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An efficient synthesis of aryl α-keto esters

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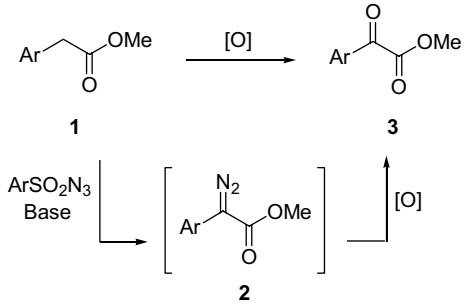
Abstract—A new one-pot approach for the synthesis of aryl α-keto ester based on the diazo transfer and oxidation of diazo group is developed.

α-Keto acids and esters have been important compounds as natural products and as the building blocks in organic synthesis. Over the past decades, various methods have been reported for the synthesis of such compounds. The most commonly applied synthesis of α-keto ester is the reaction of Grignard reagent to oxalyl chloride,[1] ethyl α-oxo-1H-imidazole-1-acetate[2] or diethyl oxalate.[3] The drawbacks of these approaches are the strict anhydrous reaction condition, the functional group tolerance in the preparation of Grignard reagent, and in some cases the low yield of the reaction. A different but interesting approach is the oxidation of alkynyl derivatives.[4] For example, Wu et al. reported a two-step (bromination and permangnate oxidation) reaction sequence that converts terminal alkynes to α-keto esters.[4b] Ruchirauat et al. have recently reported a novel synthesis of aryl α-keto esters based on the rearrangement of aryl cyanohydrin carbonate esters.[5]

The approaches through introduction of a keto group to a carbonyl group have also been applied to the synthesis of α-keto acid derivatives. For example, Wasserman et al. developed a method through the formation and singlet oxygen oxidation of enamino carbonyl intermediates.[6] On the other hand, direct oxidation of aryl acetic esters with hydrogen peroxide or molecular oxygen in the presence of transition metal catalyst has recently been reported.[7] Since aryl acetic esters are readily available starting materials, the direct oxidation approach has the advantages over other methods. However, this approach is sometimes limited to a narrow range of substrates. For example, in Nolte's system of *N*-hydroxyphthalimide/Co^{II}/O_2 the benzylic oxidation works poorly for the arylacetic esters with electron withdrawing substituent in the *para* position and any substituent in the *ortho* position.[7b] One successful direct oxidation of arylacetic esters has been reported by Choudary et al., in which case the oxidant is *tert*-butylhydroperoxide (TBHP) and the catalyst is vanadium pillared montmorillonite.[7d] Under this condition, wide range of arylacetates with different substituents were smoothly transformed to the corresponding arylglyoxylic esters, with only one exception in which no oxidation occurs when the aryl group was *o*-nitrophenyl. The drawback of this approach is that the reaction has to be carried out at 70 °C for a prolonged time (20–96 h). Here, we report a one-pot conversion of aryl acetic esters to aryl α-keto ester through diazo transfer, followed by oxidation with dimethyldioxirane generated in situ from acetone and Oxone® (Scheme 1).



Scheme 1.

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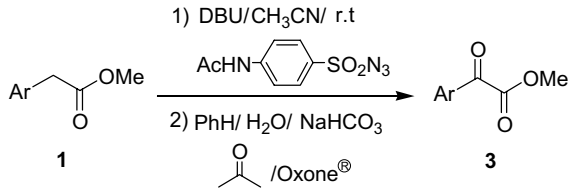


Scheme 2.

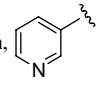
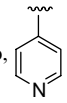
It has been well documented that the benzylic position of the aryl acetic esters can be easily diazotized.[8] On the other hand, the diazo group can be easily oxidized with dimethyldioxirane solution,[8,9] which is generated from Oxone®. Since the preparation of dimethyldioxirane is troublesome and the yield is low,[10] we considered an oxidation with dimethyldioxirane generated in situ from acetone and Oxone® after the diazotization of the aryl acetate in one-pot. Thus, methyl phenylacetate **1a** was treated with *p*-acetamidobenzene-sulfonyl azide/DBU in CH_3CN at room temperature. After the diazotization is complete as judged by TLC, a mixture of Oxone®/$NaHCO_3$/benzene/H_2O/acetone was added to the reaction mixture at 0 °C. The oxidation was completed within 25 min as determined by the disappearance of the yellow color and TLC, to yield the methyl α-oxo phenylacetate **3a** in 83% isolated yield (Scheme 2).

The scope of this one-pot reaction sequence is shown by the data summarized in Table 1.[11] The data indicate the tolerance of the aromatic substituent to the reaction conditions. The phenyl ring with electron withdrawing group generally gave satisfactory results. It is worthwhile to note that this new approach works well with the substrates with more than one halogen atom substituents (entries 5 and 6, Table 1). It would be difficult to prepare this type of α-keto esters with Grignard reagent approach. This approach is also applicable to the substrate with heteroaromatic ring. For example, the sulfur of the thiophene ring remained intact in the diazotization and oxidation, although in this particular case, the diazotization and oxidation were preformed separately due to the low efficiency in the diazotization step (excess amount of diazo transfer reagents was required).

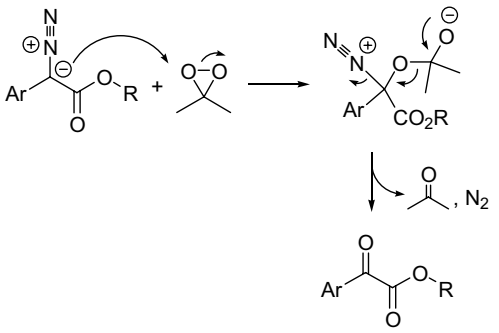
On the other hand, it is worth-noting that one-pot reaction gave low yield for aryl substrates with electron donating group, such as methoxy group. In this case, a considerable amount of unreacted starting material of methyl *p*-methoxyphenylacetate was recovered. Obviously, the low efficiency is due to the difficulty in the first diazotization step.

It was observed that the rates of the diazotization and the following oxidation were dependent on the substituent of the phenyl ring. The electron-donating group retards the diazotization but accelerates the oxidation, while the electron-withdrawing group works in the opposite way (compare entries 11 and 12 in Table 1). For the diazotization reaction, this substituent effect is easily understandable. The initial step of the diazo transfer is the deprotonation of the α-proton by base.[12] In the oxidation step, it is reasonable to propose that the diazo compounds are oxidized by the in situ generated

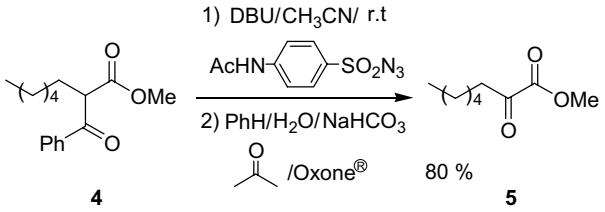
Table 1. Transformation of arylacetates to aryl α-ketoesters[11]

Entry	**1** (Ar=)	RT for diazotization (h)	RT for oxidation (min)	Yield (%)[a]
1	**1a**, C_6H_5–	12	25	83
2	**1b**, 1-naphthyl	48	30	84
3	**1c**, *o*-ClC_6H_4–	24	60	88
4	**1d**, *m*-ClC_6H_4–	12	90	83
5	**1e**, *o*,*p*-$Cl_2C_6H_3$–	24	60	92
6	**1f**, *m*,*p*-$Cl_2C_6H_3$–	12	20	81
7	**1g**, *o*-FC_6H_4–	12	90	81
8	**1h**, *o*-BrC_6H_4–	24	40	74
9	**1i**, *p*-BrC_6H_4–	14	25	84
10	**1j**, *m*-MeC_6H_4–	24	25	73
11	**1k**, *p*-$MeOC_6H_4$–	48	15	13(83)[b]
12	**1l**, *p*-$O_2NC_6H_4$–	2	120	48
13	**1m**, 	12	30	86[c]
14	**1n**, 	12	30	99[c,d]
15	**1o**, 	12	30	99[c,d]

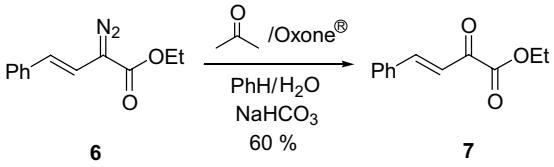
[a] Isolation yields for two steps after column chromatography.
[b] Number in bracket refers to the starting material **1k** recovered.
[c] The diazo product was isolated and purified before oxidation, and the yield refers to the oxidation step only. The diazotization step gave the diazo compounds with the isolated yields of 65–98%.
[d] The oxidation was carried out with a solution of dimethyldioxirane in acetone due to the difficulty in product purification with in situ condition. Pyridine ring was oxidized to the corresponding *N*-oxide.



Scheme 3.



Scheme 4.



Scheme 5.

dimethyldioxirane. The oxidation occurs through the nucleophilic attack of the dimethyldioxirane oxygen by the negatively polarized carbon to which the diazo group is attached (Scheme 3).

The in situ oxidation approach can be extended to aliphatic esters. For aliphatic esters, because the direct diazotization is difficult, it is necessary to convert them to β-ketoesters first.[13] Then the same one-pot diazotization/oxidation can be applied, as demonstrated by converting β-ketoester **4** to α-oxo ester **5** (Scheme 4).

On the other hand, the in situ oxidation can also be used to oxidize the diazo group of vinyl diazo carbonyl compound,[14] suggesting that a double bond may tolerate the oxidation condition (Scheme 5).

In conclusion, we have developed a new approach to aryl α-keto esters in a one-pot manner using readily available aryl acetate as starting material. The reaction condition is mild (diazotization at room temperature and oxidation at 0 °C), the operation is simple, and the reaction can be easily scaled up, which makes it a prospective method in the organic synthesis.

Acknowledgements

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11. *General procedure for the one-pot transformation of arylacetate to aryl α-ketoesters*. Methyl phenylacetate **1a** (100 mg, 0.67 mmol) was dissolved in anhydrous MeCN (5 mL), and to this solution was added DBU (72 mg, 0.48 mmol). After the solution was stirred at room temperature under N_2 for 15 min, *p*-acetamidobenzenesulfonyl azide (92 mg, 0.8 mmol) was added at 0 °C. The solution was stirred at room temperature for 12 h until the diazotization was complete as judged by TLC. To the solution were added benzene (5 mL), acetone (3.5 mL), H_2O (5 mL), $NaHCO_3$ (2.16 g, 25 mmol) and Oxone® (4.0 g, 6.5 mmol). The reaction mixture was vigorously stirred for 25 min until the oxidation was complete as judged by TLC and by the disappearance of the yellow color. Water (10 mL) was added and the mixture was extracted with diethyl ether (3 × 10 mL), and combined organic layer was dried over anhydrous Na_2SO_4. Removal of the solvent gave a crude product, which was purified by column chromatography to give pure product **3a** (90 mg, 83%).
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