Tetrahedron Letters 52 (2011) 6578–6580

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Synthesis of 2-arylacrylic esters from aryl methyl ketones via Wittig reaction/singlet oxygen ene reaction

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ARTICLE INFO

Article history:
Received 30 July 2011
Revised 21 September 2011
Accepted 28 September 2011
Available online 6 October 2011

Keywords:
2-Arylacrylic ester
Aryl methyl ketone
Methyl enol ether
Wittig reaction
Singlet oxygen ene reaction

ABSTRACT

An efficient synthetic method has been developed for the synthesis of 2-arylacrylic esters from the corresponding aryl methyl ketones via Wittig reaction and singlet oxygen ene reaction. Wittig reaction to aryl methyl ketones with (methoxymethyl)triphenylphosphonium chloride in basic condition afforded the methyl enol ethers, and then 2-arylacrylic esters were obtained by singlet oxygen ene reaction, followed by tosylation and elimination in one-pot to the methyl enol ethers in good yields.

Singlet oxygen ($^1O_2$), which can be conveniently generated by the sensitized photoreaction of molecular oxygen with light, has received remarkable attention as an important reagent for the synthesis of oxyfunctionalized product from simple precursors.[1] The peculiar types of reaction involving singlet oxygen with organic substrates are [4+2] cycloaddition, [2+2] cycloaddition, and ene reaction, etc. Among them, the ene reaction has attracted major interest to organic chemists due to its controversial reaction mechanism[2] and the availabilities to the organic synthesis[3] since it was originally discovered by Schenck in 1953.[4]

2-Arylacrylic esters have been employed as useful precursors for the enantioselective synthesis of 2-arylpropionic acids such as naproxen and flurbiprofen, which are nonsteroidal anti-inflammatory drugs, through the asymmetric hydrogenation reaction.[5–7] They have been also used for the preparation of functionalized cyclopentenes with quaternary stereogenic centers,[8] alantrypinone derivatives with antagonist activity toward insect GABA receptors,[9] 3-arylpiperidines with the therapeutic dopaminergic activities,[10] substituted stilbene derivatives by Heck reaction,[11] quaternary aldehydes by rhodium-catalyzed hydroformylation,[12] and so forth. Due to the importance of 2-arylacrylic esters as useful precursors, the synthetic methods were developed by using different starting materials. For instance, they were accessed by methylenation of the corresponding methyl arylacetates,[11] Pd-catalyzed alkoxycarbonylation of terminal alkyne,[13] Pd-catalyzed carbonylation of α-arylvinyl bromides,[14] or Pd-catalyzed cross-coupling of α-diazocarbonyl compounds with arylboronic acid.[15]

Recently, we envisioned that 2-arylacrylic esters would be prepared with another starting material, aryl methyl ketones which are cheap and commercially available, by Wittig reaction and singlet oxygen ene reaction. Treatment of aryl methyl ketone **1** with (methoxymethyl)triphenylphosphonium ylide would provide the corresponding methyl enol ether **2** (Scheme 1). Ene reaction of **2** by singlet oxygen which could be prepared with oxygen, light, and sensitizer, would induce peroxide **A** and subsequent tosylation of **A** followed by elimination reaction of the resulting tosylate **B** under basic condition would afford the desired 2-arylacrylic ester **3**.

Methyl enol ether **2** was efficiently prepared by reaction of the corresponding aryl methyl ketone **1** with a commercial (methoxymethyl)triphenylphosphonium chloride and potassium *t*-butoxide in THF at room temperature in excellent yields, except nitro(NO_2) group-substituted methyl enol ether **2j**, which was obtained in only 37% yield using these conditions.[16]

Initial experiments regarding the subsequent singlet oxygen ene reaction/tosylation/elimination in one-pot were performed with the methyl enol ether **2a** to find the suitable photosensitizer, solvent, and reaction temperatures (Table 1). The use of a catalytic amount of methylene blue as sensitizer in CH_2Cl_2 readily afforded the desired acrylic ester **3a** at various reaction temperatures (entries 1–4). In particular, we noticed that **3a** was obtained in better yield when the singlet oxygen ene reaction was performed at −78 °C and tosylation/elimination reaction was performed at a slow rising from 0 °C to room temperature (entry 2). On the other

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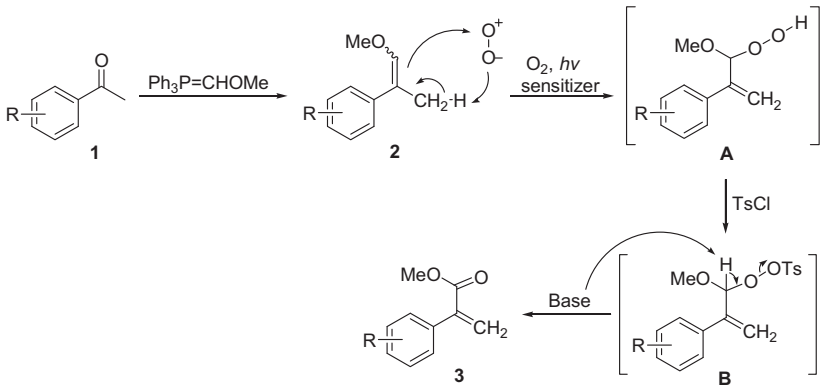
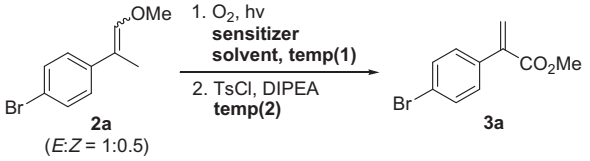
0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.127



Scheme 1. Synthetic route of 2-arylacrylic ester **3** from aryl methyl ketone **1**.

Table 1
Optimization of the reaction condition for the conversion into **3a** from **2a**



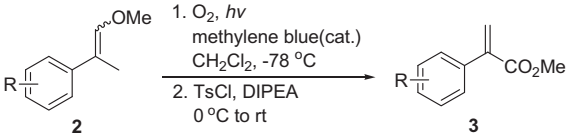
Entry	Sensitizer	Solvent	Temp (1)/Temp (2)	Yield[a] (%)
1	Methylene blue	CH_2Cl_2	0 °C/0 °C to rt	50
2	Methylene blue	CH_2Cl_2	−78 °C/0 °C to rt	65
3	Methylene blue	CH_2Cl_2	−78 °C/0 °C	52
4	Methylene blue	CH_2Cl_2	−78 °C/rt	48
5	Methylene blue	THF	−78 °C/0 °C to rt	28
6	Methylene blue	CH_2Cl_2/THF	−78 °C/0 °C to rt	49
7	Rose bengal	CH_2Cl_2	−78 °C/0 °C to rt	36

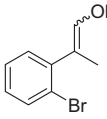
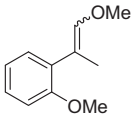
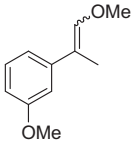
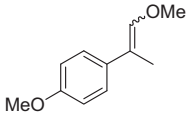
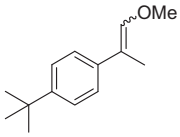
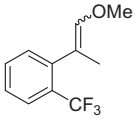
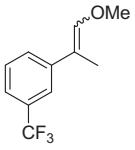
[a] Isolated yield.

hand, when we changed the solvent to THF (entry 5) or a mixture of CH_2Cl_2 and THF (entry 6) at the same reaction temperatures, **3a** was obtained in 28% and 49% yields, respectively. Additionally, the use of rose bengal as sensitizer provided the acrylic ester **3a** in 36% yield under the given reaction condition (entry 7).

Next, to clarify the scope of this reaction, a variety of methyl enol ethers **2b–2m** were treated with singlet oxygen which is generated from molecular oxygen by light in the presence of a catalytic amount of methylene blue in CH_2Cl_2 at −78 °C, followed by the addition of tosyl chloride and diisopropylamine at 0 °C.[17] All substrates investigated gave the corresponding 2-arylacrylic esters **3b–3m** from moderate to good yields (Table 2). The reaction proceeded smoothly and tolerated various functional groups such as bromo (entry 1), methoxy (entries 2–4), *t*-butyl (entry 5), trifluoromethyl (entries 6–8), nitro (entry 9), cyano (entry 10), phenyl (entry 11), and naphthyl (entry 12) groups on the phenyl ring. Generally, the methyl enol ethers possessing electron-withdrawing functional groups on the phenyl ring were found to afford better yields than those with electron-donating groups. The reaction of all substrates provided the corresponding aryl methyl ketone **1** as a major side product, which is owing to the competitive reaction, [2+2] cycloaddition, as shown in Scheme 2. The methyl enol ether **2** is converted into the corresponding 1,2-dioxetane **4** by the [2+2] cycloaddition with singlet oxygen, then the breakdown of the 1,2-dioxetane ring furnishes the aryl methyl ketone **1**. Particularly, the methyl enol ethers possessing electron-donating functional groups on the phenyl ring provided the aryl methyl ketone **1** in higher yields than those with electron-withdrawing groups.

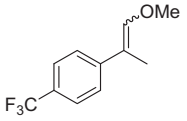
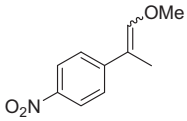
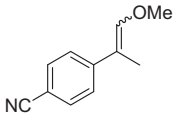
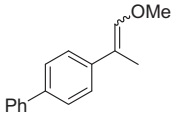
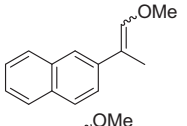
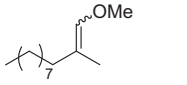
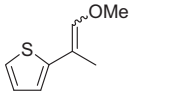
Table 2
Synthesis of 2-arylacrylic esters from various methyl enol ethers using a one-pot sequential reaction



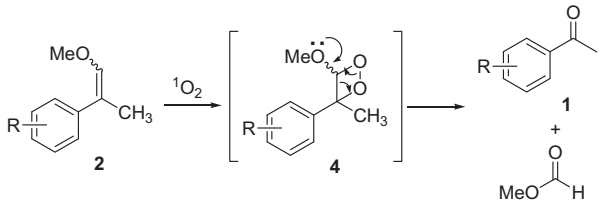
Entry	Methyl enol ether **2** (*E*:*Z*)		Product **3**	Yield[a] (%)
1		**2b** (1:0.3)	**3b**	79
2		**2c** (0.6:1)	**3c**	60
3		**2d** (1:0.6)	**3d**	55
4		**2e** (1:0.8)	**3e**	59
5		**2f** (1:0.7)	**3f**	53
6		**2g** (1:0.2)	**3g**	79
7		**2h** (1:0.7)	**3h**	64

(*continued on next page*)

Table 2 (*continued*)

Entry	Methyl enol ether **2** (*E*:*Z*)	Product **3**	Yield[a] (%)
8	 **2i** (1:1)	**3i**	72
9	 **2j** (1:0.3)	**3j**	74
10	 **2k** (1:1)	**3k**	67
11	 **2l** (1:0.5)	**3l**	68
12	 **2m** (1:0.8)	**3m**	70
13	 **2n** (0.7:1)	**3n**	57
14	 **2o** (0.7:1)	**3o**	ND[b]

[a] Isolated yield.
[b] ND, no desired product.



Scheme 2. Generation of aryl methyl ketone **1** via [2+2] cycloaddition.

To expand the scope of this reaction, we applied the protocol to methyl enol ethers **2n** and **2o**, which was prepared from 2-undecanone and 2-acetylthiophene, respectively (entries 13 and 14 in Table 2). In case of **2n** including alkyl group instead of aryl group, the desired 2-nonylacrylic ester **3n** was obtained in 57% yield using the same reaction condition. However, the reaction of **2o** including heteroaromatic group did not provide the corresponding acrylic ester **3o** at all. We could isolate only 2-acetylthiophene in 70% yield.

In summary, we have developed an efficient method for the synthesis of 2-arylacrylic esters via Wittig reaction with (methoxymethyl)triphenylphosphonium ylide and subsequent singlet oxygen ene reaction/tosylation/elimination from commercially available aryl methyl ketones.

Acknowledgment

We thank for the support of research grant of Kwangwoon University in 2011 for this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.127.

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16. Baumann, T.; Vogt, H.; Braese, S. *Eur. J. Org. Chem.* **2007**, 266.
17. Typical procedure for 2-arylacrylic ester **3**: A 100 mL three-necked round-bottom flask equipped with dispersion bubbler gas inlet, gas outlet, and a septum was charged with **2** (1.0 mmol) in dry CH_2Cl_2 (30 mL), and a tip of methylene blue was added. To the solution at −78 °C was bubbled molecular oxygen (O_2) with 250 W IR lamp at 1 in distance from the reaction flask. The reaction was monitored continuously by TLC. TLC after 1 h usually showed no starting material, then IR lamp was removed. The O_2 bubbler and outlet were removed and the reaction was placed under Ar atmosphere. To the reaction mixture were added tosyl chloride (1.3 mmol) and DIPEA (2.5 mmol) at 0 °C. The resulting solution was stirred for 2 h at a slow rising from 0 °C to room temperature, and then concentrated. The residue was subjected to column chromatography with EtOAc–hexane (1:15) as eluent to give the corresponding 2-arylacrylic ester **3**.