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Thermolysis of 2-diazo-3-aryl ketoesters: New route to α-aryl malonates and aromatic esters

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ABSTRACT

Thermochemical excitation enabled efficient α-aryl malonates synthesis from 2-diazo-3-aryl ketoesters and alcohols under transition metal-free reaction conditions. Furthermore, an unusual C—C bond cleavage and C—O/(N) bond formation occurred when MeOH/(RNH_2) was used as the nucleophile, furnishing corresponding aromatic esters/(amides) in high yields.

Introduction

Substituted phenylacetic acids and their derivatives are valuable structural motifs in natural products[1] and pharmaceuticals,[2] as found in nonsteroidal anti-inflammatory drugs (e.g., indometacin, sulindac, diclofenac).[2c] Beyond that, phenylacetic acids and derivatives showed good directing ability in palladium-catalyzed C—H functionalization for organic synthesis by Yu group in recent years.[3] Among them, α-aryl malonates have their own special potential in the synthesis of α-aryl acids and others.[4] Therefore, there is a continued demand for efficient syntheses of these compounds. In recent years, transition metal-catalyzed cross-coupling has become an important strategy to add various functional groups to aryl halides. For instance, enolates have been utilized for palladium-catalyzed α-arylation to furnish α-aryl carbonyl compounds (Fig. 1a),[5] such as α-aryl ketones,[6] amides[7] and esters.[8] Beyond that, a significant advance to access these molecules has been accomplished with copper complexes through direct arylation of aryl iodide/bromide and 1,3-dicarbonyl derivatives,[9] including the first enantioselective Ullmann-Hurtley condensation, which was developed by Ma and co-workers in 2006.[10]

On the other hand, diazo compounds, due to its high reactivity, have recently attracted considerable attention in transition-metal catalysis.[11] However, a more classic conversion of α-diazo ketones into α-aryl carbonyl derivatives has been developed over 100 years. Since the first report on the Wolff rearrangement in 1902,[12] it has been widely employed as a powerful tool for the preparation of carboxylic acid homologues[13] and the formation of strained cyclic systems.[14] Generally, the early Wolff rearrangements were induced via thermolysis[12,14b] and silver(I) catalysis[15,14b] thus yielding a ketene as an intermediate, which underwent nucleophilic attack to generate carboxylic acid derivatives (Fig. 1b).[13,14]

Thereafter, Süs[16] as well as de Jonge[17] pioneered photolysis to be an efficient procedure for the Wolff rearrangement. In 1951, Horner/Spietschka subsequently reported that methyl 2-diazo-3-oxo-3-phenylpropanoate can be excited by *uv* light in methanol or H_2O to form α-aryl carbonyl derivatives.[18,13c] Despite these major advances, we became intrigued by developing a specific method for selective synthesis of unsymmetrical α-aryl malonates by Wolff rearrangement. Thus, we herein describe a metal-free convenient and highly efficient protocol for the synthesis of diverse α-aryl malonates excited by thermolysis and an unusual nucleophilic addition/elimination to deliver corresponding aromatic esters/amides using 2-diazo-3-aryl-3-oxopropanoates as starting materials (Fig. 1c).

Generally, Wolff rearrangement is sensitive to the Ag(I) catalysts in the presence of alkaline reagents.[14a] Thus, we initiated our studies by testing the feasibility of the envisioned catalytic system, consisted of $AgSbF_6$ and Et_3N, catalyzed decomposition of ethyl 2-diazo-3-(4-methoxyphenyl)-3-oxopropanoate (**1a**), along with 2,2,2-trifluoroethanol (**2a**) as the nucleophile and reaction medium. Fortunately, the desired rearrangement product **3aa** was obtained in excellent yield (Table 1, entry 1). However,

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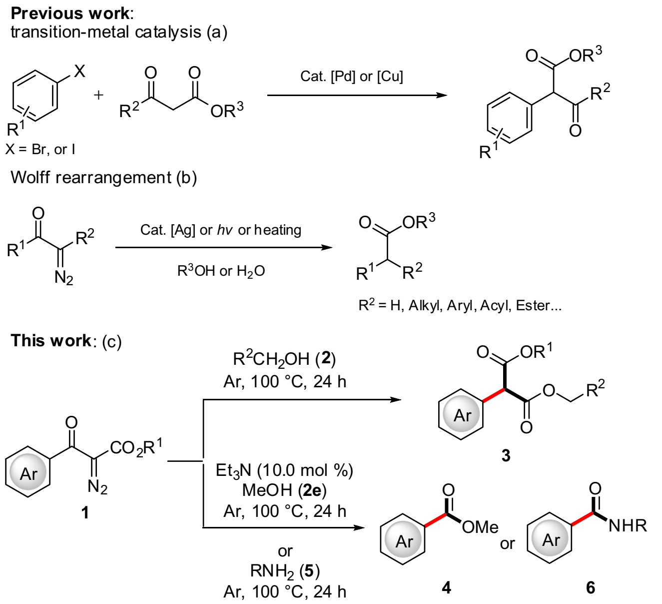


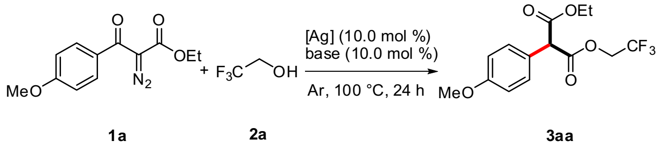
Fig. 1. Syntheses of α-aryl carbonyl compounds.

omission of Et_3N or decreasing reaction temperature resulted in a significantly negative effect (entries 2–3). Among a set of representative silver(I) sources, $AgSbF_6$ was identified to be the ideal choice (entries 1, 4–8). To our surprise, the desired product **3aa** was delivered in the same high yield in the absence of $AgSbF_6$ (entry 9), as was also observed when only employing catalytic amount of DBU as the alkaline reagents, albeit in a slightly reduced yield (entry 10). These results indicated the reaction was excited by thermolysis, rather than silver(I) catalysis. Indeed, the reaction, by only heating, gave **3aa** in 79% yield (entry 11). However, stoichiometric TFE failed to generate the rearrangement product when toluene or 1,4-dioxane as the reaction medium, which indicated solvent amount of alcohol is required for the reaction (entries 12–13).

With the optimized reaction conditions in hand (Table 1, entry 11), we next explored the substrate scope of 2-diazo-3-aryl-3-oxopropanoates with alcohols (Scheme 1). The reaction of aryl diazo compounds **1** bearing various electron-rich or electron-deficient substituents with 2,2,2-trifluoroethanol (**2a**) provided the desired α-aryl malonates **3** under transition metal-free reaction conditions. Meanwhile, parallel reactions were also repeated under $AgSbF_6$-Et_3N catalysis, showing no significant differences on the yields (**3aa**–**fa**, **3ia**). It is worth noting that indole and benzofuran derivatives (**1j**–**k**) also proved to be viable starting materials, providing the corresponding products **3ja** and **3ka** in good yields of 90% and 54%, respectively. Besides the 2,2,2-trifluoroethanol, other representative alcohols, such as ethanol (**2b**), isopropanol (**2c**) and *tert*-butanol (**2d**), were also successfully employed in the reactions, offering the products **3db**, **3dc**, **3dd** and **3jb** in moderate to good yields, respectively.

However, an unexpected C—O bond formation and C—C bond cleavage occurred under the standard reaction conditions, when methanol was utilized as the nucleophile and solvent. In contrast, the expected Wolff rearrangements, even the O—H insertion to the intermediacy of carbenes were not observed at all.[13a,19] Interestingly, the formation of product **4** could be promoted by catalytic amount of Et_3N or $AgSbF_6$, while significantly decreased yield of product **4a** was obtained in the absence of base and

Table 1
Synthesis of α-aryl malonate through thermolysis of 2-diazo-3-aryl ketoester **1a**.[a]



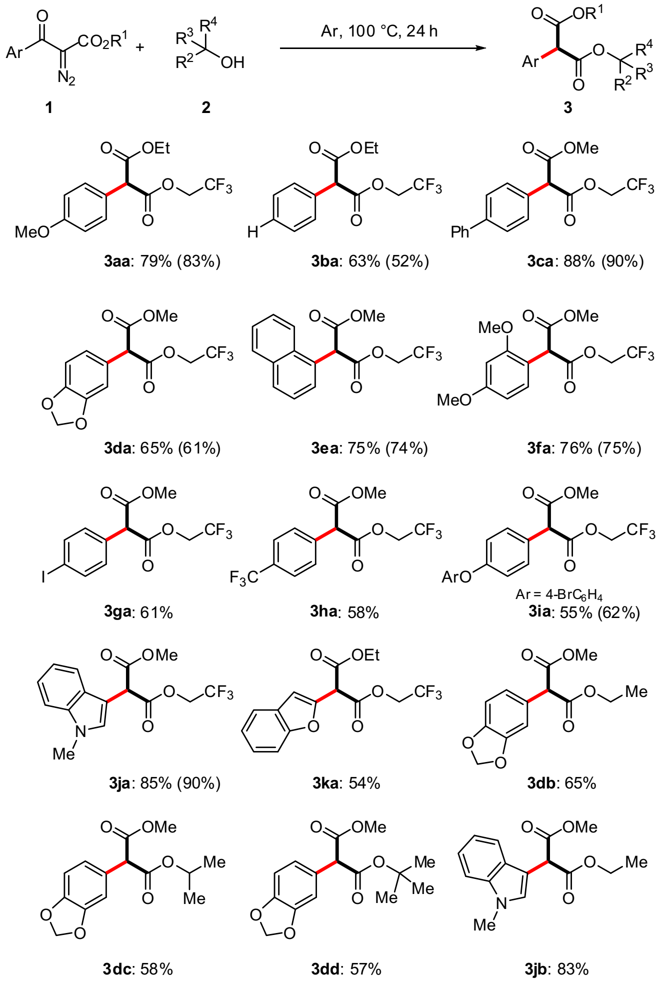
Entry	[Ag]	Base	Yield (%)[b]
1	**$AgSbF_6$**	**Et_3N**	**83**
2	$AgSbF_6$	–	Trace
3	$AgSbF_6$	Et_3N (50 °C)	9
4	$AgSbF_6$	Et_3N (50.0 mol %)	62
5	AgOAc	Et_3N	51
6	AgOTf	Et_3N	76
7	$AgBF_4$	Et_3N	69
8	$AgPF_6$	Et_3N	70
9	**–**	**Et_3N**	**83**
10	–	DBU	73
11	**–**	**–**	**79**
12	–	–	<5[c]
13	–	–	0[d]

[a] Reaction conditions **A**: **1a** (0.5 mmol), TFE (**2a**, 1.0 mL), $AgSbF_6$ (10.0 mol%), Et_3N (10.0 mol%), under Ar, 100 °C, 24 h; **B**: **1a** (0.5 mmol), TFE (**2a**, 1.0 mL), under Ar, 100 °C, 24 h. TFE = trifluoroethanol.

[b] Isolated yield.

[c] TFE (**2a**, 2.0 equiv), toluene (1.0 mL).

[d] TFE (**2a**, 2.0 equiv), 1,4-dioxane (1.0 mL).



Scheme 1. Substrates scope: Reactions of 2-diazo-3-aryl ketoesters and alcohols. Yields within parentheses were obtained under [Ag] catalysis (reaction conditions **A**).