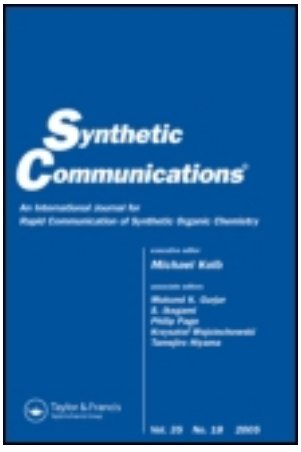
This article was downloaded by: [Universite Laval]
On: 22 February 2013, At: 13:42
Publisher: Taylor & Francis
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Efficient and Convenient Method for the Synthesis of N-Arylhydrazones using a Palladium-Catalyzed Bond-Forming Reaction

Christelle Mauger [a] & Gérard Mignani [a]
[a] Rhodia Recherches, Centre de Recherches de Lyon, Saint-Fons Cedex, France
Version of record first published: 16 Aug 2006.

To cite this article: Christelle Mauger & Gérard Mignani (2006): Efficient and Convenient Method for the Synthesis of N-Arylhydrazones using a Palladium-Catalyzed Bond-Forming Reaction, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 36:8, 1123-1129

To link to this article: http://dx.doi.org/10.1080/00397910500501292

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.tandfonline.com/page/terms-and-conditions

This article may be used for research, teaching, and private study purposes. Any substantial or systematic reproduction, redistribution, reselling, loan, sub-licensing, systematic supply, or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae, and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand, or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Synthetic Communications®, 36: 1123–1129, 2006
Copyright © Taylor & Francis Group, LLC
ISSN 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910500501292

Downloaded by [Universite Laval] at 13:42 22 February 2013

Efficient and Convenient Method for the Synthesis of *N*-Arylhydrazones using a Palladium-Catalyzed Bond-Forming Reaction

Christelle Mauger and Gérard Mignani
Rhodia Recherches, Centre de Recherches de Lyon, Saint-Fons Cedex, France

Abstract: A highly effective, convenient, and reproducible industrial process for palladium-catalyzed carbon–nitrogen cross coupling has been developed and applied on a large scale. Thus various functionalized *N*-arylhydrazones have been easily prepared and well characterized by conventional spectroscopic methods.

Keywords: Aryl chlorides, Buchwald ligands, cross coupling, hydrazone, palladium, phosphines

In the past decade palladium-catalyzed amination, independently discovered by Yang and Buchwald[1] and Baranano et al.,[2] has established itself as a useful tool for the synthesis of arylamines. Our research group was particularly interested in applying this C-N coupling methodology on a large scale for the synthesis of *N*-arylhydrazones, thus leading after hydrolysis to the corresponding *N*-arylhydrazines. Indeed arylhydrazines are extensively used as synthetic building blocks and appear as a subunit in many natural products and substances of relevance for industry.[3] They constitute intermediates to various azaheterocycles or indoles via the Fischer reaction.[4] Thus, they are important to a diverse array of fields, such as agrochemicals, pharmaceuticals, and photography.[5] Herein we describe a practical synthesis of *N*-aryl hydrazones using a palladium-catalyzed carbon–nitrogen bond-forming reaction.

Received in the U.K. April 18, 2005
Address correspondence to Christelle Mauger, Rhodia Recherches, Centre de Recherches de Lyon, 85 rue des Frères Perret, BP62, 69192 Saint-Fons Cedex, France. Tel.: (+33) 4 72 89 63 76; Fax: (+33) 4 72 89 68 94; E-mail: christelle.mauger@eu.rhodia.com

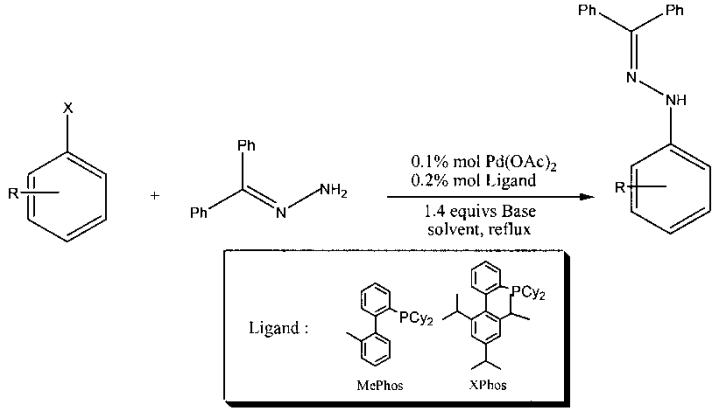
Downloaded by [Universite Laval] at 13:42 22 February 2013

RESULTS

The palladium-catalyzed cross coupling of benzophenone hydrazone with aryl halides has been shown to proceed under a variety of conditions.[6] To find optimum conditions, a series of experiments was performed using 4-chlorotoluene as the model compound.[7] Reactions were carried out under argon or nitrogen and with degassing solvent prior to use. As a base, sodium hydroxide was the best choice in *tert*-amyl alcohol. Palladium acetate and Mephos[8] displayed the best catalytic activities. This system allowed the arylhydrazone to crystallize directly in the solvent without other purification procedures. After having established the optimized coupling reaction conditions, the scope of the reaction and efficiencies of the catalyst were evaluated by investigating the coupling of benzophenone hydrazone with various aryl halides. The results are shown in Table 1.

4-Bromotoluene, 4-chlorotoluene, bromobenzene, 4-bromochlorobenzene, 4-bromoanisole, 2-bromotoluene, 4-bromofluorobenzene, and 2-bromochlorobenzene react very efficiently with benzophenone hydrazone in good yields

Table 1. Palladium-catalyzed coupling of aryl halides with benzophenone hydrazone



Entry	Substrate ArX	Ligand	Base	Temp. (°C)	Solvent	Time (h)	Yield (%)
1	4-bromotoluene	MePhos	NaOH	103	*t*-AmOH	3	92
2	4-chlorotoluene	MePhos	NaOH	103	*t*-AmOH	<3	93
3	bromobenzene	MePhos	NaOH	103	*t*-AmOH	4	95
4	4-bromochlorobenzene	MePhos	NaOH	103	*t*-AmOH	<5	97
5	4-bromoanisole	MePhos	NaOH	103	*t*-AmOH	4	87
6	2-bromotoluene	MePhos	NaOH	103	*t*-AmOH	<4	85
7	4-bromofluorobenzene	MePhos	NaOH	103	*t*-AmOH	4	91
8	2-bromochlorobenzene	MePhos	NaOH	103	*t*-AmOH	4	89
9	4-chlorobenzotrifluoride	XPhos	K_3PO_4	110	Anisole	<6	85

(>85%). As shown in some previous reports, the C-N coupling reaction is more reactive on bromides than chlorides;[9] thus, the reaction on bromochlorobenzene was totally selective at the bromine position. In contrast, in those standard conditions, no coupling reaction occurred with a deactivated substrate such as *para*-chlorobenzotrifluoride (*p*-C1-TFMB). It was subjected to other coupling conditions (solvent, base, catalyst). Thus we found that the choice of ligand was crucial to the successful Pd-catalyzed preparation of *N*-aryl benzophenone hydrazone from deactivated aromatic halides. Pd/XPhos[10] combination is the only catalyst system that allows a complete conversion of *p*-Cl-TFMB into the corresponding *N*-arylhydrazone.

In summary, we have described a C-N palladium-catalyzed coupling reaction to develop a simple, efficient, and general methodology for the synthesis of a variety of structurally diverse hydrazones. Reactions can proceed with low catalyst loadings (as low as 0.05% mol), are reproducible, and have been applied on a large scale (up to 5 kg). The scope of the reaction is broad, as it includes electron-rich and electron-poor aryl chlorides and is compatible with base-sensitive functional groups. This method presents the advantages of mild conditions, easily accessible starting materials, and ease of separation in the treatment. It is a promising method for the industrial development of *N*-arylhydrazones, intermediates to azaheterocycles.

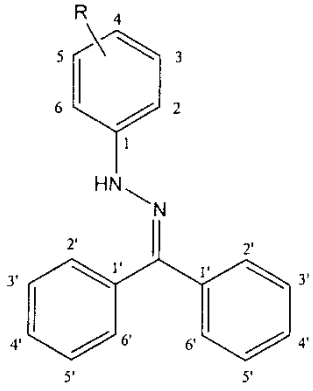
EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded using a Bruker spectrometer operating at **MHz** (^{1}H) and **MHz** (^{13}C). Chemical shifts are given in ppm relative to TMS, with coupling constants (J) in Hz. Melting points were measured in open capillary tubes with a Biichi B-545 melting-point apparatus and are uncorrected. Gas chromatography was carried out using a Varian CP-3800 gas chromatograph equipped with a FID detector and a fused silica capillary column DP-17 (30 m × 0.32 mm × 0.25 mm). All samples were examined under the following temperature gradient: temp. 1, 100 °C (0 min); temp. 2, 300 °C (5 min); rate 30 °C/min; total run time 11.67 min. Conversions were determined by direct integration of the peak areas of the gas chromatograph rather than by constructing calibration curves using standard solutions of each component. GC-MS data were acquired using a HP 5890 series II gas chromatograph using the same temperature gradient as described for GC analysis (Scheme 1).

General Procedure for the Palladium-Catalyzed Coupling Reactions

In a glass reactor equipped with a condenser and a mechanical stirrer, the aryl halide (1 mol) and ground sodium hydroxide (1.4 mol) were charged under

Downloaded by [Universite Laval] at 13:42 22 February 2013



Scheme 1. Structure of the *N*-aryl benzophenone hydrazones.

Downloaded by [Universite Laval] at 13:42 22 February 2013

nitrogen atmosphere in freshly degassed solvent ([ArX] = 1.5M in solvent). The mixture was heated at reflux. Complex catalysis was performed under argon by mixing $Pd(OAc)_2$ (0.001 mol) and ligand (0.002) in degassed solvent for 20 min at room temperature, which were then added into the glass vessel. Benzophenone hydrazone (1 mol) was added in 13 portions in 10-min intervals. Reaction was followed by Raman spectroscopy or GC analysis. When completion was reached, the reaction mixture was cooled to room temperature, and unsoluble salts were quenched with water. Layers were separated and the arylhydrazone crystallized at about 5 °C in the organic layer. The solid was filtered, washed with *tert*-amyl alcohol, and dried at 40 °C (10 mbar). The arylhydrazone was afforded as a solid in a good yield (see Table 1).

Synthesis of *N*-(*p*-Tolyl)-benzophenone Hydrazone[11,12] (1)

In a 16-L glass reactor equipped with a condenser and a mechanical stirrer, and linked by an optic fiber to a Raman spectrometer, 4-chlorotoluene (1.605 kg, 12.675 mol) and ground sodium hydroxide (709.8 g, 17.745 mol) were charged under nitrogen atmosphere in 8 L of freshly degassed *tert*-amyl alcohol. The mixture was heated at reflux. Complex catalysis was preformed under argon by mixing $Pd(OAc)_2$ (1.42 g, 6.3 mmol) and MePhos (4.61 g, 12.7 mmol) in degassed *tert*-amyl alcohol (400 mL) for 20 min at room temperature, which were then added into the glass vessel. Benzophenone hydrazone (2.487 kg, 12.675 mol) was added in 13 portions at 10-min intervals. The reaction was followed by Raman spectroscopy. When the reaction reached completion, the reaction mixture was cooled to room temperature, and unsoluble salts were quenched with water (2 L). Layers were separated, and the arylhydrazone crystallized at about 5 °C in the

organic phase. The solid was filtered, washed with 2.5 L of *tert*-amyl alcohol, and dried at 40 °C (10 mbar). The arylhydrazone was afforded as a pale yellow solid.

Yield: 3.371 kg, 93%, mp 84 °C. ^{1}H NMR ($CDCl_3$) δ: 2.21 (s, 3H, CH_3), 7.01 (s, 2H, C_3H and C_5H), 7.15 (s, 2H, C_2H and C_6H), 7.36 (s, 1H, $C_{4'}H$), 7.53 (s, 1H, NH), 7.59 (s, 2H, $C_{3'}H$ and $C_{5'}H$), 7.66 (s, 2H, $C_{2'}H$ and $C_{6'}H$). ^{13}C NMR ($CDCl_3$) δ: 20.2 (CH_3), 113 (C_2 and C_6), 125.8–129.4 (C_1–$C_{6'}$), 129.2 (C_3 and C_5), 142.2 (C═N), 143 (C_1).

Synthesis of *N*-Phenyl-benzophenone Hydrazone[13] (2)

This compound was prepared from bromobenzene (31.4 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield: 95% (52.2 g), mg 137.8 °C (lit. 136.5–137.5 °C).

^{1}H NMR ($CDCl_3$) δ: 6.85 (s, 1H, C_4H), 7.09 (s, 2H, C_2H and C_6H), 7.25 (s, 2H, C_3H and C_5H), 7.30–7.57 (m, 10H, $C_{1-6'}H$). ^{13}C NMR ($CDCl_3$) δ: 113 (C_2 and C_6), 120.1 (C_4), 129.2 (C_3 and C_5), 126.5–129.7 ($C_{2'}$–$C_{6'}$), 132.8 ($C_{1'}$), 138.4 ($C_{1'}$), 144.2 (C═N), 144.6 (C_1).

Synthesis of *N*-(4-Chloro-phenyl)-benzophenone Hydrazone[12] (3)

This compound was prepared from 4-bromochlorobenzene (38.3 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield: 97% (60 g), mp: 116.9 °C (lit. 121–122 °C).

^{1}H NMR ($CDCl_3$) δ: 6.93 (s, 2H, C_2H and C_6H), 7.11 (s, 2H, C_3H and C_5H), 7.41 (s, 1H, NH), 7.29–7.55 (m, 10H, $C_{1'-6'}H$). ^{13}C NMR ($CDCl_3$) δ: 114 (C_2 and C_6), 124.5 (C_4), 126.5–129.6 ($C_{2'}$–$C_{6'}$), 129.0 (C_3 and C_5), 132.5 ($C_{1'}$), 138.0 ($C_{1'}$), 144.6 (C_1), 144.8 (C═N).

Synthesis of *N*-(4-Methoxyphenyl)-benzophenone Hydrazone[11] (4)

This compound was prepared from 4-bromoanisole (37.4 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield: 87% (37.4 g), mp 118.9 °C.

^{1}H NMR ($CDCl_3$) δ: 3.69 (s, 3H, OCH_3), 6.75 (s, 2H, C_3H and C_5H), 6.96 (s, 2H, C_2H and C_6H), 7.32 (s, 1H, NH), 7.29–7.55 (m, 10H, $C_{1'-6'}H$). ^{13}C NMR ($CDCl_3$) δ: 55.6 (OCH_3), 114.0 (C_2 and C_6), 114.6 (C_3 and C_5), 126.5–129.6 ($C_{2'}$–$C_{6'}$), 132.9 ($C_{1'}$), 138.4 ($C_{1'}$), 138.8 (C_1), 143.3 (C═N), 153.7 (C_4).

Downloaded by [Universite Laval] at 13:42 22 February 2013

Downloaded by [Universite Laval] at 13:42 22 February 2013

Synthesis of *N*-(*o*-Tolyl)-benzophenone Hydrazone[13] (5)

This compound was prepared from 2-bromotoluene (34.2 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield: 85% (48.8 g), mp 104.2 °C (lit. 101–102 °C).

^{1}H NMR ($CDCl_3$) δ: 1.81 (s, 3H, CH_3), 6.74 (s, 1H, C_4H), 6.97 (s, 1H, C_3H), 7.19 (s, 1H, C_5H), 7.66 (s, 1H, C_6H), 7.42 (s, 1H, N_H), 7.30–7.57 (m, 10H, $C_{1'-6'}H$), ^{13}C NMR ($CDCl_3$) δ: 16.4 (CH_3), 112.4 (C_6), 119.6 (C_4), 120.3 (C_2), 128.0 (C_5), 130.2 (C_3), 126.4–129.7 ($C_{2'}$–$C_{6'}$), 132.9 ($C_{1'}$), 138.2 ($C_{1'}$), 142.4 (C_1), 145.1 (C=N).

Synthesis of *N*-(4-Fluorophenyl)-benzophenone Hydrazone (6)

This compound was prepared from 4-bromofluorobenzene (35.01 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield: 91% (52.4 g), mp 95.1 °C.

^{1}H NMR ($CDCl_3$) δ: 6.87 (s, 2H, C_3H and C_5H), 6.93 (s, 2H, C_2H and C_6H), 7.24–7.49 (m, 10H, $C_{1'-6'}H$). ^{13}C NMR ($CDCl_3$) δ: 113.7 (C_3 and C_5), 115.7 (C_2 and C_6), 126.5–129.8 ($C_{2'}$–$C_{6'}$), 132.7 ($C_{1'}$), 138.2 ($C_{1'}$), 141.0 (C_1), 144.2 (C=N), 157.1 (C_4). ^{19}F NMR ($CDCl_3$) δ: −48.9. Microanalysis: calculated (C: 78.6; H: 5.2; N: 9.6); measured (C: 78.4; H: 5.3; N: 9.5).

Synthesis of *N*-(2-Chlorophenyl)-benzophenone Hydrazone[13] (7)

This compound was prepared from 2-bromochlorobenzene (38.3 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in *tert*-amyl alcohol (180 mL). Yield >98% (62 g), mp 153.6 °C.

^{1}H NMR ($CDCl_3$) δ: 6.71 (s, 1H, C_4H), 7.15 (s, 1H, C_3H), 7.19 (s, 1H, C_5H), 7.71 (s, 1H, C_6H), 7.30–7.57 (m, 10H, $C_{1'-6'}H$), 8.03 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 114.0 (C_6), 117.4 (C_2), 119.9 (C_4), 127.8 (C_5), 129.4 (C_3), 136.7–129.7 ($C_{2'}$–$C_{6'}$), 132.6 ($C_{1'}$), 138.0 ($C_{1'}$), 140.5 (C_1), 146.6 (C=N).

Synthesis of *N*-(4-Trifluoromethylphenyl)-benzophenone Hydrazone[12] (8)

This compound was prepared from 4-chlorobenzotrifluoride (36.1 g, 0.2 mol) and benzophenone hydrazone (39.2 g, 0.2 mol) in anisole (134 mL). Yield: 85% (57.8 g), mp 94 °C (lit. 85–86 °C).

^{1}H NMR ($CDCl_3$) δ: 7.07 (s, 2H, C_3H and C_5H), 7.15 (s, 2H, C_2H and C_6H), 7.36 (s, 1H, $C_{4'}H$), 7.53 (s, 1H, NH), 7.59 (s, 2H, $C_{3'}H$ and $C_{5'}H$),

7.66 (s, 2H, $C_{2'}H$ and $C_{6'}H$). ^{13}C NMR ($CDCl_3$) δ: 20.2 (CH_3), 113 (C_2 and C_6), 125.8–129.4 ($C_{1'}$–$C_{6'}$), 129.2 (C_3 and C_5), 142.2 (C=N), 143 (C_1). ^{19}F NMR ($CDCl_3$) δ: 14.4.

REFERENCES

1. Yang, B. H.; Buchwald, S. L. *J. Organomet. Chem.* **1999**, *576*, 125.
2. (a) Baranano, D.; Mann, G.; Hartwig, J. F. *Curr. Org. Chem.* **1997**, *1*, 287; (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.
3. (a) Gilchrist, T. L. *J. Chem. Soc., Perkin Trans 1* **1999**, 2849; (b) Müller, E. *Methoden der Organischen Chemie* **1967**, Houben-Weyl band X12; (c) Robinson, B. *Chem. Rev.* **1963**, *63*, 373; (d) Ishii, H. *Acc Chem Res.* **1981**, *14*, 233; (e) Hughes, D. L. *Org. Prep Proceed. Int.* **1993**, *25*, 607.
4. (a) Robinson, B. *The Fischer Indole Synthesis*; Wiley: Chichester, 1982; (b) Robinson, B. *Chem. Rev.* **1969**, *69*, 227.
5. (a) Negwer, M. *Organic-Chemical Drugs and Their Synonyms: An international survey*, 7th ed.; Akademie Verlag GmbH: Berlin, 1994; (b) Montgomery, J. H. *Agrochemicals Desk Reference: Environmental Data*; Lewis Publishers: Chelsea, MI, 1993; (c) Loutfy, R. O.; Hsiao, C. K.; Kazmaier, P. M. *Photograph. Sci. Eng.* **1983**, *27*, 5; (d) D'Aprano, G.; Leclerc, M.; Zotti, G.; Schiavon, G. *Chem. Mater.* **1995**, *7*, 33; (e) Czarnik, A. W. *Acc. Chem. Res.* **1996**, *29*, 112.
6. Haddad, N.; Salvagno, A.; Busacca, T. *Tetrahedron Lett.* **2004**, *45*, 5935.
7. (a) Mauger, C. C.; Mignani, G. A. *Adv. Synth. Catal.* **2005**, *347* (6), 773; (b) Mauger, C. C.; Mignani, G. A. *Org. Proc. Res. Dev.* **2004**, *8* (6), 1065.
8. Tomori, H.; Fox, J. M.; Buchwald, S. L. Buchwald has proven the high efficiency of MePhos toward the carbon–nitrogen coupling reaction. *J. Org. Chem.* **2000**, *65*, 5334.
9. Littke, A. F.; Fu, G. C. For are centre view dealing with palladium-catalyzed coupling reactions of arylchlorides. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.
10. (a) Buchwald, S. L. *Adv. Synth. Catal.* **2001**, *343*, 789; (b) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653.
11. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *1212* (44), 10251.
12. Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 6621.
13. Kohling, P.; Schmidt, A. M.; Eilbracht, P. *Org. Lett.* **2003**, *5* (18), 3213.

Downloaded by [Universite Laval] at 13:42 22 February 2013