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Report

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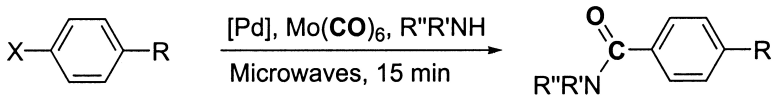

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In Situ Generation of Carbon Monoxide from Solid Molybdenum Hexacarbonyl. A Convenient and Fast Route to Palladium-Catalyzed Carbonylation Reactions

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Introduction. During the past 10 years, the techniques of high-throughput chemistry have evolved in pharmaceutical industry to meet its demand for new substances with beneficial therapeutic profiles.[1] These modern methodologies focus on an automated handling of a large number of samples rather than on advanced experimental techniques for gas handling and distribution. For applications that require heating in conjunction to gaseous reagents, closed reaction vessels make up the only suitable preparative procedure. In addition, no commercial single-mode microwave synthesizers[2] with the possibility of using reactive gases under pressure are available. The development of fast, reliable, and convenient gaseous protocols for chemistry is therefore important for the chemical development of high-throughput chemistry in general and high-speed microwave-mediated chemistry in particular. We herein report on a new protocol utilizing easily handled molybdenum hexacarbonyl as a condensed source of carbon monoxide for performing carbonylation reactions.[3]

Findings from recent investigations[4] demonstrated that the solid molybdenum hexacarbonyl feasibly could be employed as a precatalyst in microwave (MW) heated enantioselective molybdenum-catalyzed allylic alkylations. Since $[Mo(CO)_6]$ was not especially active itself as a catalyst in the absence of ligands and since high enantiomeric excess was detected in the product after addition of chiral ligands, the active species catalyzing the alkylation must be formed by substitution of one or several carbon monoxide units for the chiral ligands. Thus, carbon monoxide was emitted into the reaction mixture during heating.[5] Inspired by this observation, we began to develop a robust, high-speed protocol for carbonylations by exploiting carbon monoxide in situ liberation.

Results and Discussion. When a mixture of an aryl bromide (**1a**, 1 equiv) or aryl iodide (**1b**, 1 equiv), an amine (1.3 equiv), $[Mo(CO)_6]$ (0.5 equiv), a palladium catalyst (0.074 equiv of Pd), K_2CO_3(aq) as base, and diglyme as solvent is heated under an atmosphere of air in a closed vessel (15 min at 150 °C), amides (**2**) were formed in medium to high yields (65−83% isolated, Table 1, Figure 1, entries 1−16).[6] Under these conditions aliphatic nonhindered primary and secondary amines coupled easily, whereas sterically hindered amines or amines with low nucleophilicity, e.g. anilines, afforded low yields and incomplete conversions. There was no difference in reactivity among electron-deficient, neutral, or electron-rich aryl halides (Table 1). Yields for aryl bromides as starting materials were essentially equal to corresponding yields for aryl iodides. Among the homogeneous catalysts tested with aryl bromides, the most suitable to use was the deep-red 2:1 mixture of BINAP and Herrmann's palladacycle precatalyst[7] dissolved in toluene before addition. Iodides could be coupled with solid Pd/C (or $Pd(OAc)_2$) as catalyst, while bromides required a homogeneous catalyst.

Table 1. Fast Carbonylations According to Figures 1 and 2, Employing the in Situ Carbon Monoxide Generation Protocol

entry, aryl-X	R group	nucleophile	product	yield[a] (%)
1, **1a**	MeO−	*n*-$BuNH_2$	**2a**	70
2, **1a**	Me−	*n*-$BuNH_2$	**2b**	71
3, **1a**	F_3C−	*n*-$BuNH_2$	**2c**	75
4, **1a**	Ac−	*n*-$BuNH_2$	**2d**	77
5, **1a**	MeO−	piperidine	**2e**	65
6, **1a**	Me−	piperidine	**2f**	66
7, **1a**	F_3C−	piperidine	**2g**	74
8, **1a**	Ac−	piperidine	**2h**	83
9, **1b**	MeO−	*n*-$BuNH_2$	**2a**	69
10, **1b**	Me−	*n*-$BuNH_2$	**2b**	72
11, **1b**	F_3C−	*n*-$BuNH_2$	**2c**	78
12, **1b**	Ac−	*n*-$BuNH_2$	**2d**	79
13, **1b**	MeO−	piperidine	**2e**	66
14, **1b**	Me−	piperidine	**2f**	69
15, **1b**	F_3C−	piperidine	**2g**	75
16, **1b**	Ac−	piperidine	**2h**	76
17, **1b**	Me−	water	**3**	87[b]

[a] Average isolated yields from two to three runs (0.23 mmol scale, SmithSynthesizer, >95% by GC/MS). Amides **2** were purified by chromatography. [b] *p*-Methylbenzoic acid. Ethylene glycol was added.

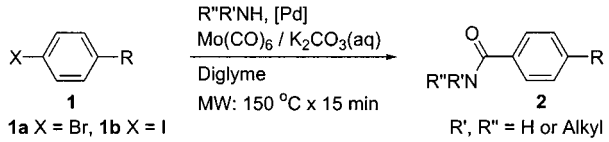

Figure 1. Microwave-assisted palladium-catalyzed amidation utilizing in situ generated carbon monoxide from $[Mo(CO)_6]$.

Thus, for Pd/C-catalyzed amidation of aryl iodides, an extremely simple workup by extraction with 2 M HCl(aq) and diethyl ether resulted in pure **2**. All tested aryl chlorides were inert under the employed conditions (Figure 1).[8,9] Interestingly, the carbonylations could be performed also with classic oil bath heated at 150 °C for 15 min, even in the case of an open vessel (with slight excess of amine, 3.0 equiv), without any loss in yield. This suggests that enough carbon monoxide was dissolved in the reaction mixture to sustain complete conversion. Despite this additional possibility of performing the amidations with classic high-temperature heating, the sealed microwave protocol was adopted because of practical convenience and safety reasons.

The addition of ethylene glycol as cosolvent to the

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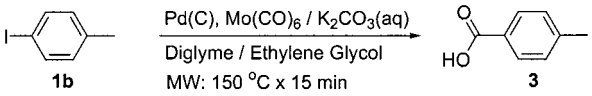

Figure 2. Microwave-assisted palladium-catalyzed generation of *p*-methylbenzoic acid from tolyl iodide utilizing in situ generated carbon monoxide from $[Mo(CO)_6]$.

diglyme/K_2CO_3(aq) mixture resulted in competitive formation of the corresponding benzoic acid derivative **3** instead of amide. The omission of amine made this procedure a rapid tool for synthesizing the corresponding benzoic acid from an aryl iodide (Figure 2, Table 1, entry 17).[10] With ethylene glycol present, a plausible intermediate could be the glycol ester, which subsequently might undergo hydrolysis by the added aqueous base into the corresponding benzoate.

On the basis of cost and documented ease of carbon monoxide liberation, two potential candidates for a solid carbon monoxide source were initially identified: $[Cr(CO)_6]$ and $[Mo(CO)_6]$.[11] Many derivatives thereof might be of use, but the costs of these are much too high compared to the cost of inexpensive binary compounds. $[Ni(CO)_4]$, theoretically a very potent carbon monoxide liberating agent, has a low boiling point and is documented to be extremely toxic.[12] Other interesting metal carbonyls, like $[Fe(CO)_5]$ and $[Co_2(CO)_8]$, did not work satisfactorily in the investigated carbonylation reaction.

Successful and reproducible carbonylations were generally dependent on two parameters: temperature and solvent. According to textbooks,[5] when thermal liberation of carbon monoxide begins for $[Cr(CO)_6]$ and $[Mo(CO)_6]$, the temperatures are 130 and 150 °C, respectively. $[Cr(CO)_6]$ demonstrated a profound tendency to undergo sublimation at these temperatures, forming clutches of a nonliberating substance in nonheated zones at the top of the reaction vial. Thus, preferentially, $[Mo(CO)_6]$ was used as a carbon monoxide source. Unless restricted by the studied organic transformation, the reaction temperature controlled the rate of formation of the carbon monoxide. Reactions at 150 °C demonstrated a smooth rate of liberation, while carbon monoxide was liberated instantaneously at 210 °C (see Supporting Information).

The employment of pure DME or other nonpolar solvents (e.g., THF, 1,4-dioxane, toluene) afforded precipitation of the solid molybdenum metal on the glass wall of the reaction vessel. This resulted in an extreme microwave absorption at that spot and thermal cracking of the Pyrex.[13] Reproducibility was clearly unsatisfactory. Addition of toluene improved reproducibility, perhaps because of coordination of the aryl ring to molybdenum. Still, thermal breakdown of the Pyrex vessel was observed in many cases. After patient elaboration, a combination of diglyme and 4 M K_2CO_3(aq) resulted in a convenient protocol for carbonylations without cracking or overpressurization (Table 1).

The important role of palladium-catalyzed coupling reactions in organic and medicinal chemistry has encouraged our development of a carbonylative coupling method suitable for fast applications. The presented methodology has overcome the trouble of using gaseous carbon monoxide in carbonylations by applying a condensed precursor (a solid-phase reagent), which upon perturbation by heat, liberates enough carbon monoxide in situ for the reaction to take place. Additional work will be required to ascertain the generality of $[Mo(CO)_6]$ as a carbon monoxide releasing solid-phase reagent in high-throughput chemistry.

General Microwave Procedure for the Synthesis of Amides 2. $[Mo(CO)_6]$ (30.0 mg, 0.114 mmol) and 1.375 mL of a fresh toluene solution of palladacycle (8.0 mg, 8.5 μmol) and BINAP (14.0 mg, 22.0 μmol) were charged into a Smith process vial (a microwave tube). A Teflon coated stirring bar was added. By use of the SmithSynthesizer, 0.200 mL of 4.0 M K_2CO_3(aq), 1.00 mL of diglyme, 0.290 mmol of amine, and aryl halide (0.229 mmol, 0.100 mL of a stock solution of 4.59 mmol of aryl halide in 2.00 mL of diglyme) were dispensed into the microwave tube. The tube was sealed (Crymper seal), and the mixture was heated by microwaves at 150 °C for 15 min. The mixture turned black during irradiation. After cooling, the reaction mixture was filtrated and concentrated at reduced pressure. The amide **2** was isolated by flash chromatography. Instead of the palladacycle and BINAP combination, corresponding amounts of 10% Pd/C (18.1 mg) were used with aryl iodides. $Pd(OAc)_2$ (3.8 mg) performed equally well with aryl iodides.

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Supporting Information Available. Experimental procedures and analytical data for the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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