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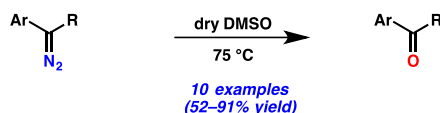
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Development of a simple system for the oxidation of electron-rich diazo compounds to ketones

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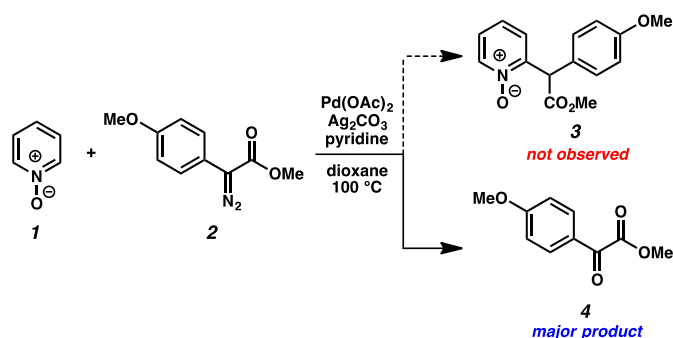
Mild heating of diazo compounds in DMSO furnishes ketone byproducts in moderate to excellent yields. The reaction is particularly effective on electron-rich substrates and exhibits high chemoselectivity, allowing for the use of diazo compounds containing additional oxidation-prone functional groups. This straightforward protocol offers an alternate route to synthetically useful α -ketoesters from readily available aryl diazoacetates.

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α -Ketoesters and their derivatives are useful synthetic building blocks,¹ and a number of methods for their synthesis have been reported.² The oxidation of diazoacetates offers a convenient route to α -ketoesters,³ as the starting materials are readily accessed by treatment of acetic acid derivatives with *p*-acetamidobenzenesulfonyl azide and DBU (see the Supporting Information for details).⁴ Various methods for this oxidation have been reported, although many require the use of expensive transition metal catalysts or harsh oxidants.

Recently, Wang and coworkers disclosed an efficient synthesis of aryl α -ketoesters from α -aryl esters by one-pot diazo transfer/oxidation using DMDO generated in situ.^{3c} This protocol offers a novel route to α -ketoesters using simple and inexpensive reagents (acetone, Oxone, and sodium bicarbonate) at room temperature. The major disadvantage is the strong oxidizing ability of DMDO, which prevents the use of this method with substrates containing other easily oxidizable functional groups.⁵ In this communication, we describe our studies on an alternative system that uses a far milder oxidant for the transformation of diazoacetates to ketones.⁶

In the course of investigations into the synthesis of functionalized pyridines by C–H activation routes, we subjected pyridine-*N*-oxide (**1**) and aryl diazoacetate **2** to conditions developed by Chang and coworkers for the synthesis of 2-arylpyridine-*N*-oxides, hoping to observe coupling to furnish diarylmethane **3** (Scheme 1).⁷ While **3** was not detected, we unexpectedly found the major product of the reaction to be α -ketoester **4**. Control experiments revealed the palladium and other additives to be unnecessary, and treatment of diazoacetate **2**



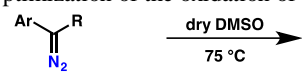
with pyridine-*N*-oxide alone resulted in a moderate yield of α -ketoester **4** (Table 1, entry 1).

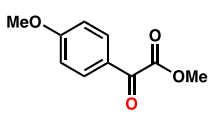
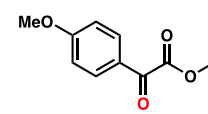
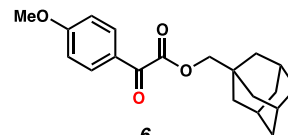
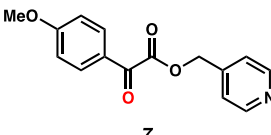
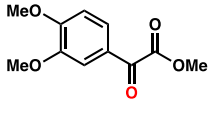
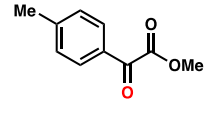
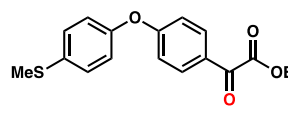
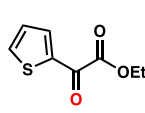
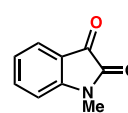
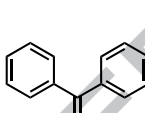
Scheme 1. Observation of an unexpected oxidation event during an attempt at pyridine 2-functionalization.

We suspected that mild conditions for the oxidation of an aryl diazoacetate to the α -ketoester might be synthetically useful. During optimization studies, we found that lowering the temperature to 50 °C increased the yield of **4** to 84% (Table 1, entry 2). A survey of other oxygen-transfer reagents showed that the use of a more electron-rich pyridine-*N*-oxide did not result in an increase in yield (entry 3). Triphenylphosphine oxide was capable of carrying out the desired oxidation, albeit in low yield (entry 4), while trimethylamine-*N*-oxide and *N,N*-dimethyl-4-nitrosoaniline were not (entries 5 and 6). The use of benchtop DMSO as both solvent and oxidant provided the oxidation product in approximately 70% yield, although we observed varying amounts of the water O–H insertion product with different batches of benchtop DMSO (entry 7). This undesired reactivity was suppressed by the use of anhydrous DMSO (entry

8). We found it optimal to use anhydrous DMSO at 75 °C, which furnished the α -ketoester **4** in an excellent 91% yield.

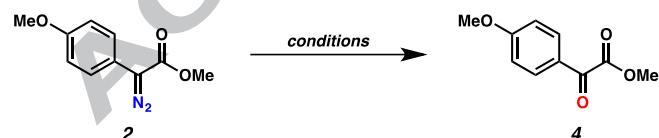
Table 1. Optimization of the oxidation of aryl diazoacetate **2**.



	
4 (91% yield)	5 (90% yield)
	
6 (85% yield)	7 (74% yield)
	
8 (78% yield)	9 (62% yield)
	
10 (68% yield)	11 (75% yield)
	
12 (52% yield)	13 (56% yield)

Conditions: Diazo compound (0.40 mmol), DMSO (0.5 mL) at 75 °C.

Sporadic examples of the oxidation of diazo compounds using DMSO have been published, although many of these examples provide only low or undisclosed yields of the observed oxidation products.⁸⁻¹² Furthermore, no reports of this reactivity offer investigations into the reaction scope and limitations.



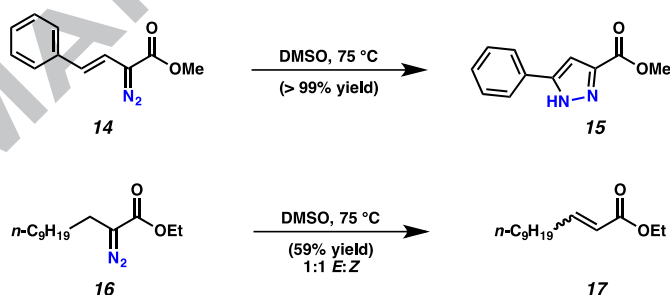
Entry	Reagent	Solvent	Temperature (°C)	Yield ^a
1	pyridine- <i>N</i> -oxide	dioxane	100	62
2	pyridine- <i>N</i> -oxide	dioxane	50	84 ^b
3	4-methoxypyridine- <i>N</i> -oxide·xH ₂ O	dioxane	50	79 ^b
4	triphenylphosphine oxide	dioxane	50	40 ^b
5	trimethylamine- <i>N</i> -oxide	dioxane	50	trace ^b
6	<i>N,N</i> -dimethyl-4-nitrosoaniline	dioxane	50	0 ^b
7 ^d	none	DMSO	50	70 ^{b,c}
8 ^{d,e}	none	DMSO	50	81
9 ^{e,f}	none	DMSO	75	91

Conditions: **2** (0.1 mmol), reagent (0.2 mmol), solvent (0.5 mL). ^a Isolated yields. ^b Incomplete conversion of **2** after 72 hours. ^c The yield varies with the water content of the DMSO. The major byproduct was the α -hydroxyester resulting from carbenoid O-H insertion. ^d Reaction run in 0.25 mL DMSO. ^e Anhydrous DMSO was used. ^f Reaction run with 0.4 mmol of **2** in 0.5 mL DMSO.

Figure 1. Substrate scope of the oxidation of diazo compounds.

The substrate scope of the reaction is shown in Figure 1. An electron-rich aryl ring was generally found to be necessary, with 4-methoxyphenyl (**4–7**), 3,4-dimethoxyphenyl (**8**), and 4-methylphenyl (**9**) substituents furnishing the α -ketoester products in excellent yields. Unfortunately, compounds with less electron-rich aryl rings afforded the products in lower yields, and acceptor-acceptor diazos were completely unreactive.¹³ Notably, substrates containing functional groups susceptible to oxidation, including an olefin (**5**), an adamantyl group (**6**),¹⁴ a pyridyl ring (**7**), a thioether (**10**), and a thiophene ring (**11**) were all smoothly converted to the α -ketoesters with no overoxidation observed. An oxindole scaffold was compatible with the reaction, allowing for the formation of *N*-methylisatin (**12**) in moderate yield. Finally, an electron-withdrawing group on the diazo carbon was found to be unnecessary, as diphenyldiazomethane was converted to benzophenone (**13**) in moderate yield.

Subjection of styrenyl diazoacetate **14** to the reaction conditions resulted in smooth isomerization of the starting material to pyrazole **15** in quantitative yield (Scheme 2).¹⁵ An alkyl-substituted diazo compound (**16**) also did not undergo the desired oxidation, but rather was converted to the enoate (**17**) as a mixture of olefin isomers via a 1,2-hydrogen shift.¹⁶



Scheme 2. Alternative reactivity of styrenyl and alkyl diazoacetates.

A representative procedure is as follows: To an oven-dried 1-dram vial equipped with a magnetic stir bar were added methyl 2-diazo-2-(4-methoxyphenyl)acetate (**2**, 82 mg, 0.40 mmol) and anhydrous DMSO (0.5 mL). The vial was sealed with a Teflon-lined plastic cap and placed in a metal heating block at 75 °C. Upon completion (as determined by TLC analysis and a color change from deep orange to pale yellow, approx. 2 hours), the reaction mixture was allowed to cool to room temperature. Olfactory analysis of the crude mixture suggests dimethyl sulfide is a byproduct. The mixture was loaded directly onto a silica gel column, eluting with 20% ethyl acetate in hexanes to obtain 71 mg of methyl 2-(4-methoxyphenyl)-2-oxoacetate (**4**, 91% yield).

In summary, we have identified optimized conditions for a highly chemoselective and extremely simple method for the oxidation of diazo compounds to ketones. A study of the reaction scope reveals a range of aryl diazoacetates to be compatible with the reaction, even those containing other easily oxidizable functional groups. Given the ready availability of aryl diazoacetates, we envision this oxidation will find utility as an alternative route to synthetically useful α -ketoesters, particularly when the desired compounds contain other functional groups sensitive to oxidation.

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Supplementary Material

Supplementary data associated with this article can be found, in the online version, at _____

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