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Fast microwave promoted palladium-catalyzed synthesis of phthalides from bromobenzyl alcohols utilizing DMF and $Mo(CO)_6$ as carbon monoxide sources

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Abstract—A fast method utilizing in situ generated CO for the synthesis of phthalides has been developed. DMF and $Mo(CO)_6$ were applied as two alternative CO-sources in these microwave promoted carbonylation–lactone formation reactions. $Mo(CO)_6$ was found to be the more generally applicable CO-source and provided phthalides as well as dihydroisocoumarin, dihydroisoindone, and phthalimide from the corresponding aryl bromide via an efficient CO insertion within a 1 h reaction time.

Phthalides (3*H*-isobenzofuran-1-one) are commonly found in many naturally occurring substances,[1–6] as well as some of their synthetically related compounds and exhibit a broad spectrum of biological activities, for example, noscapine, bicuculline.[7] Furthermore, phthalides are versatile starting materials for the synthesis of a variety of structures, including key intermediates in the synthesis of functionalized naphthalenes and anthracenes, which in turn are used as synthons for tricyclic and tetracyclic linear aromatic natural products.[8–13]

Due to their importance, several methods have been developed for the synthesis of phthalides.[14–17] Classical methods for the preparation of phthalides rely on the chloromethylation of benzoic acids, which unfortunately often result in low yields and are not suitable for the regioselective preparation of substituted phthalides.[18–20] Alternatively, the reduction of phthalic anhydrides or the oxidation of diols have been developed as useful approaches to phthalides, although the regioselectivity of the product via these methods is frequently a problem.[21–23] More recently, palladium-catalyzed carbonylation reactions of *ortho*-halobenzyl alcohols have been reported as a convenient route for the synthesis of phthalides with CO gas as the carbonylation source.[24–28] This synthetic approach has also been successfully combined with supercritical CO_2 as solvent.[29]

Today, the trend in industrial medicinal chemistry is to move toward high-throughput chemistry, employing small reaction scales and short reaction times.[30–32] In this context, microwave heating has emerged as an attractive energy source for accelerated metal-catalyzed transformations and has proven powerful in many different applications.[33] Carbon monoxide is an important building block but the somewhat troublesome gas handling procedure and the toxicity of carbon monoxide limit the use of carbonylation reactions for the small-scale synthesis of compound libraries.[32,30,34]

Recent reports from our laboratory describe a fast microwave promoted palladium-catalyzed carbonylation protocol employing in situ generated carbon monoxide from solid molybdenum hexacarbonyl ($Mo(CO)_6$)[35–37] or liquid dimethylformamide[38] (DMF) and formamide.[39] In light of the synthetic usefulness of phthalides we wanted to explore the use of these sources of carbon monoxide for the formation of this heterocyclic scaffold.

We selected (2-bromophenyl)methanol as the model substrate for a series of optimization experiments (Scheme 1). Different palladium sources, ligands,

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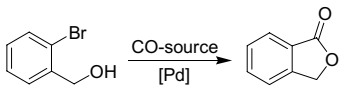


Scheme 1.

temperatures, and reaction times were examined and controlled microwave heating in sealed borosilicate vessels was employed. Initially, DMF was explored as the in situ CO generating source. The results are summarized in Table 1. As a starting point, we utilized the conditions used previously for formation of amides, that is, $Pd(OAc)_2$ (5 mol%), dppf (5 mol%), KO*t*-Bu (1 equiv), and imidazole (1 equiv) in DMF (190 °C, 15 min).[38] Unfortunately, these conditions were not ideal with a benzyl hydroxyl group as nucleophile and no phthalide product was detected in the reaction mixture. The major side product was the debrominated benzyl alcohol and not the expected dimethyl amide, derived from the dimethylamine formed in the decomposition of DMF. The temperature was therefore lowered to 170 °C and the sample was heated for 15 min. At this temperature, the phthalide could be detected but the starting bromide was not fully consumed. Prolonging the time to one hour gave full conversion of the starting material and the product was isolated although only in 8% yield (entry 1). Different ligands were evaluated to optimize the reaction further. The best result was obtained with P(*o*-Tol)$_3$ at 170 °C, which gave an isolated yield of 45%. Increasing or decreasing the reaction temperature resulted in a reduced yield of the phthalide. Although, an improved yield could be obtained with P(*o*-Tol)$_3$ as ligand, the major side product was still the debrominated benzyl alcohol. In order to minimize formation of this side product, the reaction was performed under dry conditions. However, the competing debromination reaction was not suppressed and the yield of the phthalides could not be improved further with this carbonylation method. We therefore decided to investigate $Mo(CO)_6$ as an alternative carbon monoxide source.

The solid CO-source, $Mo(CO)_6$ has previously been proved to give noncyclic esters in good yields.[36] In these series palladium on charcoal was used as the catalyst with aryl iodides as the substrate, and the palladacycle was used as the palladium source with the aryl bromides. We wanted to explore aryl bromides and therefore the palladacycle and other palladium sources were evaluated. The results are summarized in Table 2. Different catalytic systems were examined at a reaction temperature of 180 °C with 1,4-dioxane as solvent. After a reaction time of 30 min most of the catalytic systems used gave full conversion, except for P(*o*-Tol)$_3$ (entry 3). The best result was obtained with $Pd(OAc)_2$ and dppf resulting in 88% of the desired phthalide (entry 5). Increasing the temperature to 190 °C did not improve the isolated yield of the product and full conversion of the starting material was not achieved when the temperature was lowered to 160 °C (entries 6–7).

Table 1. Examination of different ligands in the carbonylation–lactone formation reaction with DMF as CO-source[a]

Entry	Pd-source	Ligand	Temperature (°C)	Isolated yield (%)
1	$Pd(OAc)_2$	dppf	170	8
2	$Pd(OAc)_2$	Binap	170	8
3	$Pd(OAc)_2$	P(*c*-Hex)$_3$	170	25
4	$Pd(OAc)_2$	P(*o*-Tol)$_3$	170	45
5	$Pd(OAc)_2$	P(*o*-Tol)$_3$	150	Trace
6	$Pd(OAc)_2$	P(*o*-Tol)$_3$	180	18

[a] Reaction time 1 h.

Table 2. Examination of different palladium sources and ligands in the carbonylation–lactone formation reaction with $MoCO_6$ as CO-source[a]

Entry	Pd-source	Ligand	Temperature (°C)	Isolated yield (%)
1	Palladacycle		180	77
2	$Pd(PPh_3)_4$		180	79
3	$Pd(OAc)_2$	P(*o*-Tol)$_3$	180	62[b]
4	$Pd(OAc)_2$	—	180	Trace
5	$Pd(OAc)_2$	dppf	180	88[c]
6	$Pd(OAc)_2$	dppf	190	87
7	$Pd(OAc)_2$	dppf	160	70[b]

[a] Reaction time 30 min.

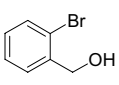
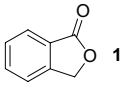
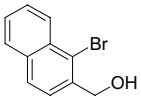
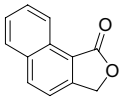
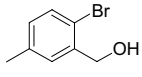
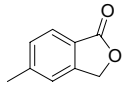
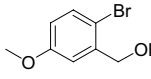
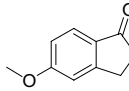
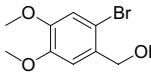
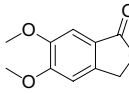
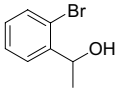
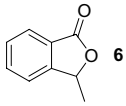
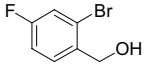
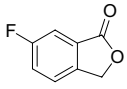
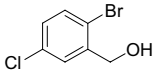
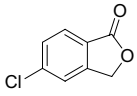
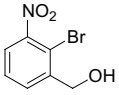
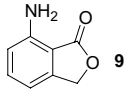
[b] Full conversion was not achieved during irradiation.

[c] Literature data of a similar reaction with 2-iodophenylmethanol as the reagent gave the same product in 76% yield after 18 h at 5 atm $CO_{(g)}$.[29]

To determine the effect of substituents on the phenyl ring a series of electron-rich and electron-poor bromobenzyl alcohols were evaluated in the reaction. The preparative results are summarized in Table 3. The electron-rich bromobenzyl alcohols (entries 2–4) all gave good yields of the corresponding phthalides. However, in the case of 2-bromo-4,5-dimethoxyphenylmethanol the solubility of the starting material in 1,4-dioxane was very low and consequently the isolated yield was only 27%. By changing the solvent to DMF the yield was improved but unfortunately the competing dehydroxylation reaction was more pronounced and the product could only be isolated in 52% yield (entry 5). The reaction of the secondary alcohol gave a good yield of the 3-methyl substituted phthalide (entry 6) but slightly lower than that of the primary alcohol. Both of the halogen substituted compounds provided good yields, although the chloride-encompassing compound had to be treated at a lower temperature to suppress the concomitant dehalogenation of the product (entry 8). The compound containing the nitro group was not a good substrate for the phthalide formation reaction. Many side products were produced due to simultaneous CO reduction of the nitro group. Nevertheless, the aniline phthalide compound could be isolated from the reaction mixture in a 10% yield.

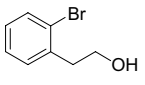
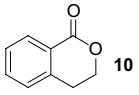
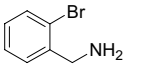
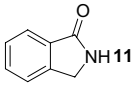
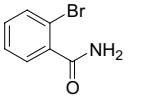
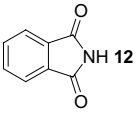
This carbonylation–cyclization method can also be applied in the synthesis of other important naturally occurring scaffolds, that is dihydroisocoumarin, dihydroisoindone, and phthalimide (Table 4). 2-(2-Bromophenyl)ethanol gave the dihydroisocoumarin in 74% yield (entry 1) after 1 h of microwave irradiation at

Table 3. Rapid palladium-catalyzed carbonylation–lactonization of bromobenzyl alcohols using $Mo(CO)_6$ as the CO source[a]

Entry	Bromide	Product	Isolated yield (%)
1		 **1**	88
2		 **2**	92
3		 **3**	90
4		 **4**	84
5		 **5**	52[b]
6		 **6**	75
7		 **7**	77
8		 **8**	76[c]
9		 **9**	10

[a] Reaction conditions: 2-bromo-aryl alcohol (1.0 mmol), $Mo(CO)_6$ (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), dppf (0.05 mmol), DMAP (2.0 mmol), DIEA (2.0 mmol), and dioxane (1 mL); 30 min, 180 °C.
[b] DMF as solvent, reaction time 1 h.
[c] Reaction temperature 150 °C.

Table 4. Rapid palladium-catalyzed carbonylation–cyclization reactions of bromoaryls using $Mo(CO)_6$ as the CO-source[a]

Entry	Bromide	Product	Isolated yield (%)
1		 **10**	74[b]
2		 **11**	72[c]
3		 **12**	70[d]

[a] Reaction conditions: Aryl bromide (1.0 mmol), $Mo(CO)_6$ (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), dppf (0.05 mmol), DMAP (2.0 mmol), DIEA (2.0 mmol), and dioxane (1 mL).
[b] Reaction time 1 h (180 °C).
[c] Reaction temperature 160 °C (30 min).
[d] Reaction temperature 150 °C (30 min).

180 °C. With the more nucleophilic 2-bromobenzylamine, the temperature had to be lowered to 160 °C to permit isolation of the dihydroisoindone in a good yield (entry 2). This was also the case for the phthalimide, which required irradiation at 150 °C and was isolated in 70% yield.

In summary, a fast method utilizing in situ generated CO for the synthesis of phthalides has been developed. Heat and base decomposed DMF has been used as a liquid carbon monoxide source. This procedure was found not to be optimal due to competing debromination of the starting material. $Mo(CO)_6$ was, on the other hand, an excellent and more generally applicable CO-source in these carbonylation–lactonization reactions. Under the present conditions, $Mo(CO)_6$ gave phthalides as well as dihydroisocoumarin, dihydroisoindone, and phthalimide from aryl bromide precursors within a one hour reaction time. We envisage that these reaction conditions could be applied to parallel synthesis of these synthetically important structures in the future.

General procedure: A process vial was charged with 2-bromobenzyl alcohol (1.0 mmol), $Mo(CO)_6$ (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), 1,1′-bis(diphenylphosphino)ferrocene (dppf) (0.05 mmol), DMAP (2.0 mmol), DIEA (2.0 mmol), and dioxane (1 mL). The reaction mixture was flushed with nitrogen and the cap was tightened thoroughly. The vessel was exposed to microwave heating for 30–60 min. The reaction tube was thereafter cooled to room temperature and the mixture was extracted with ethyl acetate. The organic layer was washed with water and brine, dried over potassium carbonate, and the solvent was removed under reduced pressure. The products were purified on silica gel.[40–51]

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