Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

A Convenient New Synthesis of Aryl α-Keto Esters

Syed J. Mahmood [a], Mike McLaughlin [a] & M. Mahmun Hossain [a]

[a] Department of Chemistry, University of Wisconsin-Milwaukee, P.O. Box 413, Milwaukee, WI, 53201

Published online: 25 Sep 2007.

To cite this article: Syed J. Mahmood, Mike McLaughlin & M. Mahmun Hossain (1999) A Convenient New Synthesis of Aryl α-Keto Esters, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 29:17, 2967-2972, DOI: 10.1080/00397919908086470

To link to this article: http://dx.doi.org/10.1080/00397919908086470

SYNTHETIC COMMUNICATIONS, 29(17), 2967-2972 (1999)

A Convenient New Synthesis of Aryl α-Keto Esters

Syed J. Mahmood, Mike McLaughlin and M. Mahmun Hossain*

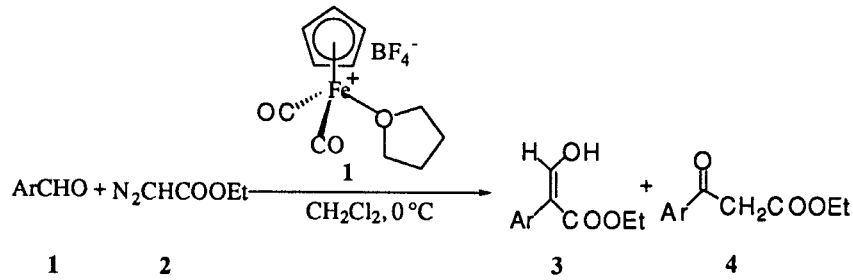
Department of Chemistry, University of Wisconsin-Milwaukee, P.O. Box 413, Milwaukee, WI 53201

A few of the many uses for α-keto esters include enzyme inhibitors[1] and antiinflammitory agents.[2] They are also useful reagents in organic synthesis.[3] Until now, most efficient methods for synthesizing these compounds typically involved either toxic side products, such as hydrogen cyanide,[4] or required expensive or highly reactive starting reagents, such as substituted ethynyl ethers.[5] Other simple synthetic methods had only moderate yields or were effective with specific substrates.[6] Now, we are proposing a convenient method to prepare aryl α-keto esters which minimizes these problems.

During our research in the area of epoxides, we discovered an iron Lewis acid-catalyzed reaction for the synthesis of aryl-substituted 3-hydroxyacrylic acid ethyl esters **3**, using aryl aldehydes and ethyl diazoacetate (Scheme I).[7]

*To whom correspondence should be addressed

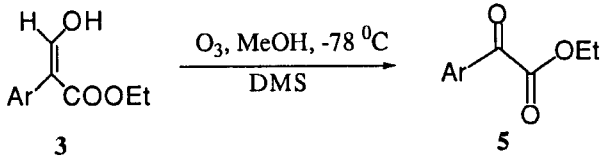
Scheme I: *Synthesis of 3-hydroxy-2-arylacrylic acid ethyl esters 3*



1 **2** **3** **4**

Ester **3a** was found to undergo oxidation when exposed to atmospheric conditions for several weeks, which has also been documented before.[8] Our goal was to speed up the process and make it inclusive for air-stable acrylic acid esters, such as **5c**. In order to do this we used ozone for oxidative cleavage of the acrylic double bond in these esters (Scheme II).

Scheme II: *Syntheis of aryl α-keto esters 5*



3 **5**

3a, Ar=Ph
3b, Ar=*p*-ClPh
3c, Ar=*p*-CH_3OPh
3d, Ar=*p*-CH_3Ph
3e, Ar=2,4-$(CH_3O)_2$Ph

Oxidation was achieved by bubbling ozone through a methanolic solution of **3** at -78 °C for 5 to 15 min. The isolated yields for these reactions ranged from 89 to 97 percent (Table 1). Earlier attempts by our group using $KMnO_4$ to oxidize **3a** did not react completely and yielded a mixture of products.[9] Ozone, however, produced only **5** and a quantitative amount of formic acid.

Table 1. ***Isolated Yields of α-Keto Esters***

Entry	Aryl Group	% Yield
1	Phenyl	97
2	*p*-Chlorophenyl	91
3	*p*-Methoxyphenyl	95
4	*p*-Methylphenyl	95
5	2,4-Dimethoxyphenyl	89

In summary, ozonolysis of aryl-substituted 3-hydroxyacrylic acid ester produced the corresponding aryl α-keto esters with excellent yields (89-97%). The final products were easily isolated and purified. This process was effective with a variety of substrates and avoided toxic side products and expensive or highly reactive reagents.

Experimental Section

General Considerations. Proton and carbon 13 spectra were obtained on a Bruker 250 and 62.9 MHz NMR spectrometer, respectively. The chemical shifts (δ) are expressed in ppm relative to tetramethylsilane, and $CDCl_3$ was used as the solvent. HR-MS were determined on a GC/MS VG-AUTOSPEC-3000. Ozone was generated using a Welsbach ozonator. HPLC grade methanol was distilled under nitrogen from magnesium iodide. Reagent grade diethyl ether was freshly distilled from sodium under nitrogen prior to use. Dimethyl sulfide was purchased from commercially available sources and was used without any further purification. The 3-hydroxy-2-arylacrylic acid ethyl esters were prepared by the method developed in our lab.[7]

Ozonolysis. General Procedure. Oxidation of **3** was achieved by using a typical ozonolysis procedure.[10] Approximately 100 mg of **3** was dissolved in 50 mL of freshly distilled methanol and cooled to -78 °C. Ozone was bubbled through the solution for 5 to 15 minutes, followed by purging with nitrogen until colorless. Three milliliters of dimethyl sulfide were added as a reducing agent. The solution was allowed to warm slowly to room temperature. The solvent was removed under vacuum and the crude product was dissolved in diethyl ether. The organic solution was washed with water and dried over sodium sulfate. The solvent was removed under vacuum. The products were finally identified by comparing the ^{1}H NMR spectra to those of the known compounds.

Phenyl-glyoxalic acid ethyl ester (5a) was isolated in 97% yield from the ozonolysis of 3-hydroxy-2-phenylacrylic acid ethyl ester at -78 °C; bp 70-72 °C (0.3 mm) [lit.[11] bp 118 °C (5 mm)]; ^{1}H NMR ($CDCl_3$, 250 MHz, lit. ref 12): δ 8.15-7.40 (m, 5H), 4.45 (q, 2H), 1.40 (t, 3H). HR-MS calcd for $C_{10}H_{10}O_3$ 178.0630, found 178.0677.

(4-Chlorophenyl)-glyoxalic acid ethyl ester (5b) was isolated in 91% yield from the ozonolysis of 3-hydroxy-2-(4-chlorophenyl)acrylic acid ethyl ester at -78 °C; bp 85-86 °C (0.3 mm) [lit.[13] bp 135-137 °C (5 mm)]; ^{1}H NMR ($CDCl_3$, 250 MHz, lit. ref 14): δ 8.16-7.90 (dd, 2H), 7.28 (t, 2H), 4.45 (q, 2H), 1.42 (t, 3H). HR-MS calcd for $C_{10}H_9O_3Cl$ 212.0240, found 212.0279.

(4-Methoxyphenyl)-glyoxalic acid ethyl ester (5c) was isolated in 95% yield from the ozonolysis of 3-hydroxy-2-(4-methoxyphenyl)acrylic acid ethyl ester at -78 °C; bp 120-122 °C (0.3 mm) [lit.[15] bp 178-179 °C (13 mm)]; ^{1}H NMR ($CDCl_3$, 250 MHz, lit. ref 12): δ 8.0 (d, 2H), 6.98 (d, 2H), 3.86 (q, 3H), 1.40 (t, 3H). HR-MS calcd for $C_{11}H_{12}O_4$ 208.0736, found 208.0753.

***p*-Tolyl-glyoxalic acid ethyl ester (5d)** was isolated in 95% yield from the ozonolysis of 3-hydroxy-2-*p*-tolylacrylic acid ethyl ester at -78 °C; bp 100-101 °C (0.3 mm) [lit.[16] bp 112 °C (0.6 mm)]; ^{1}H NMR ($CDCl_3$, 250 MHz, lit. ref 17): δ 8.01 -7.73 (m, 2H), 7.43-7.12 (m, 2H), 4.40 (q, 2H), 2.41 (s, 3H), 1.39 (t, 3H). HR-MS calcd for $C_{11}H_{12}O_3$ 192.2128, found 192.2102.

(2,4-Dimethoxyphenyl)-glyoxalic acid ethyl ester (5e) was isolated in 89% yield from the ozonolysis of 3-hydroxy-2-(2,4-dimethoxyphenyl)acrylic acid ethyl ester at -78 °C; mp 37-39 °C [lit.[18] mp 40-41 °C]; ^{1}H NMR ($CDCl_3$, 250 MHz, lit. ref 6a): δ 7.71 (d, 1H), 6.46 (dd, 1H), 6.31 (d, 1H), 4.24 (q, 2H), 3.78 (s, 3H), 3.37 (s, 3H), 1.33 (t, 3H). HR-MS calcd for $C_{12}H_{14}O_5$ 238.0841, found 238.0841.

References

1. (a) Patel, D. V.; Rielly-Gauvin, K.; Ryono, D. E.; Free, C. A.; Smith, S. A.; Petrillo, E. W. Jr. *J. Med. Chem.* **1993**, *36*, 2431. (b) Angelastro, M. R.; Mehdi, S.; Burkhart, J. P.; Peet, N. P.; Bey, P. *J. Med. Chem.* **1990**, *33*, 11.
2. Wong, C. H.; Munoz, B.; Yuan, W. *J. Med. Chem.* **1993**, *36*, 211.
3. (a) Wasserman, H. H.; Amici, R.; Frechett, R.; van Duzer, J. H. *Tetrahedron Lett.* **1989**, *30*, 869. (b) Wasserman, H. H.; Kou, G. H.; *Tetrahedron Lett.* **1989**, *30*, 873. (c) Ghosh, A. K.; Chen, Y. *Tetrahedron Lett.* **1995**, *36*, 6811.
4. Wasserman, H. H.; Ho, W. B. *J. Org. Chem.* **1994**, *59*, 4364.
5. Tatlock, J. H. *J. Org. Chem.* **1995**, *60*, 6221.
6. (a) Mali, R. S.; Tilve, S. G. *Synth. Commun.* **1990**, *20*, 1781. (b)

Weinstock, L. M.; Currie, R. B.; Lovell, A.V. *Synth. Commun.* **1981**, *11*, 943.

7. Mahmood, Syed J.; Hossain, M. Mahmun *J. Org. Chem.* **1998**, *63*, 3333. An alternative method for making these esters was published previously by Beccalli, E. M.; La Rosa, C.; Marchesini, A. *J. Org. Chem.* **1984**,*49*, 4287.
8. Dieckmann, W. *Ber.* **1917**, *50*, 1375.
9. The $KMnO_4$ oxidation of **3a** was also noted before, but the yield of the product **5a** was not mentioned, see: Ref 8.
10. Posner, G. H.; Switzer, C. *J. Am. Chem. Soc.* **1986**, *108*, 1239.
11. Gilman, H.; Ed. "Organic Synthesis": Wiley and Sons: New York, 1941; Collect. Vol I, p 241.
12. Wasserman, H. H.; Ives, J. L.; *J. Org. Chem.* **1985**, *50*, 3573.
13. Lapkin, I.; Dormidontov, P. Yu; Kazakov, A. F.; Zhukov, M. A. *J. Org. Chem. of the U.S.S.R.*, **1970**, *6*, 2431.
14. Hu, S.; Neckers, D. C. *J. Org. Chem.* **1996**, *61*, 6407.
15. Kindler, K.; Metzendorf, W.; D-y-Kwok. *Chem. Ber.* **1943**, *76*, 308.
16. Nimitz, Jonathan S.; Mosher, Harry S. *J. Org. Chem.* **1981**, *46*, 211.
17. McDonald, R. N.; Cousins, R. C. *J. Org. Chem.* **1980**, *45*, 2976.
18. Clark-Lewis, J. W.; Edgar, J. A.; Moody, K. *J. Chem. Soc (c)* , **1966**, 1221.

(Received in the USA 08 February 1999)