HETEROCYCLES, Vol. 69, 2006, pp. 99 - 105. © The Japan Institute of Heterocyclic Chemistry
Received, 29th June, 2006, Accepted, 19th September, 2006, Published online, 22nd September, 2006. COM-06-S(O)30

4-ARYL-2-QUINOLONES *VIA* A DOMINO HECK REACTION/CYCLIZATION PROCESS

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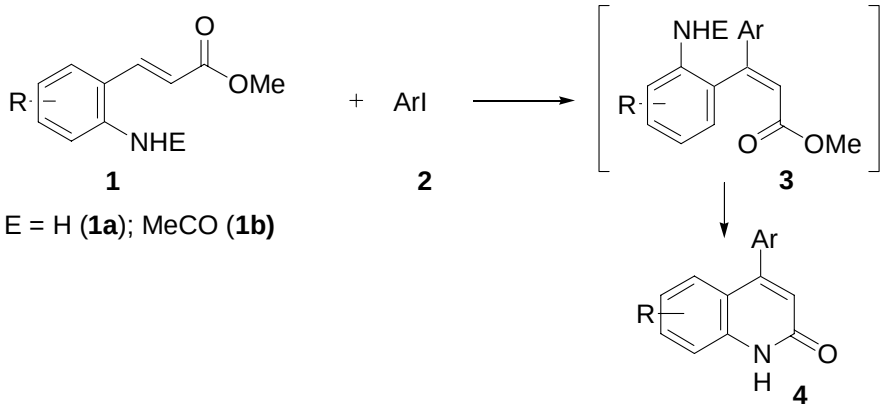
Abstract – The reaction of methyl β-(*o*-acetamidophenyl)acrylates with aryl iodides in the presence of $Pd(OAc)_2$ and KOAc in DMF at 120 °C affords 4-aryl-2-quinolones in allowable to good yields.

During our studies on the Heck reaction of β-substituted α,β-unsaturated carbonyl compounds we have found that an appropriate choice of reaction conditions may favor the formation of vinylic substitution products with the original β-substituent on the same side of the carbon-carbon double bond as the carbonyl group.[1] Because of this, β-substituted α,β-unsaturated carbonyl compounds containing a nucleophile at the *ortho* position of the β substituent can give rise to cyclization reactions following the vinylic substitution step and the whole process can be used as a useful tool for the preparation of cyclic derivatives. We have taken advantage of this synthetic strategy to develop new syntheses of quinolines,[2] coumarins,[2,3] butenolides[4] and cardenolides.[1c] Since many 2-quinolones show interesting biological activities[5] - including tipifarnid, a 4-aryl-2-quinolone derivative which exhibits anticancer activity[6] - and are also useful synthetic intermediates,[7] it appeared of interest to us to explore the preparation of 4-aryl-2-quinolones from readily available methyl β-arylacrylates containing a nitrogen nucleophile in the ortho position of the β-substituent through a domino Heck/cyclization reaction (Scheme 1).

Herein we report the results of this study.

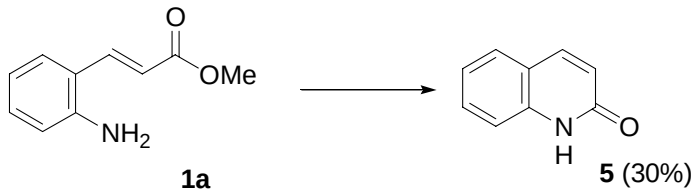
p-Iodoanisole and methyl β-(*o*-aminophenyl)acrylate **(1a)** were initially selected as the model system and the first attempt was carried out in the presence of 0.05 equiv of $Pd(OAc)_2$ as the source of Pd(0) using a molten Bu_4NOAc/Bu_4NBr mixture as the reaction medium at 100 °C.

This paper is dedicated to Dr. Satoshi Omura on the occasion of his 70th birthday.



Scheme 1

These conditions were successfully used by us in the diastereoselective synthesis of β,β-diarylacrylates from cinnamate esters and aryl iodides[1d] (subsequently extended to aryl bromides by Calò et al.[8]) and in the formation of coumarins from 3-(*o*-hydroxyaryl)acrylate esters and aryl iodides or bromides.[3] Unfortunately, no formation of the desired 4-substituted quinolone product was observed, the main product being the parent quinolone **(5)** (Scheme 2), most probably derived from **1a** via an *E/Z* isomerization/cyclization reaction which is faster than the desired Heck/cyclization reaction.



Scheme 2

Surmising that the easy *E/Z* isomerization might be favored by the presence of the free, strongly electron-donating amino group, we switched to the acetyl derivative **(1b)** (prepared in 80% overall isolated yield from commercially available *o*-iodoaniline via acetylation and palladium-catalyzed vinylic substitution with methyl acrylate) as the olefin partner. Indeed, subjecting **1b** to the same conditions used for **1a** led to the isolation of the free NH quinolone derivative **(4a)**, but only in 15% yield (Table 1, Entry 1). No evidence of **5** or its *N*-acetyl derivative was attained in this case. We next conducted the model reaction in DMF in the presence of mixtures of KOAc and Bu_4NCl (Table 1, Entry 2) or KOAc and KCl (Table 1, Entry 3) and found that the quinolone product could be isolated in 45 and 40% yield, respectively. By omitting chloride salts, **4a** was isolated in 36% yield with Bu_4NOAc (Table 1, Entry 4) and 50% yield in the presence of KOAc (Table 1, Entry 5) suggesting that chloride source is unnecessary for this transformation. An increase of the reaction temperature to 120 °C resulted in the formation of **4a** in 39% yield with Bu_4NOAc (Table 1, Entry 6) and in a satisfactory 60% yield by using KOAc (Table 1,

Entry 7). A further increase of temperature caused a drop in the yield of **4a** (Table 1, Entry 8). This reaction was subsequently carried out using other solvents such as NMP and DMA. NMP gave a slightly lower yield (Table 1, Entry 9) whereas with DMA the yield was only moderate (Table 1, Entry 10). Lower yields were also obtained when NaOAc was used instead of KOAc (Table 1, Entries 11 and 12). Interestingly, a result comparable to that obtained with KOAc at 120 °C was obtained when the reaction was carried out in Et_3N at 100 °C (Table 1, Entry 13). These conditions, however, proved unsatisfactory when they were applied to other aryl iodides (see Table 2, footnote c).

Table 1. Bases, Additives, Solvents, and Temperature in the Reaction of Methyl β-(*o*-Acetamidophenyl)acrylate **(1b)** with *p*-Iodoanisole.[a]

Entry	Base	Additive	Solvent	Temperature (°C)	Time (h)	Yield % of **(4a)**[b]
1			Bu_4NOAc (2.1 equiv), Bu_4NBr (1.5 equiv)	100	15	15
2	KOAc	Bu_4NCl (1 equiv)	DMF	100	48	45
3	KOAc	KCl (1 equiv)	DMF	100	24	40
4	Bu_4NOAc	–	DMF	100	24	36
5	KOAc	–	DMF	100	48	50
6	Bu_4NOAc	–	DMF	120	24	39
7	KOAc	–	DMF	120	48	60
8	KOAc	–	DMF	140	48	52
9	KOAc	–	NMP	120	48	57
10	KOAc	–	DMA	120	48	33
11	NaOAc	–	NMP	120	48	30
12	NaOAc	–	DMF	120	48	45
13	Et_3N (5 equiv)	–	–	100	24	59
14	Et_3N (2 equiv)	–	DMF	100	48	30
15	Bu_3N (5 equiv)	–	–	120	24	55

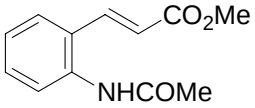
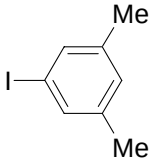
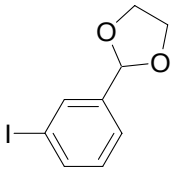
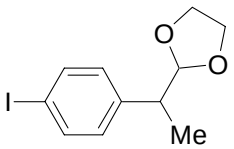
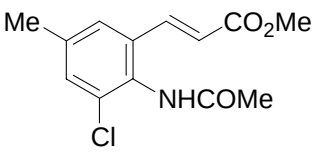
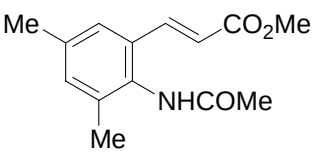
[a]Unless otherwise stated, reactions were carried out on a 0.4 mmol scale in 1.5 mL of solvent using 1 equiv of **(1b)**, 1.5 equiv of *p*-iodoanisole, 2 equiv of acetate base and 0.05 equiv of $Pd(OAc)_2$ under argon. [b]Yields are given for isolated products.

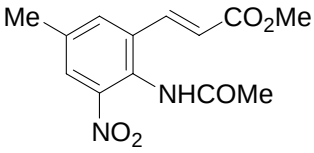
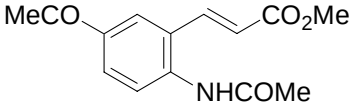
In conclusion, the "optimal" reaction conditions for this domino reaction utilize 0.05 equiv of $Pd(OAc)_2$ and 2 equiv of KOAc in DMF at 120 °C. No evidence of the vinylic substitution intermediate **(3a)** was attained by monitoring the reaction mixture by TLC or HPLC, suggesting that under these conditions the Heck reaction is followed by a fast cyclization step. Formation of **3a** was observed at lower reaction temperatures. At 80 °C (48 h) it was isolated in 25% yield along with 8% of **4a** and a 30% yield of the recovered **1b**. Decreasing further the reaction temperature to 60 °C led to the isolation of **3a** in 30% yield

after 48 h. The quinolone derivative **(4a)** was not formed and the starting material was recovered in 50% yield.

The results obtained subjecting a variety of aryl iodides and methyl β-(*o*-acetamidoaryl)acrylates to the optimal conditions are shown in Table 2.

Table 2. Synthesis of 4-Aryl-2-quinolones **(4)** from Methyl β-(*o*-Acetamidoaryl)acrylates **(1)** and Aryl Iodides **(2)** through a Domino Heck/Cyclization Reaction.[a]

Entry	Methyl β-(*o*-Acetamidophenyl)acrylate **(1)**	Aryl Iodide **(2)**	Time (h)	Yield % of **(4)**[b]	
1	 **1b**	*p*-MeO-C_6H_4-I	48	60	**4a**
2	**1b**	*p*-Me-C_6H_4-I	24	62	**4b**
3	**1b**	*m*-MeO-C_6H_4-I	24	62	**4c**
4	**1b**	*o*-MeO-C_6H_4-I	24	–	
5	**1b**		48	80	**4d**
6	**1b**	*p*-MeCONH-C_6H_4-I	48	55[c]	**4e**
7	**1b**	*m*-Me-C_6H_4-I	24	61	**4f**
8	**1b**	PhI	24	51	**4g**
9	**1b**	*o*-F-C_6H_4-I	24	11	**4h**
10	**1b**	*m*-F-C_6H_4-I	48	30	**4i**
11	**1b**	*p*-F-C_6H_4-I	24	65	**4j**
12	**1b**	*p*-Cl-C_6H_4-I	24	51	**4k**
13	**1b**	*m*-CHO-C_6H_4-I	48	–	
14	**1b**		24	53	**4l**
15	**1b**	*p*-MeCO-C_6H_4-I	48	–	
16	**1b**		48	52	**4m**
17	 **1c**	*p*-MeO-C_6H_4-I	24	62	**4n**
18	**1c**	*p*-Me-C_6H_4-I	24	55	**4o**
19	 **1d**	*p*-MeO-C_6H_4-I	48	59	**4p**

20	**1d**	*p*-Me-C_6H_4-I	48	55	**4q**
21	**1d**	*p*-F-C_6H_4-I	48	48	**4r**
22	 **1e**	*p*-MeO-C_6H_4-I	48	40	**4s**
23	**1e**	*p*-Me-C_6H_4-I	48	42	**4t**
24	 **1f**	*p*-MeO-C_6H_4-I	48	41	**4u**

[a]Reactions were carried out on a 0.4 mmol scale in 1.5 mL of DMF using 1 equiv of **(1)**, 1.5 equiv of aryl iodide, 2 equiv of KOAc and 0.05 equiv of $Pd(OAc)_2$ under argon at 120 °C. [b]Yields are given for isolated products. [c]Compound **(4e)** was isolated only in 10% yield when the reaction was carried out in Et_3N, according to the conditions shown in Table 1, Entry 13.

4-Aryl-2-quinolones were isolated in allowable to good yields with a variety of methyl β-(*o*-acetamidoaryl)acrylates and aryl iodides. *p*-Iodobenzaldehyde and *p*-iodoacetophenone did not afford the corresponding 2-quinolone products under our standard conditions (Table 2, Entries 13 and 15). However, appropriately protected aldehydic and ketonic aryl iodides gave the desired products in satisfactory yields (Table 2, Entries 14 and 16).

In conclusion, we have developed a new straightforward approach to 4-aryl-2-quinolones from readily available starting materials using a phosphine free palladium-based catalyst system which may represent a convenient alternative to known olefine-based[9] palladium-catalyzed syntheses of this class of compounds.

ACKNOWLEDGEMENTS

Work carried out in the framework of the National Project "Stereoselezione in Sintesi Organica. Metodologie ed Applicazioni" supported by Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR). The authors are also greatly indebted to the University "La Sapienza" for financial support of this research.

EXPERIMENTAL

Melting points were determined with a Büchi B-545 apparatus and are uncorrected. All of the reagents, catalysts, and solvents are commercially available and were used as purchased, without further purification. Reaction products were purified on axially compressed columns, packed with SiO_2 25-40 μm (Macherey Nagel), connected to a Gilson solvent delivery system and to a Gilson refractive index detector, and eluting with *n*-hexane/AcOEt mixtures. ^1H NMR (400 MHz), ^{13}C NMR (100.6 MHz) and ^{19}F NMR (376.5 MHz) spectra were recorded with a Bruker Avance 400 spectrometer using TMS as shift

reference. EI (70 EV) mass spectra were recorded with a Varian Saturn 2100T GC/MS apparatus. IR spectra were recorded with a Jasco FT/IR 430 spectrometer.

Typical Procedure for the Synthesis of Methyl β-(*o*-Acetamidophenyl)acrylates (1). Preparation of 1b.To a stirred solution of *N*-(2-iodophenyl)acetamide (2.05 g, 7.85 mmol), methyl acrylate (2.12 mL, 23.56 mmol), KOAc (0.77 g, 7.85 mmol), K_2CO_3 (1.35 g, 9.81 mmol) at 80 °C in DMF (8 mL), $Pd(OAc)_2$ (0.044 g, 0.196 mmol) was added. The mixture was stirred for 1 h. After cooling, the mixture was diluted with AcOEt and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel; 30/70 v/v *n*-hexane/AcOEt) to give 1.55 g (90 % yield) of **1b**: mp 137-138 °C; IR (KBr) 3275, 1723, 1658 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.83 (d, *J* = 15.8 Hz, 1H), 7.73 (m, 1H), 7.55 (m, 1H), 7.48 (bs, 1H), 7.39 (m, 1H), 7.21 (m, 1H), 6.40 (d, *J* = 15.8 Hz, 1H), 3.81 (s, 3H), 2.24 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 168.4, 166.6, 139.1, 135.4, 130.3, 127.2, 126.6, 125.4, 124.8, 119.7, 51.3, 23.6; MS *m/z* (relative intensity) 146 (100 %), 118 (94 %), 117 (95%) 219 (M^+ 23 %).

Typical Procedure for the Synthesis of 4-Aryl-2-quinolones (4). Preparation of (4a). To a stirred solution of methyl β-(*o*-acetamidophenyl)acrylate (0.088 g, 0.40 mmol), *p*-iodoanisole (0.140 g, 0.60 mmol), KOAc (0.078 g, 0.8 mmol) at 120 °C in DMF (1.5 mL), $Pd(OAc)_2$ (0.0045 g, 0.020 mmol) was added. The mixture was stirred for 48 h After cooling, the mixture was diluted with AcOEt and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, 35 g; 25/75 v/v *n*-hexane/AcOEt) to give 0.061 g (60 % yield) of **4a**: mp 196-198 °C; IR (KBr) 3131, 1672 cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.83 (bs, 1H), 7.64-7.62 (m, 1H), 7.57-7.51 (m, 2H), 7.45-7.43 (m, 2H), 7.20-7.18 (m, 1H), 7.06 (m, 2H), 6.35 (s, 1H), 3.91 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 164.4, 160.2, 153.2, 139.1, 130.7, 130.3, 129.5, 126.8, 122.5, 120.6, 119.8, 116.8, 114.2, 55.6; MS *m/z* (relative intensity) 251 (M^+, 100 %), 252 (40 %), 236 (30%) 208 (50 %).

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