Tetrahedron Letters 51 (2010) 3633–3635

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Arylmaleic anhydrides via Heck arylation of fumaric acid

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ARTICLE INFO

Article history:
Received 12 March 2010
Revised 26 April 2010
Accepted 7 May 2010
Available online 12 May 2010

Keywords:
Palladium
Heck reaction
Fumaric acid
2-Arylmaleic anhydrides

ABSTRACT

Palladium-catalyzed arylation of fumaric acid with aryl iodides is found to be a very simple, economic and scalable approach to arylmaleic anhydrides. The reaction is facilitated by the presence of donor moieties on the aryl fragment and does not occur with strong acceptor groups.

1. Introduction

Arylmaleic anhydrides are useful reagents, which can be converted, for example, into various polycyclic adducts,[1–3] 3-arylfuran-2(5*H*)-ones,[4] 6-aryl-3-oxauracils,[5] or 2-chloro-3-arylmaleimides.[6] The substituted maleic anhydride moiety is sometimes associated with biological activity.[7–9]

The title compounds have been obtained by a number of methods; examples include condensations of aryl α-oxoacetates with cyanoacetic ester,[10] with the Emmons reagent,[3] or, quite recently, with Ac_2O in a $TiCl_4$–Bu_3N system.[11] Another modern approach involves the palladium-catalyzed double carbonylation of terminal aryl acetylenes.[12,13] As reported, these synthetic methods are quite efficient, however they are limited by the availability of the starting materials.

Another approach using the Meerwein arylation of maleic acid derivatives[4,14,15] is straightforward, but tends to give substantial amounts of byproducts, including diarylated olefins. Similar results have been reported for the palladium-catalyzed arylation of maleic anhydride with an aryl diazonium fluoroborate.[16]

In 1978, Heck and coworkers found that the reaction of iodobenzene with diethyl fumarate in an Et_3N–$Pd(OAc)_2$–*o*-Tol_3P system gave rise to 2-phenylmaleic ester in 80% yield.[17] This inversion of the olefin configuration results from the typical stereochemical requirements of the reaction mechanism (Scheme 1): intermediate **1** is formed by *syn*-addition of Ar-PdI to the olefin and the following step, β-hydride elimination, requires a *syn*-arrangement of the IPd–C–C–H fragment.[18]

A few other protocols for the Heck arylation have been developed, including the K_2CO_3–H_2O–DMF–$PdCl_2$ system,[19] which allowed minimization of the palladium loading and the use of highly hydrophilic olefin substrates such as acrylic acid. Using this system we previously achieved fine and scale-up catalytic arylation of fumaric acid with 4- and 2-iodoanisoles to give the corresponding arylmaleic acids in high yields.[1]

2. Results and discussion

Here we present our further results on the scope and limitations of this synthetic method. Thus, a set of aryl iodides (including some hetaryl halides) bearing different substituents on the aromatic ring were studied in the palladium-catalyzed arylation of fumaric acid (Scheme 1). The isolated yields of the final products, arylmaleic anhydrides, are summarized in Table 1.

The effect of substituents on the reactivity of ArI is the most surprising feature of this reaction. It was found that π-donor moieties on the aryl fragment markedly facilitate the arylation, while acceptor groups, even more markedly, retard it. The data obtained suggest the following reactivity sequence:

4-AcNH > 4-MeO ≈ 4-F > 3-MeO > 4-Cl > 4-CN = 2-CN =
$2\text{-}NO_2$ = no reaction

No arylated products were obtained with 4-cyano-, 2-cyano-, and 2-nitroiodobenzenes and 3-bromopyridine; only about 5% of the product was obtained with 2-bromothiophene, and with 2-iodothiophene only decomposition was observed.

This behavior, although unusual for the Heck reaction and not yet explained, is not completely without precedent. Similar retarding

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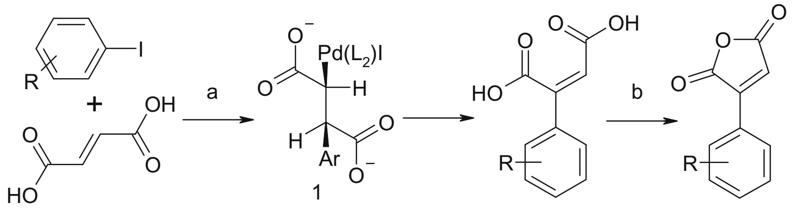
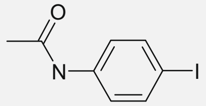
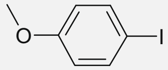
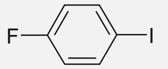
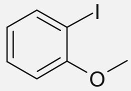
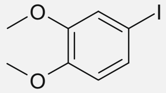
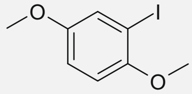
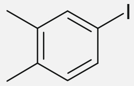
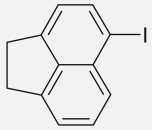
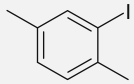
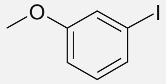
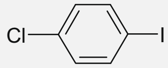
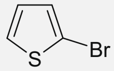
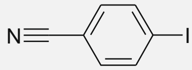
doi:10.1016/j.tetlet.2010.05.023



Scheme 1. Reagents and conditions: (a) $PdCl_2$ (0.4 mol %), Ph_3P (1.6 mol %), K_2CO_3, DMF–H_2O or dioxane–H_2O, 100 °C, 2.5–48 h; (b) 200–300 °C, 0.5–2 Torr or Ac_2O, 100 °C, 0.5 h.

Table 1
Yields of 2-arylmaleic anhydrides from aryl iodides and fumaric acid

Entry	Ar-X	Method	Time (h)	Yield[a] (%)
1		B	2.5	74
2		A	4	79
3		A	4	76
4		A[b]	12	75
5		B	3	70
6		B[b]	20	58
7		A	18	79[c]
8		B	48	59
9		A	48	–
10		A	20	76
11		A	26	51
12		A	10	5
13		A	48	–

[a] Isolated product was of satisfactory purity according to the NMR spectrum.

[b] 1,4-Dioxane was used instead of DMF.[23]

[c] A 4:1 mixture of 3,4- and 2,3-dimethyliodobenzenes resulting from the iodination of *ortho*-xylene[22] was used. Only the major 3,4-isomer participates in the reaction, and the yield of the product is based on its content.

influence of acceptor moieties was observed in palladium-catalyzed arylations of maleimides[20] and cinnamonitrile[21] in a base–Bu_4NCl–DMF system. Arylation of fumarate with aryl iodides, bearing acceptor substituents, under Heck conditions,[17] has not been reported to date.

The arylation of fumaric acid is also sensitive to steric hindrance in the aryl fragment; for the 2-methoxy moiety this effect is comparable with its electronic promoting influence. With mono-iodo-*ortho*-xylene,[22] comprised of a 4:1 mixture of 3,4- and 2,3-dimethyliodobenzenes, the arylation product was only obtained from the 3,4-isomer, while both the minor isomer and the mono-iodo-*para*-xylene (2,5-dimethyliodobenzene) were found to be unreactive. These data can be summarized in the following sequence:

$$\text{3,4-dimethoxy} > \text{2-MeO} \approx \text{2,5-dimethoxy} \approx \text{3-MeO} \approx$$
$$\text{3,4-dimethyl} > \text{2,5-dimethyl} = \text{2,3-dimethyl} = \text{no reaction}$$

In conclusion, the palladium-catalyzed reaction of aryl iodides with fumaric acid represents a simple and very economical method to obtain a variety of arylmaleic anhydrides. We are working to give further theoretical explanation of the observed substituent effects, and also to employ the newly available arylmaleic anhydrides for the synthesis of polycyclic systems.

3. Typical experimental procedure

A mixture of fumaric acid (1.45 g, 12.5 mmol), K_2CO_3 (3.45 g, 25 mmol), Ph_3P (0.055 g, 0.20 mmol, 1.6 mol %), DMF (12 mL), H_2O (12 mL), and $PdCl_2$ (0.5 mL of a 0.1 M aq soln, 0.05 mmol, 0.4 mol %) was stirred under argon at 100–105 °C (Table 1).[23] The solvents were evaporated in vacuo, the residue washed with EtOAc (26 mL), dried, suspended in water (15 mL) and treated with concd aq HCl (5 mL) to give a precipitate of the crude arylmaleic acid, which was dried in air.[24] Method A: the precipitate was sublimed at 0.5–2 Torr and 200–300 °C, followed, if required, by crystallization from toluene or a toluene–hexane mixture. Method B: a mixture of the crude arylmaleic acid and Ac_2O (3 mL/g) was heated at 100 °C for 30 min followed by solvent evaporation in vacuo and crystallization from toluene.

4. Characterization data of arylmaleic anhydrides

N-[4-(2,5-Dioxo-2,5-dihydrofuran-3-yl)phenyl]acetamide (Table 1, entry 1). Yellow crystals (MeCN or AcOH), mp 254 °C dec. ^1H NMR (300 MHz, $(CD_3)_2SO$) δ: 2.09 (s, 3H, Ac), 7.55 (s, 1H, =CH), 7.75 (d, 2H, $J = 9$ Hz, Ar), 8.03 (d, 2H, $J = 9$ Hz, Ar), 10.33 (s, 1H, NH). MS (EI) m/z: 231 (39%, $M^{\cdot+}$), 189 (61%, M–CH_2CO), 159 (3%, M–CO–CO_2), 117 (100%). Anal. Calcd for $C_{12}H_9NO_4$ (231.20): C, 62.34; H, 3.92; N, 6.06. Found: C, 62.43; H, 4.01; N, 6.00.

3-(4-Methoxyphenyl)furan-2,5-dione[1,4,13,14,16] (entry 2). Yellow crystals (toluene + hexane), mp 145 °C with partial sublimation, lit.[25] mp 143–144 °C. ^1H NMR (250 MHz, $CDCl_3$) δ: 3.90 (s, 3H, OMe), 6.83 (s, 1H, =CH), 7.01 (d, 2H, $J = 9$ Hz, Ar), 7.98 (d, 2H, $J = 9$ Hz, Ar).

3-(4-Fluorophenyl)furan-2,5-dione[12] (entry 3). Colorless shiny crystals (toluene + hexane), mp 114 °C with partial sublimation,

^{1}H NMR (250 MHz, CDCl$_3$) δ: 6.98 (s, 1H, =CH), 7.21 (m, 2H, Ar), 8.02 (m, 2H, Ar). ^{13}C NMR (62.9 MHz, CDCl$_3$) δ: 116.82 (d, *J* = 11 Hz), 123.26, 124.06, 131.57 (d, *J* = 4.5 Hz), 145.71 (C$_{Ar}$, =C<), 163.29, 163.49, 164.63, 167.37 (CO, CF). MS (EI) *m*/*z*: 192 (43%, M^+), 120 (100%, M–CO–CO$_2$).

3-(2-Methoxyphenyl)furan-2,5-dione[1,25] (entry 4). Bright yellow crystals (toluene + hexane), mp 134–136 °C with partial sublimation, lit.[25] mp 135–136 °C. ^{1}H NMR (250 MHz, CDCl$_3$) δ: 3.98 (s, 3H, OMe), 7.00–7.15 (m, 2H, Ar), 7.38 (s, 1H, =CH), 7.52 (t, 1H, *J* = 8 Hz, Ar), 8.34 (dd, 1H, *J* = 8 Hz, *J* = 1 Hz, Ar).

3-(3,4-Dimethoxyphenyl)furan-2,5-dione (entry 5). Orange crystals (toluene), mp 171.5–172.5 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.97 (s, 3H, OMe), 3.98 (s, 3H, OMe), 6.86 (s, 1H, =CH), 6.98 (d, 1H, *J* = 9 Hz, Ar-H5), 7.51 (d, 1H, *J* = 2 Hz, Ar-H2), 7.72 (dd, 1H, *J* = 2 Hz, *J* = 9 Hz, Ar-H6). MS (EI) *m*/*z*: 234 (46%, $M^{\cdot+}$), 162 (100%, M–CO–CO$_2$), 147 (43%). Anal. Calcd for $C_{12}H_{10}O_5$ (234.20): C, 61.54; H, 4.30. Found: C, 61.38; H, 4.34.

3-(2,5-Dimethoxyphenyl)furan-2,5-dione (entry 6). Dark red crystals (toluene), mp 167–169 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.84 (s, 3H, OMe), 3.94 (s, 3H, OMe), 6.96 (d, 1H, *J* = 9 Hz, Ar-H3), 7.08 (dd, 1H, *J* = 9 Hz, *J* = 3 Hz, Ar-H4), 7.41 (s, 1H, =CH), 7.95 (d, 1H, *J* = 3 Hz, Ar-H6). MS (EI) *m*/*z*: 234 (78%, $M^{\cdot+}$), 175 (6%, M–CO–OCH$_3$), 162 (100%, M–CO–CO$_2$), 147 (84%), 119 (20%). Anal. Calcd for $C_{12}H_{10}O_5$ (234.20): C, 61.54; H, 4.30. Found: C, 61.44; H, 4.22.

3-(3,4-Dimethylphenyl)furan-2,5-dione (entry 7). Pale yellow crystals (toluene), mp 151–153 °C with partial sublimation, ^{1}H NMR (300 MHz, CDCl$_3$) δ: 2.35 (two overlapping s, 6H, 2Me), 6.90 (s, 1H, =CH), 7.27 (d, 1H, *J* = 8 Hz, Ar-H), 7.73 (m, 2H, Ar-H). MS (EI) *m*/*z*: 202 (36%, $M^{\cdot+}$), 187 (5%, M–Me), 130 (100%, M–CO–CO$_2$), 115 (60%). Anal. Calcd for $C_{12}H_{10}O_3$ (202.21): C, 71.28; H, 4.98. Found: C, 71.26; H, 5.11.

3-(Acenaphthen-5-yl)furan-2,5-dione (entry 8). Yellow crystals (toluene + hexane), mp 153–155 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.47 (s, 4H, 2CH$_2$), 7.16 (s, 1H, =CH), 7.42 (d, 1H, *J* = 7 Hz, Ar-H), 7.44 (d, 1H, *J* = 7 Hz, Ar-H), 7.63 (t, 1H, *J* = 7 Hz, Ar-H), 7.80 (d, 1H, *J* = 7 Hz, Ar-H), 8.05 (d, 1H, *J* = 7 Hz, Ar-H). MS (EI) *m*/*z*: 250 (46%, $M^{\cdot+}$), 222 (14%, M–CO), 194 (7%), 178 (100%, M–CO–CO$_2$). Anal. Calcd for $C_{16}H_{10}O_3$ (250.25): C, 76.79; H, 4.03. Found: C, 76.62; H, 4.17.

3-(3-Methoxyphenyl)furan-2,5-dione[25,26] (entry 10). Bright yellow shiny crystals (toluene), mp 149–150 °C with partial sublimation, lit.[25] mp 146–147 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 3.88 (s, 3H, OMe), 7.00 (s, 1H, =CH), 7.12 (d, 1H, *J* = 8 Hz, Ar), 7.44 (t, 1H, *J* = 8 Hz, Ar), 7.52–7.56 (m, 2H, Ar).

3-(4-Chlorophenyl)furan-2,5-dione (entry 11). Colorless crystals (toluene), mp 147 °C, lit.[14] mp 149–150 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ: 7.02 (s, 1H, =CH), 7.52 (d, 2H, *J* = 9 Hz, Ar), 7.95 (d, 2H, *J* = 9 Hz, Ar).

3-(2-Thienyl)furan-2,5-dione (entry 12). Yellow crystals, mp 127–129 °C. ^{1}H NMR (250 MHz, CDCl$_3$) δ: 6.76 (s, 1H, =CH), 7.26 (t, 1H, *J* = 5 Hz, Ar-H^4), 7.75 (d, 1H, *J* = 5 Hz, Ar-H), 8.03 (d, 1H, *J* = 4 Hz, Ar-H). MS (EI) *m*/*z*: 180 (88%, $M^{\cdot+}$), 136 (4%, M–CO$_2$), 108 (100%, M–CO–CO$_2$). Anal. Calcd for $C_8H_4O_3S$ (180.18): C, 53.33; H, 2.24; S, 17.80. Found: C, 53.20; H, 2.32; S 17.69.

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