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Bromination of *α*-Diazo Phenylacetate Derivatives Using Cobalt(II) Bromide

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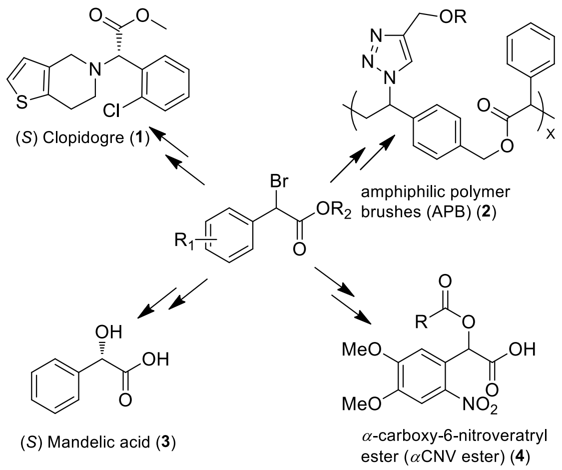
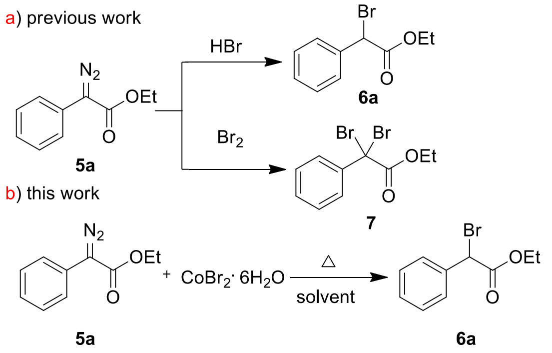
Abstract. A method for the bromination of *α*-diazo phenylacetate derivatives using cobalt(II) bromide is described. This bromination reaction features a short reaction time, broad substrate scope, operational simplicity, acid-free conditions, and gram-scalability.

Keywords: bromination; *α*-diazo phenylacetate derivatives; cobalt(II) bromide; cobalt-mediated; bromides

As electrophiles in a wide variety of reactions, bromides can be converted through simple transformations to generate various valuable synthetic intermediates and significant products (Scheme 1).[1] Many methodologies for the construction of carbon−bromine bonds have been reported.[2] Among them, the bromination of diazo compounds is an especially practical and useful strategy.[3] However, to the best of our knowledge, very few studies have been designed to achieve the bromination of *α*-diazo phenylacetate derivatives. To date, traditional synthetic routes for this transformation use elemental bromine or hydrogen bromide (Scheme 2a).[4] While this approach facilitates the replacement of a diazo group by a readily available, highly specific brominating reagent, the reaction is generally conducted under harsh conditions. Additionally, secondary precautions are required to ensure safe handling as bromine is a hazardous irritant that causes painful skin blisters and severe respiratory damage. Hydrogen bromide has limited applicability due to its strong acidity and long reaction time. Therefore, continued efforts should be dedicated to investigating new routes and reagents for the synthesis of brominated *α*-phenylacetate derivatives.



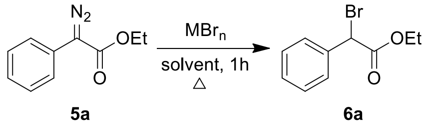
Scheme 1. Various routes of synthesis using bromides as intermediates



Scheme 2. Previous work and our current strategy

Cobalt bromide salts are versatile reagents in many organic reactions,[5] which can be used to mediate the bromination of the diazo compounds. Thus, they are attractive alternatives for the synthesis of *α*-brominated phenylacetate derivatives without the use of any acid (Scheme 2b). In our study, the initial optimization of the bromination of donor−acceptor diazo compounds was conducted using ethyl 2-diazo-2-phenylacetate as the model substrate to react with various metal bromides.

Table 1. Optimization of the reaction conditions

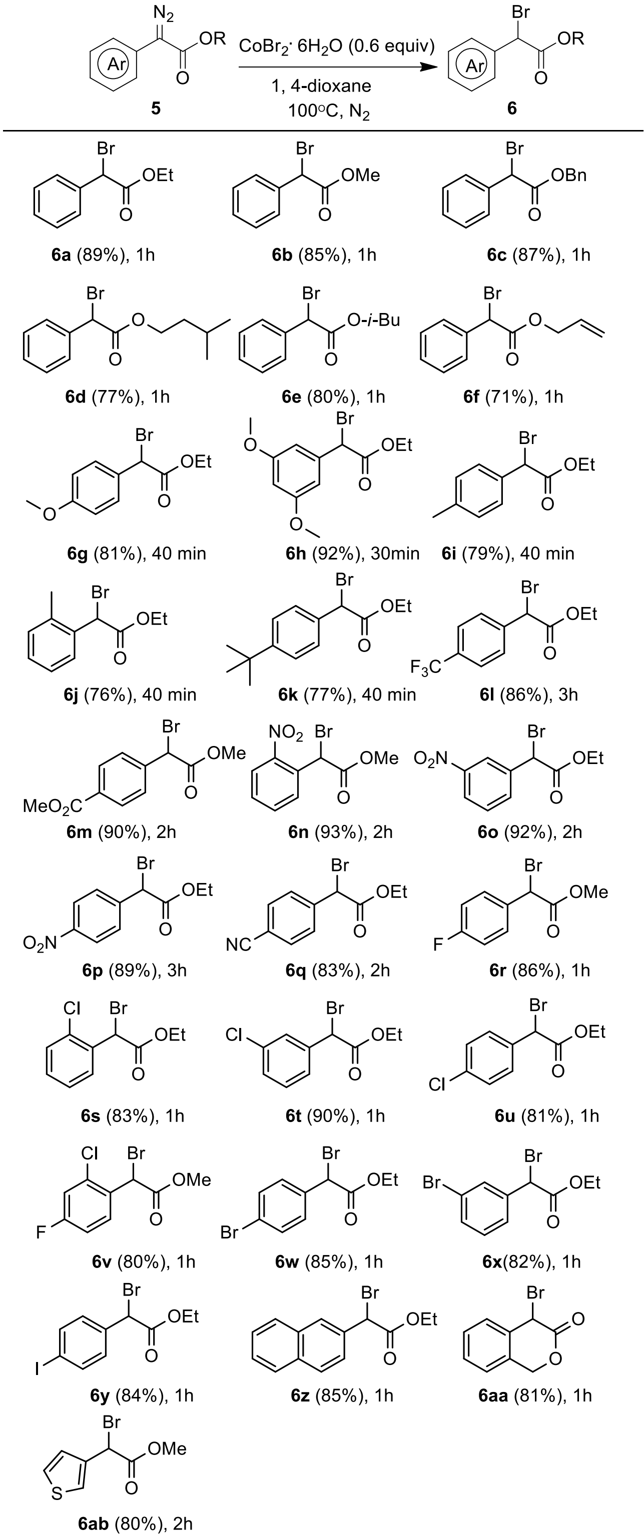


Entry	Brominating agents	Solvent	Yield [g] (%)
1	$NiBr_2$	THF	N.R.
2	$CuBr_2$	THF	21
3	CuBr	THF	8
4	$FeBr_3$	THF	47
5	$CoBr_2\cdot 6H_2O$	THF	71
6	$CoBr_2\cdot 6H_2O$	CH_3CN	63
7	$CoBr_2\cdot 6H_2O$	EtOH	67
8	$CoBr_2\cdot 6H_2O$	DMF	56
9	$CoBr_2\cdot 6H_2O$	DMSO	46
10	$CoBr_2\cdot 6H_2O$	toluene	70
11	$CoBr_2\cdot 6H_2O$	1,4-dioxane	78
12[b]	$CoBr_2\cdot 6H_2O$	1,4-dioxane	89
13[c]	$CoBr_2\cdot 6H_2O$	1,4-dioxane	67
14[d]	$CoBr_2\cdot 6H_2O$	1,4-dioxane	86
15[e]	$CoBr_2\cdot 6H_2O$	1,4-dioxane	63
16[f]	$CoBr_2\cdot 6H_2O$	1,4-dioxane	58

[a] Unless otherwise noted, all reactions were conducted with ethyl 2-diazo-2-phenylacetate (0.5 mmol) and $CoBr_2\cdot 6H_2O$ (0.3 mmol) at 80 °C under N_2 atmosphere. [b] The reaction temperature was 100 °C. [c] The reaction temperature was 70 °C. [d] The amount of the brominating reagent was 0.4 mmol. [e] The amount of the brominating reagent was 0.2 mmol. [f] The reaction proceeded in air. [g] Yield of the isolated product.

The effects of various promoters, metal salts, solvents, and temperatures were examined using a model reaction (Table 1). Initially, four different brominating reagents were screened (MBr_n, M = Ni, Cu, Fe, Co) (Entries 1−5). There was no reaction with $NiBr_2$, whereas $CuBr_2$ and CuBr gave product **6a** in 21% and 8% yields, respectively (Entries 1–3). Similarly, $FeBr_3$ resulted in the expected product **6a** in 47% yield (Entry 4). It is noteworthy that **6a** was obtained in 71% yield when 0.6 equiv. of $CoBr_2\cdot 6H_2O$ was used in THF at 80 °C for 1 h under N_2 atmosphere (Entry 5). Several other solvents were screened, and a lower or comparable yield was obtained when acetonitrile (CH_3CN), ethanol (EtOH), *N*,*N*-dimethylformamide (DMF), dimethylsulfoxide (DMSO), or toluene were used as the solvent (Table 1, Entries 6−10). The highest product yields were observed when 1,4-dioxane was used as the solvent (Entry 11). Encouraged by this initial result, we focused on optimizing other reaction parameters. Raising the reaction temperature enhanced the yield dramatically (Entry 12), whereas decreasing the reaction temperature led to lower yields. No further improvement of the product yield was noted when the

Table 2. Reaction scope [a]



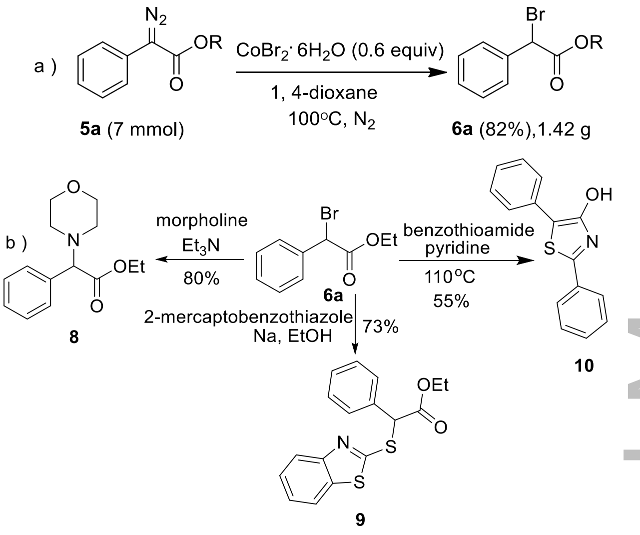
[a] Unless otherwise noted, all reactions were conducted with ethyl 2-diazo-2-phenylacetate (0.5 mmol) and $CoBr_2\cdot 6H_2O$ (0.3 mmol) at 100 °C under N_2 atmosphere.

reaction time was extended (Table 1, Entry 13). The yield of **6a** was not further improved when the amount of the brominating reagent was increased to 0.4 mmol (Table 1, Entry 14). Lowering the amount of $CoBr_2{\cdot}6H_2O$ diminished the yield of this transformation drastically (Table 1, Entry 15). A negative control experiment with $CoBr_2{\cdot}6H_2O$/air highlighted the critical role played by the N_2 atmosphere (Entry 16). In air atmosphere, **5a** tends to undergo an oxidation reaction which gives an oxidized byproduct. That is a common side reaction observed in metal carbene chemistry.[6] Attempting to reduce the amount of cobalt salt and use inexpensive KBr as bromine source, various bromine-free cobalt salts as catalysts were tested in the bromination reaction. However, no desired product was afforded, whereas a low yield (8%) of **6a** was obtained when only using a catalytic amount of $CoBr_2{\cdot}6H_2O$ (see Supporting Information). Thus, after careful investigation, the optimized reaction conditions were identified as $CoBr_2{\cdot}6H_2O$ (0.3 mmol) in 1,4-dioxane at 100 °C under N_2 atmosphere for 1 h.

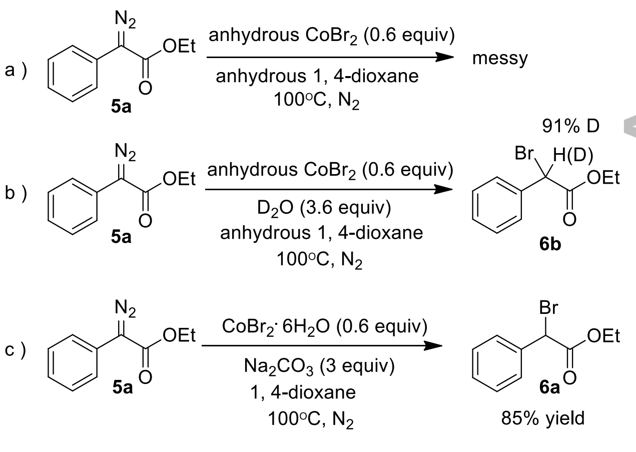
With the optimized reaction conditions in hand, we then undertook an extensive survey of the substrate scope. Diverse α-diazo phenylacetate derivatives **5a–5ab** were reacted with $CoBr_2{\cdot}6H_2O$ to give the desired products in good to excellent yields under the optimized reaction conditions (Table 2).

Generally, we found that ester moieties bearing linear, branched, bulky, and saturated alkoxy chains were well tolerated as the corresponding products were obtained in good yields (**6a–e**). A substrate bearing a lactone also gave the desired product in high yields (**6aa**). We observed that unsaturated alkoxy chains had little influence on this reaction, giving the desired product **6f** in 71% yield. Satisfactory results were obtained when there were methyl, *tert*-butyl, or methoxy groups on the phenyl moiety of the diazoacetate as good yields were obtained in short reaction time; this trend was possibly due to the presence of the electron-donating substituents, which increased the overall reactivity of the diazoacetate (**6g**, **6i–k**). This explanation was supported by the high yield obtained in 30 min for the 3,5-dimethoxy group on the bis-substituted substrate **6h**. In contrast, although strongly electron-withdrawing functional groups had no adverse effect on the reaction yield (83%–93%), longer reaction times were observed, presumably due to the relatively low activity imparted by these substituents (**6l–q**). Substrates bearing a halide substitution (F, Cl, Br, and I) on the *ortho*, *meta*, or *para* positions of the aryl group also gave the desired products in good to excellent yields (**6r–y**). The reaction also proceeded well with a 2-naphthyl group to give the product **6z** in 85% yield. Furthermore, a substrate containing a thiophene ring was also compatible, affording the desired product in 80% yield (**6ab**). Alkyl substrates were also examined, but no desired product was obtained (see Supporting Information).

The synthetic potential of this process was demonstrated by conducting a gram-scale reaction of ethyl 2-diazo-2-phenylacetate and $CoBr_2{\cdot}6H_2O$, thereby affording **6a** in 82% yield (Scheme 3a). Treatment of **6a** with morpholine in the presence of Et_3N at room temperature resulted in the formation of the amination product **8** in 80% yield (Scheme 3b). Substitution of the bromide using 2-mercaptobenzothiazole gave the corresponding thioether **9** in 73% yield. The cyclization reaction was performed at 110 °C with benzothioamide and proceeded smoothly to deliver compound **10** in 55% yield.[7]



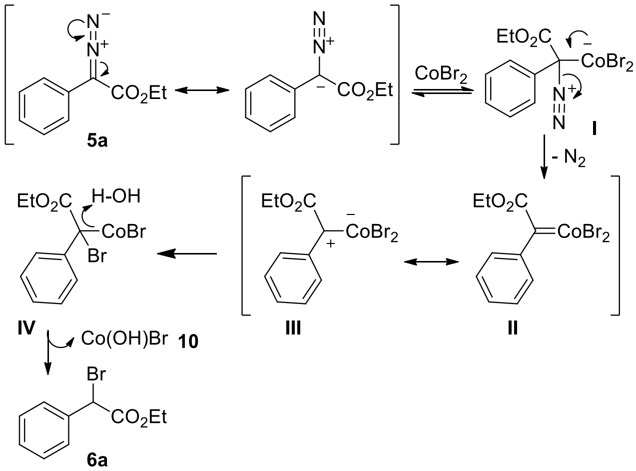
Scheme 3. Gram-scale synthesis and synthetic transformations



Scheme 4. Control experiment

Further insight into the bromination reaction came via the control experiments (Scheme 4). The reaction products are rather complicated, and the formation of a small amount of product **6a** might be attributed to the existence of trace amount of H_2O (Eq. a). When D_2O was added to the reaction system, product **6a** was deuterated with a yield percentage of 91% based on ^{1}H NMR analysis (Eq. b). These results revealed that the crystal water of the cobalt bromide salts participated in the proton shuttle process. Additionally, the reaction proceeded smoothly in basic conditions (Na_2CO_3 or Et_3N), which indicated that the transformation did not occur through the HBr pathway from $CoBr_2{\cdot}6H_2O$ with heating (Eq. c).

Building on the information gathered from the control experiments, a plausible mechanism was proposed (Scheme 5). Nowadays, cobalt carbenes are important reaction intermediates or catalysts for many organic reactions.[8] Typically, the process is initiated by the generation of intermediate **I** *in situ* from the diazo ester **5a**, leading to complete conversion to the highly active cobalt carbenoid **II** via the loss of nitrogen under thermal conditions. Nucleophilic attack of the carbocation of intermediate **III** by the bromine atom gives intermediate **IV**. At the same time, the proton from the crystal water is trapped to afford the corresponding brominated *α*-phenylacetate **6a.** The cobalt species **10** is released, which then regenerates similar cobalt carbenes for the final transformation step.



Scheme 5. Proposed reaction mechanism

In summary, we have developed a novel process for the cobalt-mediated bromination of *α*-diazo phenylacetate derivatives using cobalt (II) bromide. Compared to the strong acidity required during reactions mediated by hydrogen bromide, this new method offers the advantage of being feasible, practical, and rapid. This reaction is also compatible with a wide range of substrates, has excellent functional group tolerance, and affords good to excellent yields, thus providing facile and useful access to a variety of brominated *α*-phenylacetate derivatives. More importantly, the synthetic potential of this novel method is documented through a series of valuable follow-up transformations. Further efforts toward developing viable routes for the iodination and chlorination of diazo compounds are currently underway.

Experimental Section

General procedure for the bromination of *α*-diazo phenylacetate derivatives

To a stirred solution of the respective *α*-diazo phenylacetate derivative (0.5 mmol) in 1,4-dioxane (1 mL) was added $CoBr_2{\cdot}6H_2O$ (0.3 mmol). The resulting solution was stirred at 100 °C under N_2 atmosphere. After completion, the resulting mixture was filtered, and the solvent was removed under vacuum. The resulting crude product was purified using column chromatography (silica gel, petroleum ether/ethyl acetate = 40:1) to afford the corresponding brominated *α*-phenylacetate derivative.

Acknowledgments

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COMMUNICATION

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