the HM reaction in Matsuda's earliest report,[6] and more recently the cinnamate ester products were investigated as substrates for arylation by our group in the synthesis of unsymmetrical β,β-diarlyacrylates.[7] The arylation of alkyl acrylates is frequently carried out using an excess

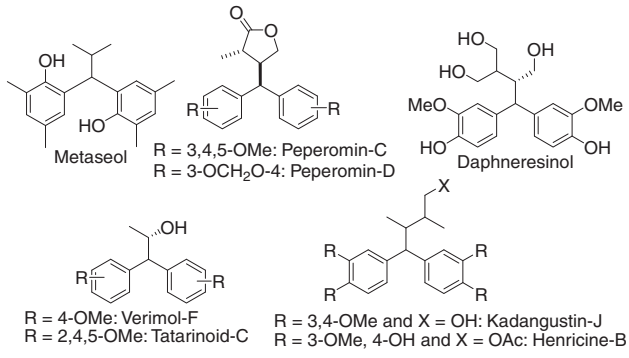

Figure 1. Natural products bearing symmetrical diaryl substituted carbon centers.

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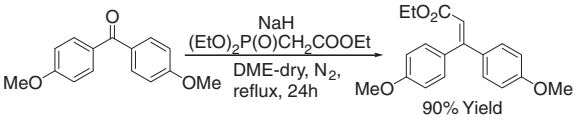
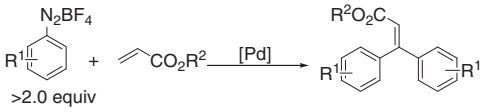
doi:10.1016/j.tetlet.2011.05.039



Scheme 1. Synthesis of 3,3-diarylacrylate by a HWE reaction.



Scheme 2. Synthesis of 3,3-diarylacrylate by a HM reaction.

of the olefin. Therefore, we reasoned that by simply inverting the stoichiometry of the reactants, symmetrical β,β-diarylacrylates would be provided in a one step procedure in somewhat smoother conditions (Scheme 2).

Herein, we describe a method of synthesising symmetrical β,β-diarylacrylates in a one pot procedure from methyl acrylates and arenediazonium tetrafluoroborates. The utility of this protocol is further exemplified by the its application towards the synthesis of a highly active antineoplastic 3-aryl indanone compound **5**.

2. Results and discussion

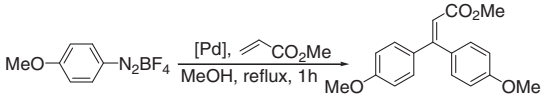
Our previous results involving the arylation of methyl cinnamate indicated that a base was not necessary for the attainment of high yields, so we initiated an optimization study that basically evaluated the Pd source (Table 1).

Using methyl acrylate and 2.5 equiv of 4-methoxyarenediazonium tetrafluoroborate as a model reaction, we found that 7 mol% catalytic loading of $Pd(OAc)_2$ in MeOH were the optimum conditions (entry 2). Although heterogeneous $Pd(OAc)_2$ supported on charcoal was equally as effective, its use was abandoned due to diminished reactivity upon reuse. Interestingly, Pd_2dba_3 as catalyst gave only the monoarylated product in 72% yield (entry 4).

Next, we turned our attention to evaluating the substrate scope with respect to the aryl donor (Table 2).[8]

Generally, yields were modest to excellent for alkoxy and phenoxy substituted arenediazonium salts (entries 1–9) and only reasonable for the most highly substituted arenediazonium tetrafluoroborate evaluated (entries 4 and 6). Where yields are only modest (entries 4 and 6), the main side product was the monoarylated compound. Somewhat surprisingly, repeat reactions using more equivalents of arenediazonium salt did not improve the yields. Diarylation with the 4-hydroxy arenediazonium tetrafluoroborates provided only the monoarylated Heck adduct in a modest isolated yield of 33% (entry 10).

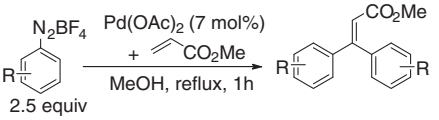
Table 1
Optimization studies

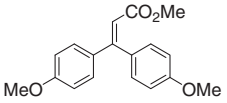
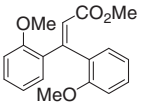
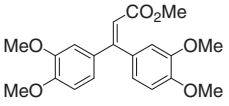
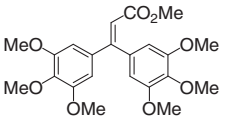
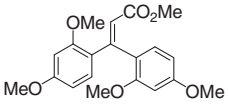
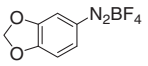
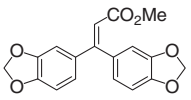
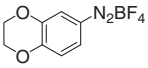
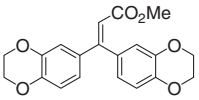
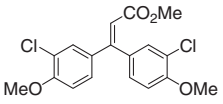
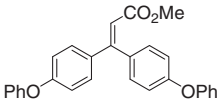
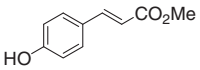


Entry	[Pd]/(mol %)	Yield/%
1	$Pd(OAc)_2$ (10)	96
2	$Pd(OAc)_2$ (7)	95
3	$Pd(OAc)_2$ (5)	77
4	Pd_2dba_3 (5)	–
5	$Pd(OAc)_2$/C (5)	90
6[a]	$Pd(OAc)_2$/C (5)	23

[a] First re-use of the heterogeneous catalyst.

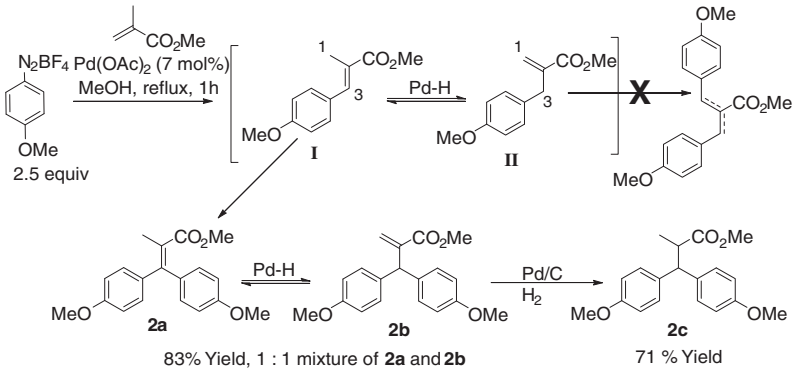
Table 2
Evaluation arenediazonium tetrafluoroborates



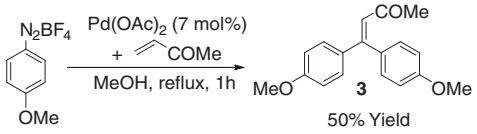
Entry	R	Product	Yield/%
1	4-OMe	 **1a**	95
2	2-OMe	 **1b**	90
3	3,4-$(OMe)_2$	 **1c**	85
4	3,4,5-$(OMe)_3$	 **1d**	53
5	2,4-$(OMe)_2$	 **1e**	95
6		 **1f**	58
7		 **1g**	75
8	3-Cl, 4-OMe	 **1h**	74
9	4-OPh	 **1i**	86
10[a]	4-OH	 **1j**	33

[a] Reaction ran at room temperature for 15 min.

The effect of an alkyl substituent at the alpha carbon of the acrylate was explored and unexpectedly gave rise to a 1:1 mixture of isomers **2a** and **2b** as determined by GC–MS (Scheme 3). This was further confirmed by reduction of the mixture under hydrogen over Pd/C affording one single compound **2c**. Interestingly, although double bond isomerisation for the initially formed



Scheme 3. Arylation of methyl methacrylate.



Scheme 4. Direct diarylation of methyl vinyl ketone.

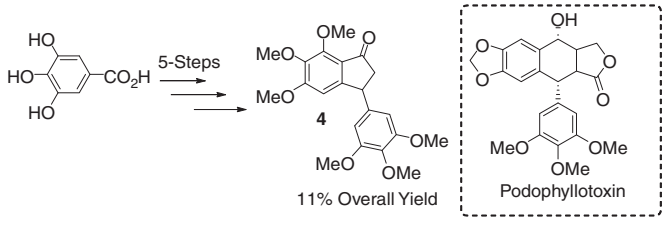
cinnamate ester **I** under catalytic conditions is plausible, no Heck adducts corresponding to arylation at the 'C1 position' of **II** were observed.

A preliminary study with similar conjugated olefin substrates such as methyl vinyl ketone was also carried out. In spite of the fact that monoarylation can be conducted in high yields,[9] it was only possible to carry out a direct diarylation of methyl vinyl ketone in a modest 50% yield (Scheme 4, compound **3**).

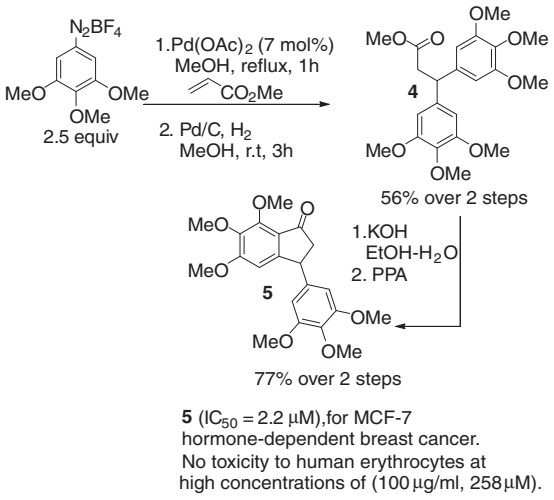
These promising results with the acrylates prompted us to explore the application of this chemistry for the preparation of the anticancer indanone compound **5**.[10] Not only did **5** display very good activities for hormone dependent cancer cell lines, but it also showed virtually no toxicity for human erythrocytes being four times more active than the natural product Podophylotoxin. In the literature, the target compound **5** was prepared from gallic acid in 5 steps with an overall yield of 11% (Scheme 5).[10]

We envisaged that the target compound could be prepared via a process involving a one pot Pd-catalysed HM-reduction[11] procedure followed by hydrolysis of the ester **4** to afford the corresponding carboxylic acid. Finally, as the last step, an acid catalysed cyclization reaction was employed to provide compound **5**. Pleasingly, we were able to complete the synthesis of **5** in only three steps (two purifications steps only) in an overall yield of 43% (Scheme 6). Furthermore, this approach is very simple, inexpensive and amenable to multigram synthesis.

In summary, we have developed a convenient methodology for the synthesis of a variety of symmetrical 3,3-diarylacrylates via a regio-stereoselective Heck-Matsuda reaction. Various arenediazonium salts bearing electron-donating groups were



Scheme 5. Synthesis of anticancer indanone from gallic acid.



Scheme 6. Synthesis of indanone **5** via a HM reaction.

tested. This methodology provides an easy access to a biologically active 3-aryl indanones. Further investigations towards the synthesis of natural products via a Heck-Matsuda diarylation reaction are currently underway in our laboratory.

Acknowledgements

Authors gratefully acknowledge the generous financial support from the Brazilian funding agencies Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

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8. Typical procedure for the synthesis of 3,3-diarylacrylates is as follows; a test tube (inside diameter 13 mm; length 100 mm), equipped with a magnetic bar was charged with methyl acrylate (0.55 mmol), $Pd(OAc)_2$, (0.038 mmol) and analytical grade methanol (5 mL). After vigorous stirring at room temperature for 30 s, the diazonium salt (1.38 mmol) was added in portion and the reaction left to stir at reflux for 1 h. Upon completion, the reaction mixture was concentrated under reduced pressure and loaded directly onto Silica gel (using a small amount of DCM to transfer the oily residue) then chromatographed with ethyl acetate–hexanes to give the desired Heck-adducts. **1d** obtained as a white solid (53% yield). mp 126–127 °C; R_f = 0.17 (hexanes/EtOAc, 4:1) after visualization by vanillin; δ_H (250 MHz, $CDCl_3$): 6.52 (2H, s), 6.44 (2H, s), 6.26 (1H, s), 3.90 (3H, s), 3.81 (3H, s), 3.80 (6H, s), 3.78 (6H, s), 3.63 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.5, 156.4, 153.0, 152.7, 139.5, 138.2, 136.1, 133.8, 116.2, 106.9, 106.0, 61.0, 60.9, 56.2, 56.2, 51.3; MS *m*/*z* (EI): calcd for $C_{22}H_{26}O_8$ 418.1628, found 418.1617. **1f** obtained as a white solid (58% yield). mp 95–96 °C; R_f = 0.35 (hexanes/EtOAc, 4:1) after visualization by vanillin; δ_H (500 MHz, $CDCl_3$): 6.81–6.84 (3H, m), 6.77 (1H, d, *J* 9.0), 6.69–6.71 (2H, m), 6.21 (1H, s), 6.01 (2H, s), 5.99 (2H, s), 3.64 (3H, s); δ_C (125 MHz, $CDCl_3$): 166.7, 156.6, 149.2, 148.1, 147.9, 147.5, 135.5, 132.7, 123.5, 123.4, 115.5, 110.2, 108.7, 108.3, 108.1, 101.7, 101.4, 51.5; MS *m*/*z* (EI): calcd for $C_{18}H_{14}O_6$ 326.0790, found 326.0775. **1g** obtained as a white solid (75% yield). mp 107–108 °C; R_f = 0.46 (hexanes/EtOAc, 1:1) after visualization by vanillin; δ_H (250 MHz, $CDCl_3$): 6.81–6.86 (4H, m), 6.67–6.71 (2H, m), 6.19 (1H, s), 4.24–4.27 (8H, m), 3.63 (3H, s); δ_C (62.5 MHz, $CDCl_3$): 166.5, 156.1, 144.9, 143.7, 143.1, 142.9, 134.5, 131.9, 122.7, 121.8, 118.4, 117.6, 116.6, 114.9, 64.5, 64.4, 64.3, 51.1; MS *m*/*z* (EI): calcd for $C_{20}H_{18}O_6$ 354.1103, found 354.1117.
9. Conditions not yet optimized for this type of transformation. For a prior and interesting work concerning the mono arylation of methyl vinyl ketone, see: Stern, T.; Rückbrod, S.; Czekelius, C.; Donner, C.; Brunner, H. *Adv. Synth. Catal.* **2010**, *352*, 1983.
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