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ARTICLE TYPE

A Convenient Palladium-Catalyzed Carbonylative Synthesis of 4(3*H*)-Quinazolinones from 2-Bromoformanilides and Organo nitros with $Mo(CO)_6$ as a Multiple Promoter

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A novel and convenient procedure for the synthesis of quinazolinones has been developed. By using 2-bromoformanilides and organo nitros as substrates, $Mo(CO)_6$ as multiple promoter, the desired products were isolated in moderate to excellent yields in the presence of palladium catalyst. Here, $Mo(CO)_6$ was not only a CO source, but also nitro compounds reducing reagent and cyclization promoter.

Nitrogen-containing heterocycles are widely distributed in nature and are essential to life, playing a vital role in the metabolism of all living cells. Among these, 4(3*H*)-quinazolinones represent one of the most prevalent compounds found in natural products and biologically active pharmaceuticals (Figure 1).[1] They are now known to have a wide range of useful biological properties, e.g., anticancer, antiviral, anti-inflammatory, anti-microbial cholineesterase inhibitor, antifolate, antitumor, protein kinase inhibitor and many others.[2] In view of their importance, a number of methods for 4(3*H*)-quinazolinone preparation have been developed. These routes, however, mainly rely on using anthranilic acid or its derivatives as the starting materials, and generally suffer from low yields and multistep reactions.[3] The search for new methodologies to synthesize this class of compounds is a research field of undoubted current attention.

Palladium-catalyzed carbonylative transformation has already become a unique, powerful, and versatile tool for the synthesis of carbonyl containing compounds.[4] In contrast to the traditional use of carboxylic acids to form nucleophile-acyl bonds, aryl halide carbonylation generates these same products with palladium catalysts and CO. Regrettably, the high toxicity and the cumbersome handling of CO gas severely limit the usefulness of this transformation in drug discovery and other small-scale applications. Therefore, solid reagents that can release CO in a controlled manner, has gained considerable interest over the past decades. Among them, $Mo(CO)_6$ has emerged as an ideal candidate and has been previously demonstrated in a wide range of carbonylative reactions.[5] However, to date, the application of $Mo(CO)_6$ as the CO supplier for the synthesis of carbonyl containing heterocycles is rarely exploited.

Regarding the nitrogen sources, nitro compounds are attractive due to their low cost and wide availability.[6] In industry, they are used as the the major raw materials for the synthesis of a wide range *N*-containing compounds.[7] But compared to the impressive progress being made in the palladium-catalyzed aminocarbonylation (a key step in the *N*-containing heterocycles synthesis) with amines as starting materials, there are scarcely available reports dealing with the direct use of organo nitros for such transformations. This is not surprising as the selective reduction of the nitro group in the presence of other sensitive competing functionalities is still a challenging problem.[8] Moreover, the compatibility between the conditions of nitro reduction and aminocarbonylation is generally hard to be achieved. To address these critical issues, we wish to report here our discovery on palladium-catalyzed carbonylative synthesis of quinazolinones. In this new procedure, nitro compounds (aromatic and aliphatic) and 2-bromoformanilides were applied as the substrates and $Mo(CO)_6$ as a multirole reactant, the desired quinazolinones were formed in moderate to excellent yields.

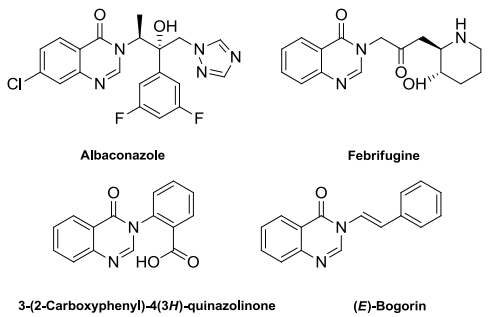
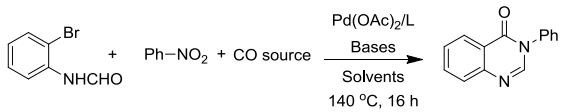


Figure 1. Selected examples of bio-active quinazolinones.

Initially, the direct transformation of nitrobenzene, 2-bromoformanilide and $Mo(CO)_6$ in 1,4-dioxane, using NEt_3 as base was investigated as a model reaction to identify the potential catalysts. Summarizing these experiments, we observed that $Pd(OAc)_2$/$BuPAd_2$ catalyst system gave an impressive conversion of starting materials to afford the desired product 4(3*H*)-quinazolinone in 87% isolated yield at 140 °C within 16 h (Table 1, entry 1). In the absence of a ligand only trace of product is observed (Table 1, entry 2). Other monodentate and bidentate phosphine ligands including PPh_3, PCy_3, Xantphos, DPPB, BINAP and DPPF gave poor yields (Table 1, entries 3-8). Variations of bases and solvents were also examined, but no better yields were resulted, except in the case of using DiPEA as base (Table 1, entries 9-15).

Notably, by using CO gas (either 10 bar, 5 bar, or 2 bar) instead of $Mo(CO)_6$, only 10-13% of the corresponding quinazolinone was produced with low conversion of starting materials (nitrobenzene and 2-bromoformanilide) (Table 1, entries 16-18). This scenario, in conjunction with the significantly retarded yield identified for using other metal carbonyl compounds as the CO sources (Table 1, entries 19, 20), strongly suggests the $Mo(CO)_6$ is not just a solid CO in the title reaction. To clarify this point, we investigated the catalytic performance in the absence of $Pd(OAc)_2$/$BuPAd_2$. Although $Mo(CO)_6$ did not promote the carbonylation step, the complete reduction of nitrobenzene to aniline went smoothly. Taken together, these results indicate that the cooperation between the palladium-catalyzed aminocarbonylation and the $Mo(CO)_6$-mediated reduction is essential to facilitate the desired reaction in a domino fashion. The attempting in temperature decreasing was performed at the last stage, decreased conversion and yield was observed if run the reaction at 120 °C (Table 1, entry 21).

Table 1. Cross-coupling of 2'-bromoformanilide with nitrobenzene under various conditions.[a]

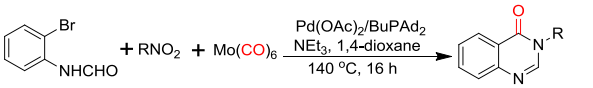


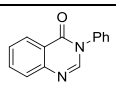
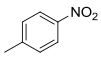
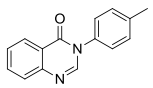
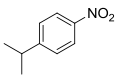
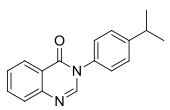
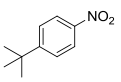
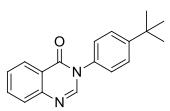
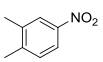
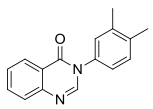
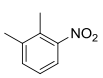
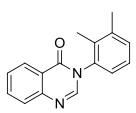
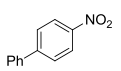
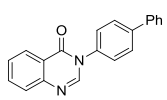
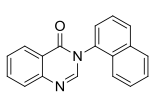
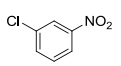
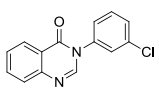
Entry	CO source	Ligands	Bases	Solvents	Yield [%][b]
1	$Mo(CO)_6$	$BuPAd_2$	NEt_3	dioxane	94(87)
2	$Mo(CO)_6$	-	NEt_3	dioxane	trace
3	$Mo(CO)_6$	PPh_3	NEt_3	dioxane	15
4	$Mo(CO)_6$	PCy_3	NEt_3	dioxane	8
5	$Mo(CO)_6$	Xantphos	NEt_3	dioxane	33
6	$Mo(CO)_6$	DPPB	NEt_3	dioxane	20
7	$Mo(CO)_6$	BINAP	NEt_3	dioxane	31
8	$Mo(CO)_6$	DPPF	NEt_3	dioxane	41
9	$Mo(CO)_6$	$BuPAd_2$	K_3PO_4	dioxane	9
10	$Mo(CO)_6$	$BuPAd_2$	Na_2CO_3	dioxane	25
11	$Mo(CO)_6$	$BuPAd_2$	DiPEA	dioxane	91
12	$Mo(CO)_6$	$BuPAd_2$	NEt_3	DMF	11
13	$Mo(CO)_6$	$BuPAd_2$	NEt_3	Mesitylene	41
14	$Mo(CO)_6$	$BuPAd_2$	NEt_3	DMSO	7
15	$Mo(CO)_6$	$BuPAd_2$	NEt_3	THF	34
16	CO (10 bar)	$BuPAd_2$	NEt_3	dioxane	11
17	CO (5 bar)	$BuPAd_2$	NEt_3	dioxane	10
18	CO (2 bar)	$BuPAd_2$	NEt_3	dioxane	13
19	$Co_2(CO)_8$	$BuPAd_2$	NEt_3	dioxane	19
20	$Fe_3(CO)_{12}$	$BuPAd_2$	NEt_3	dioxane	6
21	$Mo(CO)_6$	$BuPAd_2$	NEt_3	dioxane	59[c]

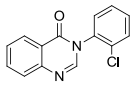
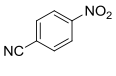
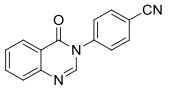
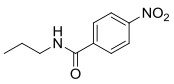
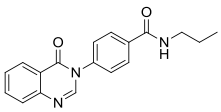
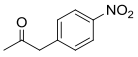
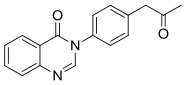
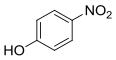
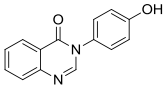
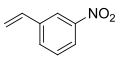
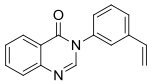
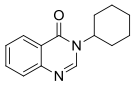
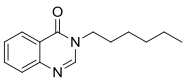
[a] 2'-Bromoformanilide (1 mmol), nitrobenzene (1.1 mmol), CO source (1 mmol), $Pd(OAc)_2$ (2 mol%), ligand (6 mol%), solvent (2 mL), base (2 mmol), N_2 (10 bar). [b] Yields were determined by GC analysis using hexadecane as internal standard (number in parenthesis refer to isolated yield). [c] 120 °C.

Once suitable reaction conditions for the model system were identified, the scope and limitations of this novel procedure were explored (Tables 2 and 3). Several alkyl substituted nitrobenzenes, such as methyl-, isopropyl-, and *tert*-butyl-, were tested at the first stage, 61-97% of the desired quinazolinones were isolated (Table 2, entries 2-6). 1-Nitronaphthalene can be applied as substrate as well and gave the corresponding 3-(naphthalen-1-yl)quinazolin-4(3*H*)-one in 81% isolated yield (Table 2, entry 8). Several electron-withdrawing groups substituted aromatic nitro compounds were tested subsequently. Moderate to excellent yields can be achieved without further optimization (Table 2, entries 9-13). However, this procedure seems quite sensitive to the steric property of the substrates. Detailly, 41% of product was isolated from *ortho*-chloro substituted nitrobenzene while 95% yield was achieved with *meta*-chloro substituted substrate (Tale 2, entries 9, 10). Additionally, groups like hydroxyl and alkene, which are potentially active in palladium-catalyzed coupling reactions, can be tolerated under our conditions and gave the corresponding quinazolinones in 53-59% yields (Table 2, entries 14, 15). More interestingly, in addition to aromatic nitro compounds, aliphatic nitro compounds can be applied as substrates as well (Table 2, entries 16, 17). 53-74% of the desired quinazolinones were isolated from the reaction between 2'-bromoformanilide and the corresponding alkyl nitros.

Table 2. Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2'-bromoformanilide with nitro compounds.[a]



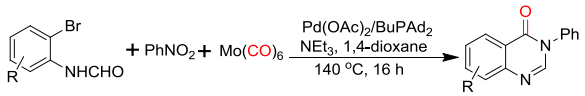
Entry	Nitro compounds	Product	Yield [%][b]
1	Ph−NO2		87
2			79
3			90
4			97
5			61
6			63
7			80
8			81
9			95

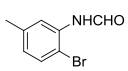
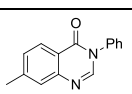
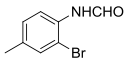
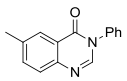
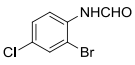
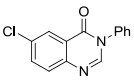
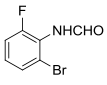
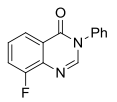
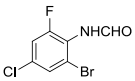
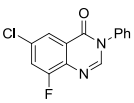
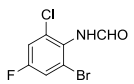
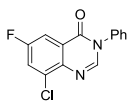
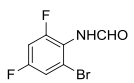
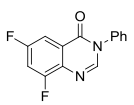
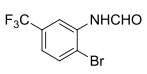
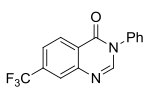
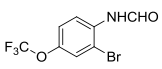
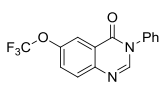
10			41
11			57
12			49
13			71
14			59
15			53
16[c]			53
17[c]			74

[a] 2'-Bromoformanilide (1 mmol), nitro compounds (1.1 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), NEt_3 (2 mmol), N_2 (10 bar). [b] Isolated yield. [c] 2'-Bromoformanilide (0.5 mmol), nitro compounds (0.55 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (4 mol%), ligand (12 mol%), 1,4-dioxane (2 mL), NEt_3 (1 mmol), N_2 (10 bar).

Then we choose nitrobenzene as the model substrate to test with various 2'-bromoformanilides (Table 3). In general, 63-83% of different substituted quinazolinones were isolated. Both electron-donating and withdrawing functional groups are tolerable (Table 3, entries 1-3). Of particular note is the utility of our method for the preparation of fluorinated 4(3*H*)-quinazolinones from 2-bromoformanilides. It is well known that fluorine-containing functional groups can drastically change both the biological and physical properties of organic molecules. We are pleased to find that all six 2-bromoformanilides bearing fluoro, trifluoromethyl and trifluoromethoxyl are suitable substrates for this procedure (Table 3, entries 4-9).

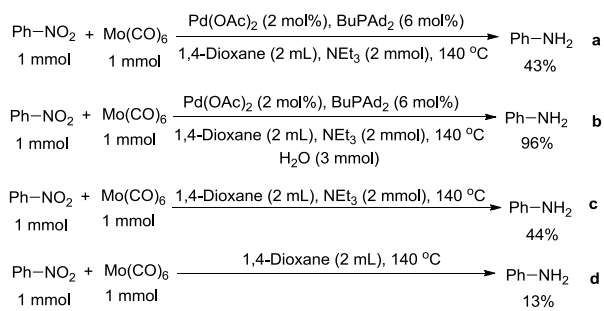
Table 3. Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2'-bromoformanilides with nitrobenzene.[a]



Entry	2'-Bromoformanilides	Product	Yield [%][b]
1			69
2			76
3			70
4			68
5			74
6			74
7			63
8			77
9			83

[a] 2'-Bromoformanilides (1 mmol), nitrobenzene (1.1 mmol), $Mo(CO)_6$ (1 mmol), $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 1,4-dioxane (2 mL), NEt_3 (2 mmol), N_2 (10 bar). [b] Isolated yield.

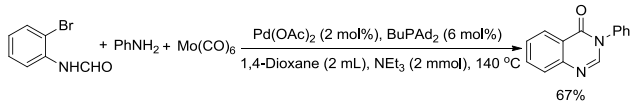
In order to understand the reaction in more detail, several control experiments on nitrobenzene reduction were carried out (Scheme 1). Under our standard reaction conditions, 43% of aniline was produced from nitrobenzene with $Mo(CO)_6$ as the reductant (Scheme 1, **a**); and the yield of aniline can be improved to 96% by adding 3 mmol of water (Scheme 1, **b**). These results indicated the importance of water for nitro reduction, as the solvent was used as received and the already containing water can initiate the reaction. The water will be regenerated after intramolecular condensation; this explains why we do not need adding additional water in our reaction system. The presence of palladium catalyst was found not necessary for nitro reduction while the presence of base was proved to be crucial (Scheme 1, **a** *vs* **c** *vs* **d**).



Scheme 1. Reduction of nitrobenzene with $Mo(CO)_6$.

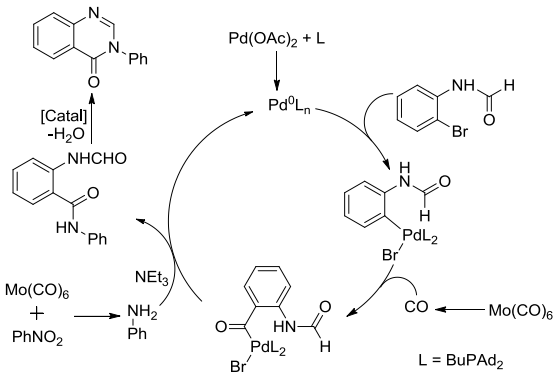
Then aniline was tested in place of nitrobenzene under our typical conditions (Scheme 2). To our delight, 67% of the desired quinazolinone was formed without any optimization. This result

further proven that nitro compounds were reduced into the corresponding amines initially and then get ready for further transformations.



Scheme 2. Palladium-catalyzed, $Mo(CO)_6$-mediated carbonylative coupling of 2'-bromoformanilides with aniline.

Based on the previous mechanistic studies on palladium-catalyzed carbonylations,[9] a most possible reaction pathway is proposed and given in Scheme 3. The reaction started with the oxidative addition of 2'-bromoformanilide to Pd(0) to give the organopalladium intermediate. Then followed by the coordination and insertion of CO which was released from $Mo(CO)_6$, the acylpalladium complex was formed as the key intermediate. At the same time, nitro compound was reduced by $Mo(CO)_6$ under this condition and the formed amine went for nucleophilic attack on the acylpalladium complex. Finally, the eliminated 2-formamido-*N*-phenylbenzamide will gave the final quinazolinone product after intramolecular condensation which promoted by palladium or molybdenum salts as Lewis acids.



Scheme 3. Proposed reaction mechanism.

Conclusions

In conclusion, an interesting and convenient procedure for the synthesis of quinazolinones from 2'-bromoformanilides and nitro compounds has been developed. 26 Examples of the desired products were isolated in 41-97% yields. Not only aromatic nitros but also aliphatic nitros are suitable substrates for this novel transformation. Both electron-donating and withdrawing substitutents are tolerable under our conditions. Notably, $Mo(CO)_6$ plays more than CO source in this system.

General Procedure for the Synthesis of Quinazolinone: A 12 mL vial was charged with $Pd(OAc)_2$ (2 mol%), $BuPAd_2$ (6 mol%), 2'-bromoformanilide (1 mmol), $Mo(CO)_6$ (1 mmol) and a stirring bar. Then, nitro compounds (1.1 mmol), NEt_3 (2 mmol) and 1,4-dioxane (2 mL) were injected by syringe under argon. The vial (or several vials) was placed in an alloy plate, which was transferred into a 300 mL autoclave of the 4560 series from Parr Instruments® under argon atmosphere. After flushing the autoclave three times with N_2, a pressure of 10 bar N_2 was adjusted at ambient temperature. Then, the reaction was performed for 16 h at 140 °C. After the reaction finished, the autoclave was cooled down to room temperature and the pressure was released carefully. The solution was extracted 3-5 times with 2-3 ml of ethyl acetate. After evaporation of the organic solvent the residue was adsorbed on silica gel and the crude product was purified by column chromatography.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

[+] These authors contributed equally to this work.

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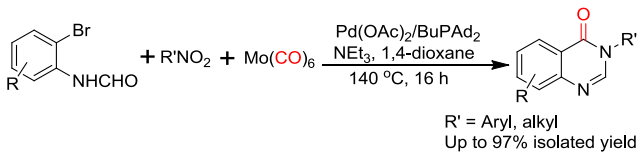

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