Direct Microwave Synthesis of *N*,*N*′-Diacylhydrazines and Boc-Protected Hydrazides by in situ Carbonylations under Air

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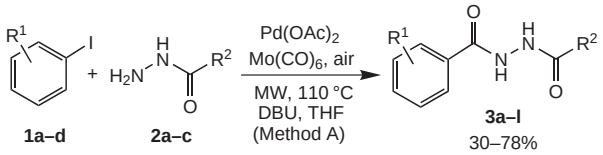
Abstract: Palladium-catalyzed hydrazidocarbonylations of aryl iodides and bromides were performed by controlled microwave irradiation, employing $Mo(CO)_6$ as a convenient CO source. A fluorous phosphine ligand was succesfully used to recycle the catalytic system. Finally, dehydration of a diacylhydrazine to the corresponding 1,3,4-oxadiazole was achieved with $POCl_3$ in a one-pot procedure.

Key words: microwave, carbonylation, molybdenum hexacarbonyl, hydrazide, fluorous

The demands made on innovative drug discovery are changing at an unprecedented pace, and the techniques of organic synthesis and high throughput chemistry must thus continue to evolve. Today, various strategies have been developed to rapidly and cleanly deliver novel lead molecules.[2] Although many high throughput chemistry methods have their roots in efficient separation methods,[3,4] the interest in accelerating organic reactions by high-density microwave heating (MW) has increased over the last few years.[5] In the field of microwave chemistry, the use of different solid phase protocols combines short reaction times with convenient product isolation and purification.[6] The difficulties encountered in performing gaseous reactions under microwave irradiation have further spurred the invention of carbon monoxide releasing solid phase reagents for high-speed carbonylative applications.[7–10]

N,*N*′-Diacylhydrazines are well known starting materials for the preparation of various heterocycles,[11] but this functionality can also be found in different types of protease inhibitors.[12,13] Despite their obvious importance, very few examples of direct carbonylative synthesis of these structures have been reported in the literature.[14,15] By linking our interest of microwave-promoted metal-catalysis[16] and in situ carbonylation with the quest for an efficient synthesis of diacylhydrazines, we hoped to demonstrate several preparative advantages. The possibility of converting aryl halides to protected arylhydrazides by using Boc-hydrazine as the nucleophile was also recognized.

We herein report on a new protocol exploiting easily handled and convenient molybdenum hexacarbonyl as a solid source of carbon monoxide for performing rapid hydrazidocarbonylation reactions with aryl halides. Initially, four aryl iodides **1a**–**d** (0.40 mmol) were allowed to react with hydrazides **2a**–**c** (3 equiv) in dry THF using palladium acetate (10 mol%) as the precatalyst, DBU (3 equiv) as the base and $Mo(CO)_6$ (1 equiv) as the CO-source (Method A). The reactions were performed in sealed vessels under air during 15 minutes of high-density microwave irradiation (Scheme 1). Hydrazidocarbonylation were predominantly achieved at a reaction temperature of 110 °C, generating *N*,*N*′-diacylhydrazine products **3a**–**l** in moderate to good isolated yields (30–71%, Table 1). The yields of the protected hydrazides **3c**,**f**,**i**,**l** were fairly low (30–43%). Importantly, full conversions of **1a**–**c** were always obtained. Analysis of the reaction mixtures by GC- and LC-MS indicated that benzamide and benzonitrile side products were formed in most cases, but only traces of dehalogenated starting material could be detected. We therefore suspected that the moderate yields obtained were a consequence of thermal decomposition of products **3** and/or loss of material in the purification step.



Scheme 1

Attempts to lower the reaction temperature to minimize side-product formation resulted in a need for undesirably long reaction times to reach full conversion.

Decreasing the reaction time, to avoid thermal degradation,[17] led to the observation that most reactions were completed after only five minutes, with the exception of the electron rich **1a**. The shorter reaction times presented in Table 1 also generally improved the isolated yields to 36–78%.

We have previously reported that aryl bromides can be used as substrates in aminocarbonylation reactions with Herrmann's palladacycle[18] as the precatalyst.[8,9] In the present hydrazidocarbonylation application the catalytic activity was further improved by addition of Fu's robust phosphonium salt, $[(t\text{-}Bu)_3PH]BF_4$, designed to liberate free $t\text{-}Bu_3P$ under basic reaction conditions (Method B).[19] Thus, three different reactions starting from aryl bromides **4a**,**b**,**d** were performed with hydrazide **2a** at 130 °C for five minutes, affording slightly reduced isolated yields (43–57%) compared to the corresponding aryl iodides

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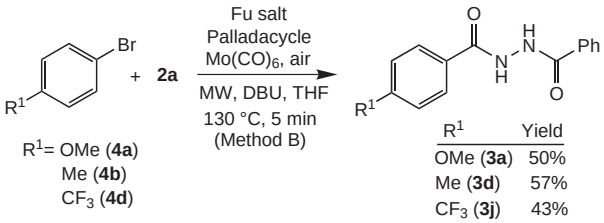
Table 1 Microwave-Heated Hydrazidocarbonylation of Aryl Iodides

Entry	Aryl iodide R^1	Hydrazide R^2	Time (min)	Product	Yield (%)[a]
1	4-MeO (**1a**)	Ph (**2a**)	15	**3a**	62
2	4-MeO	Ph	11	**3a**	65
3	4-MeO	Bn (**2b**)	15	**3b**	53
4	4-MeO	Bn	11	**3b**	58
5	4-MeO	O*t*-Bu (**2c**)	15	**3c**	43
6	4-MeO	O*t*-Bu	13	**3c**	44
7	4-Me (**1b**)	Ph	15	**3d**	71
8	4-Me	Ph	5	**3d**	78
9	4-Me	Bn	15	**3e**	56
10	4-Me	Bn	5	**3e**	59
11	4-Me	O*t*-Bu	15	**3f**	39
12	4-Me	O*t*-Bu	7	**3f**	40
13	2-Me (**1c**)	Ph	15	**3g**	44
14	2-Me	Ph	5	**3g**	53
15	2-Me	Bn	15	**3h**	30
16	2-Me	Bn	5	**3h**	54
17	2-Me	O*t*-Bu	15	**3i**	30
18	2-Me	O*t*-Bu	5	**3i**	36
19	4-CF_3 (**1d**)	Ph	15	**3j**	51
20	4-CF_3	Ph	5	**3j**	57
21	4-CF_3	Bn	15	**3k**	39
22	4-CF_3	Bn	5	**3k**	48
23	4-CF_3	O*t*-Bu	15	**3l**	40
24	4-CF_3	O*t*-Bu	5	**3l**	45

[a] Method A, isolated yield after flash chromatography.

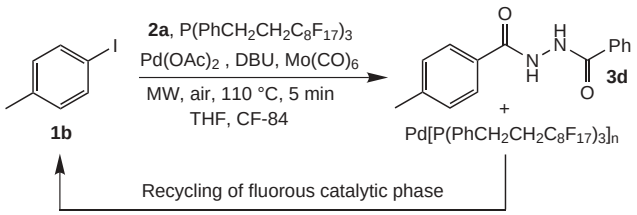
(Scheme 2). The somewhat lower yields were probably a consequence of decomposition of temperature-sensitive diacylhydrazines **3a**,**d**,**j** at the elevated reaction temperature.



Scheme 2

Unfortunately, aryl chlorides were found to be inert under the carbonylation conditions of Method B.

Catalyst recycling and reuse can be of crucial importance in homogeneous reaction protocols employing expensive metal catalysts. With fluorous biphasic catalysis the ability of fluorous solvents to form mono- or biphasic systems with conventional organic solvents, above and below the consolute temperature is utilized to enable efficient recycling of the fluorous catalyst.[20–22] The major advantage with the fluorous/microwave combination is that the consolute temperature can be very rapidly reached by high-density microwave heating, enabling a catalytic reaction under truly homogeneous conditions.[23] Subsequently, the biphasic catalyst separation can be accelerated with the very efficient air-jet cooling system commonly built into modern microwave synthesizers. Thus, within this hydrazidocarbonylation project it was decided to investigate a commercially available fluorous version of triphenyl phosphine {*tris*[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]phosphine} (**5**) in an organic/fluorous biphasic system.



Scheme 3

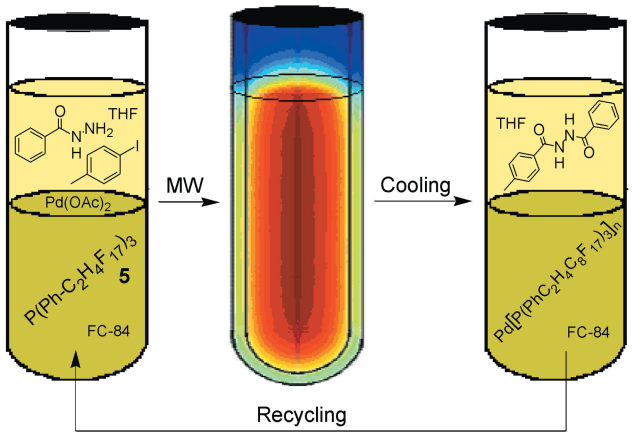


Figure 1 Illustration of fluorous biphasic catalysis before, during and after high-density microwave irradiation.

The degree to which the catalytic fluorous layer could be recycled was studied using 4-iodotoluene (**1b**) and benzhydrazide (**2a**) as reactants, essentially employing identical microwave conditions as with the organic parent reaction (Table 1, entry 8) but also including ligand **5** and the perfluorinated solvent FC-84 (Scheme 3). After each heating/cooling cycle (Figure 1), the organic layer was separated and the product isolated. Thereafter charging a

reaction vial with the fluorous catalytic media and fresh **1b**, **2a**, $Mo(CO)_6$, DBU and THF, we were able to achieve full conversion of **1b** and good isolated yields of **3d** (64–79%, Figure 2). This multiple carbonylation protocol may represent the first example of recycling of a fluorous metal catalyst in a microwave heated biphasic reaction system.[24] Using the same procedure but omitting the fluorous phosphine ligand **5** yielded only traces of product **3d** after the first recycling (second heating) of the reaction cocktail.

Finally, we confirmed that the hydrazidocarbonylation method could be conveniently employed for a one-pot, two-step generation of an 1,3,4-oxadiazole **6**. The cyclization/dehydration of intermediate **3j** was performed with $POCl_3$ (Scheme 4).[14,15] The increased yield of **6** in this one-pot, two-step procedure, compared to the 43% yield of pure diacylhydrazine **3j** (Scheme 2) indicates the problems in purifying the free *N*,*N*′-diacylhydrazine products by flash chromatography.

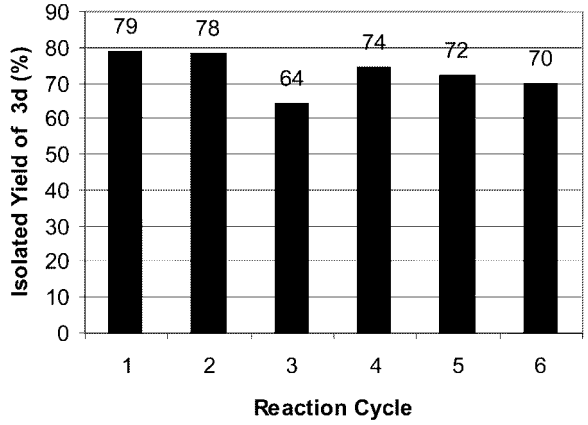
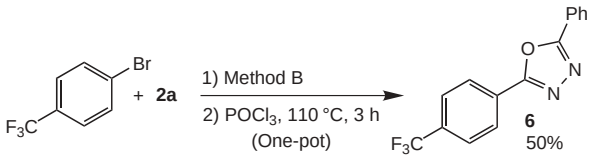


Figure 2 Recyclability of the fluorous catalyst phase. Reactions were performed on 0.40 mmol scale with **5** and THF / FC-84.



Scheme 4

By combining the power of high-density microwave heating with in situ release of carbon monoxide, a novel and direct method for preparation of aryl substituted diacylhydrazines has been demonstrated. The presented hydrazidocarbonylation reactions deliver moderate to good yields and were executed under air in 5–15 minutes. By using a fluorous ligand, the fluorous catalyst was reused five times.

The microwave reactions were performed in a SmithSynthesizer producing controlled irradiation at 2450 MHz with a power of 0–300 W. The reaction temperature was determined using the built-in on-line IR-sensor. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100.5 MHz, respectively. GC-MS was used to analyze the conversion of **1** and **4**. Reaction mixtures and pure products were analyzed using an analytical LC-MS system with a Chromolith Performance RP-18e column (100 × 4.6 mm). The mobile phase was MeCN–H_2O with 0.05% HCOOH (4 mL/min, 0–50% MeCN in H_2O, 8 min gradient) employing UV-detection (214 nm and 254 nm) and a mass selective detector (ESI). Flash column chromatography was performed on Silica gel 60 or 60 RP-18 (0.040-0.063 mm). THF was freshly distilled over Na/benzophenone. All other chemicals were commercially available and used as received.

General Method A. Hydrazidocarbonylation of Aryl Iodides:
A 0.5–2.0 mL process vial was charged with aryl iodide (0.40 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), $Mo(CO)_6$ (0.106 g, 0.40 mmol), hydrazide (1.20 mmol), DBU (0.18 mL, 1.20 mmol) and dry THF (1.00 mL). The vial was immediately capped with a Teflon septum and irradiated with microwaves to 110 °C for 5–15 min. After cooling, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography using 1:1 hexane–EtOAc as the eluent to obtain the pure product (>95% purity by ^{1}H NMR).[25]

General Method B. Hydrazidocarbonylation of Aryl Bromides:
A 0.5–2.0 mL process vial was charged with aryl bromide (0.40 mmol), and Herrman's palladacycle {$Pd_2(OAc)_2[P(o\text{-tol})_3]_2$, 9.4 mg, 0.01 mmol}, Fu's salt {$[(t\text{-Bu})_3PH]BF_4$), 11.6 mg, 0.04 mmol}, $Mo(CO)_6$ (0.106 g, 0.40 mmol), hydrazide (1.20 mmol), DBU (0.18 mL, 1.20 mmol) and dry THF (1.0 mL). The vial was immediately capped with a Teflon septum and irradiated with microwaves to 130 °C for 5 min. After cooling, the reaction mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by reversed phase flash column chromatography (Silica gel 60 RP-18) using a 10–60% MeCN in H_2O (0.05% HCOOH) gradient to obtain the pure product (>95% purity by ^{1}H NMR).[25]

Recycling of the Palladium/Fluorous Liquid Catalyst:
A 2.0–5.0 mL process vial was charged with 4-iodotoluene (0.180 g, 0.40 mmol), $Pd(OAc)_2$ (9.00 mg, 0.04 mmol), $Mo(CO)_6$ (0.106 g, 0.40 mmol), benzhydrazide (0.163 g, 1.20 mmol), DBU (0.18 mL, 1.20 mmol), *tris*[4-(1*H*,1*H*,2*H*,2*H*-perfluorodecyl)phenyl]-phosphine (0.192 g, 0.12 mmol), dry THF (1.0 mL) and CF-84 (1.5 mL). The vial was immediately capped with a teflon septum under air and irradiated with microwaves to 110 °C for 5 min. After cooling, in order to recycle the fluorous catalytic system, the fluorous phase was carefully transferred by Pasteur pipette to the second process vial which was pre-charged with 4-iodotoluene (0.180 g, 0.40 mmol), $Mo(CO)_6$ (0.106 g, 0.40 mmol), benzhydrazide (0.163 g, 1.20 mmol), DBU (0.18 mL, 1.20 mmol) and dry THF (1.00 mL). The second vial was immediately capped with a teflon septum under air and irradiated with microwaves to 110 °C for 5 min. This process was repeated until a total of six reactions had been performed. The flourous phase containing the palladium fluorous-tagged phosphine catalytic system was then left under air for one week (at r.t.) and then used for one more reaction as described above, showing no more than 5% consumption of starting material. In all the cases, the remaining organic parts of the reaction mixtures were filtered and volatile material removed under reduce pressure. The residues were then purified by silica flash column using 1:1 hexane–EtOAc as the eluent to obtain the six batches of *N*-benzoyl-*N*′-(4-methyl)benzoylhydrazine (>95% purity by ^{1}H NMR).

One-Pot Dehydration to 1,3,4-Oxadiazole 6:
The carbonylation step was performed according to procedure B although using 2 mL of a mixture of 10% THF in toluene as a solvent. After cooling, 4 mL of $POCl_3$ was added by syringe through the septum. The needle was left in the septum to allow formed gases to

escape. The mixture was stirred in a heating block at 110 °C for 3 h and then poured onto 100 mL of H_2O and extracted with 3 × 100 mL CH_2Cl_2. The combined organic layers were dried with $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography (0–2% MeOH in $CHCl_3$) to give **6** in 50% yield (57.6 mg).[26]

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(25) ***N*-(4-Methoxy)benzoyl-*N′*-phenylacetylhydrazine (3b).** Colorless solid; mp 153–154 ºC. LC-MS t_R = 4.26 min, *m/z* = 285 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3OD): δ = 3.58 (s, 2 H), 3.80 (s, 3 H), 6.94 (AA′XX′, 2 H), 7.15–7.34 (m, 5 H), 7.79 (AA′XX′, 2 H) ppm. ^{13}C NMR (100.5 MHz, CD_3OD): δ = 43.0, 57.6, 116.5 (2), 127.2, 129.6, 131.2 (2), 131.9 (2), 132.2 (2), 137.9, 166.0, 170.6, 174.9 ppm. Anal. Calcd for $C_{16}H_{16}N_2O_3$ (%): C, 67.59; H, 5.67; N, 9.85. Found: C, 67.40; H, 5.78; N, 9.70.
***N*-(4-Methoxy)benzoyl-*N′*-*tert*-butoxycarbonylhydrazine (3c).** Colorless solid; mp 148–149 °C. LC-MS t_R = 4.58 min, *m/z* = 267 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3CN): δ = 1.44 (s, 9 H), 3.83 (s, 3 H), 6.95 (AA′XX′, 2 H), 7.76 (AA′XX′, 2 H) ppm. ^{13}C NMR (100.5 MHz, CD_3CN): δ = 28.3 (3), 56.1, 81.2, 114.7 (2), 125.8, 130.1 (2), 156.5, 163.5, 167.4 ppm. Anal. Calcd for $C_{13}H_{18}N_2O_4$ (%): C, 58.64; H, 6.81; N, 10.52. Found: C, 58.54; H, 6.72; N, 10.66.
***N*-(4-Methyl)benzoyl-*N′*-phenylacetylhydrazine (3e).** Colorless solid; mp 175–176 °C. LC-MS t_R = 4.71 min, *m/z* = 269 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.39 (s, 2 H), 3.63 (s, 2 H), 7.20–7.39 (m, 5 H), 7.76 (AA′XX′, 2 H) ppm. ^{13}C NMR (100.5 MHz, CD_3OD): δ = 21.5, 41.7, 127.9, 128.7 (2), 129.5 (2), 129.8 (2), 130.1, 130.2 (2), 130.6, 136.2, 144.1, 169.2, 173.1 ppm. Anal. Calcd for $C_{16}H_{16}N_2O_2 + 0.4H_2O$ (%): C, 69.75; H, 6.15; N, 10.17. Found: C, 69.71; H, 6.04; N, 10.11.
***N*-(4-Methyl)benzoyl-*N′*-*tert*-butoxycarbonylhydrazine (3f).** Colorless solid; mp 153–154 °C. LC-MS t_R = 5.05 min, *m/z* = 251 [M + H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 2.38 (s, 3 H), 7.20 (AA′XX′, 2 H), 7.70 AA′XX′, 2 H) ppm. ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 21.7, 28.3 (3), 82.1, 127.4 (2), 129.1, 129.4 (2), 142.9, 155.9, 167.0 ppm. Anal. Calcd for $C_{13}H_{18}N_2O_3$ (%): C, 62.38; H, 7.25; N, 11.19. Found: C, 62.22; H, 7.11; N, 11.06.
***N*-(2-Methyl)benzoyl-*N′*-phenylacetylhydrazine (3h).** Colorless solid; mp 174–175 °C. LC-MS t_R = 4.40 min, *m/z* = 269 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3OD): δ = 2.40 (s, 3 H), 3.60 (s, 2 H), 7.17–7.36 (m, 8 H), 7.43 (dd, *J* = 7.7, 1.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (100.5 MHz, CD_3OD): δ = 18.3, 40.3, 125.4, 126.7, 127.2, 128.2, 128.9, 130.2, 130.5, 134.0, 134.9, 136.4, 165.5, 171.6 ppm. Anal. Calcd for $C_{16}H_{16}N_2O_2 + 0.5H_2O$ (%): C, 69.30; H, 6.18; N, 10.10. Found: C, 69.45; H, 6.19; N, 9.96.
***N*-Phenylacetyl-*N′*-(4-trifluoromethyl)benzoylhydrazine (3k).** Colorless solid; mp 195–196 °C. LC-MS t_R = 5.92 min, *m/z* = 323 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3OD): δ = 3.61 (s, 2 H), 7.15–7.35 (m, 5 H), 7.76 (AA′XX′, 2 H), 7.99 (AA′XX′, 2 H) ppm. Anal. Calcd for $C_{16}H_{13}F_3N_2O_2$ (%): C, 59.63; H, 4.07; N, 8.69. Found: C, 59.41; H, 3.96; N, 8.59.
***N*-*tert*-Butoxycarbonyl-*N′*-(4-trifluoromethyl)-benzoylhydrazine (3l).** Colorless solid; mp 143–144 °C. LC-MS t_R = 6.29 min, *m/z* = 305 [M + H$^+$]. ^{1}H NMR (400 MHz, CD_3OD): δ = 1.45 (s, 9 H), 7.80 (AA′XX′, 2 H), 7.94 (AA′XX′, 2 H) ppm. Anal. Calcd for $C_{13}H_{15}F_3N_2O_3$ (%): C, 51.32; H, 4.97; N, 9.21. Found: C, 51.07; H, 5.06; N, 9.35.
(26) **2-Phenyl-5-(4-trifluoromethyl)phenyl-1,3,4-oxadiazole (6).** Colorless solid; mp 151–152 °C. LC-MS (4 mL/min, 0–70% MeCN in H_2O, 8 min gradient, ESI+) t_R = 6.91 min, *m/z* = 291 [M + H$^+$]. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50–7.60 (m, 3 H), 7.80 (AA′XX′, 2 H), 8.16 (dd, *J* = 7.9 and 1.7 Hz, 2 H), 8.27 (AA′XX′, 2 H). Anal. Calcd for $C_{15}H_9F_3N_2O$ (%): C, 62.07; H, 3.13; N, 9.65. Found: C, 62.08; H, 3.18; N, 9.73.