Organic & Biomolecular Chemistry

Accepted Manuscript

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/obc

Journal Name

RSCPublishing

COMMUNICATION

Efficient Palladium-Catalyzed Double Carbonylation of *o*-Dibromobenzenes: Synthesis of Thalidomide

Cite this: DOI: 10.1039/xoxxoooooox

Jianbin Chen,[+] Kishore Natte,[+] Anke Spannenberg, Helfried Neumann, Matthias Beller, and Xiao-Feng Wu*

Received ooth January 2012,
Accepted ooth January 2012

DOI: 10.1039/xoxxoooooox

www.rsc.org/

Abstract. We describe here a convenient and mild, double carbonylation of *o*-dibromobenzene with various 2-amino pyridines and naturally occurring amines providing in good to excellent yield of *N*-substituted phthalimides by using palladium-catalyzed carbonylation procedure. Furthermore, for the first time we have applied our developed synthetic protocol for the synthesis of active biological molecule thalidomide *via* a single step carbonylative cyclization reaction in excellent yield.

Imide derivatives especially phthalimides carrying additional substituents are an important class of compounds with various biological activities such as antimicrobial, anticonvulsant, antihistaminic, anti-inflammatory, antitumor, anxiolytic and hypolipidemic and also they are used predominantly as chiral building blocks in organic synthesis and have numerous applications in dyes, liquid crystals, functional materials and pesticides.[1] Also, the related pyromellitic diimide is an important structure in high-performance polymers like Kapton.

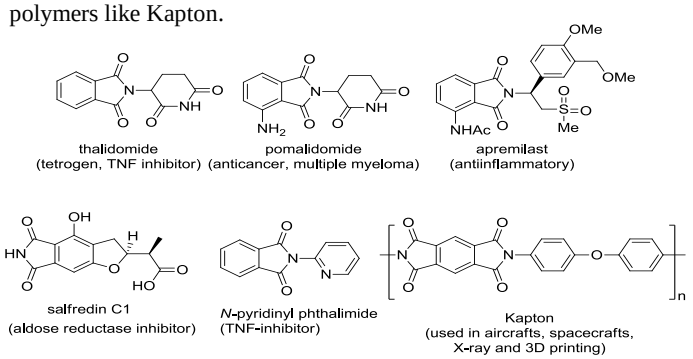


Figure 1. Selected structure of pharmaceutically and polymeric important phthalimide derivatives.

Ever since the pioneering work of Heck and Schoenberg in 1974, palladium-catalyzed carbonylations using CO enabled the synthesis of a variety of carbonyl compounds.[2] Nowadays, these reactions are routinely applied for constructing carbonyl-containing compounds, such as aldehydes, amides, esters, and etc.[3]

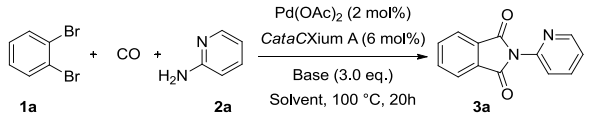
Due to the wide range and applicability of phthalimides and its related derivatives in medicinal chemistry and pharmaceutical industry, their synthesis has been received great attention. Typically, the synthesis of *N*-substituted phthalimides involves the dehydrative condensation of a phthalic acid anhydride with a primary amine and the cyclization of the amic acid in the presence of acidic reagents. However, these reactions require relatively high temperature and long reaction time.[4] Interestingly, carbonylation reactions were applied in the phthalimide preparation as well.[5] Perry and Turner reported a palladium-catalyzed carbonylation of 1,2-diiodoarenes with primary amines under CO pressure (~6.2 bar) at 115 °C. Recently, Cao and Alper reported an interesting Pd-catalyzed carbonylative synthesis of phthalimides under atmospheric pressure of CO in ionic liquids. Bhanage and co-workers have reported an elegant Pd/C as a recyclable catalyst and applied this catalytic species in the carbonylation of *o*-diiodoarenes with primary amines as well.[6] More recently, some of us reported a palladium-catalyzed procedure to obtain *N*-substituted phthalimides with molybdenum hexacarbonyl as carbon monoxide precursor.[7] Nevertheless, the using of 2-aminopyridines as substrates were scarcely reported which can provide *N*-pyridinyl phthalimides as a class of biological active compounds.

On the other hand, as it was said that *N*-substituted phthalimides represent an important class of biologically active molecules. In this regard, thalidomide (see, Figure 1) which was reported to act as a hypnotic/sedative agent but withdrawn from the market because of its teratogenicity.[8] However, even with its teratogenic effects, thalidomide continued to be used clinically. In 1991, Kaplan and co-workers[9] reported thalidomide as an inhibition of the production of TNF. Later in 1995, clinical trials using TNF-α antibodies have shown efficacy in the treatment of rheumatoid arthritis and Crohn's disease confirming the role of TNF-α in these diseases.[10] In 2001, Petit and co-workers reported that phthalimidic containing nitrogen allows a significant inhibition of TNF-α production.[1d,11] Inspiring from these reports and our continuous interest in carbonylations, we describe herein a facile and convenient palladium-catalyzed procedure for the synthesis of *N*-pyridinyl phthalimides. To the best of our knowledge, until now there is no brief report about the carbonylative synthesis of *N*-pyridinyl phthalimides.

As the starting point for the optimization, the reaction of *o*-bromobenzene (**1a**) with 2-aminopyridine (**2a**) and CO in the presence of base and solvent was chosen as a model reaction (Table 1).

Preliminary experiments showed that $Pd(OAc)_2$ and *CataC*Xium A [di(1-adamantyl)-*n*-butylphosphine; $BuPAd_2$] proved to be the optimal catalyst system. A series of experiments were performed to optimize various reaction parameters such as the effects of solvents and bases. The results obtained are summarized in Table 1. As shown in Table 1, 90% of the corresponding *N*-substituted phthalimide was obtained under the optimized reaction conditions (Table 1, entry 10).

Table 1. Optimization of the palladium-catalyzed double carbonylation reaction.[a]



1a 2a 3a

Entry	Base	Solvent	**3a** Yield (%)[b]
1[c]	DBU	DMAc	51
2	DBU	DMAc	65
3	DBU	Toluene	20
4	DBU	Dioxane	5
5	DBU	MeCN	5
6	DBU	THF	5
7	DBU	DMSO	3
8	DiPEA	DMAc	46
9	NEt_3	DMAc	85
10	**NEt_3**	**DMAc (degassed)**	**90**

Reaction conditions: **1a** (1.0 mmol), **2a** (1.1 mmol), base (3.0 mmol), solvent (5 mL), CO (30 bar), time (20 h). [b] GC yield using hexadecane as internal standard. [c] 1.2 mmol of $Mo(CO)_6$ as the CO source.

Having identified our active catalytic system, we tested various amines with *o*-dibromobenzene to afford *N*-substituted phthalimide derivatives (Table 2). Excellent activities were observed with methyl substituted 2-amino pyridines (Table 2, entries 1–4). Remarkably, chloro-substituted amino pyridines can be applied as substrates in this reaction as well and succeeded to provide the desired products in good yields (Table 2, entries 5-6). Noticeably, electron-with-drawing cyano substituted amino pyridine was also obtained in good yield (Table 2, entry 7). In the case of trifluroethyl amine hydrochloride, the reaction worked well and the corresponding product was isolated in excellent yield (Table 2, entry 12).

Excited by the facile synthesis of phthalimide derivatives from *o*-dibromobenzene, various substituted *o*-dibromobenzenes were also screened and generated their corresponding phthalimides in good yields (Table 2, entries 8-11). The product was further confirmed by X-ray analysis (Figure 2).

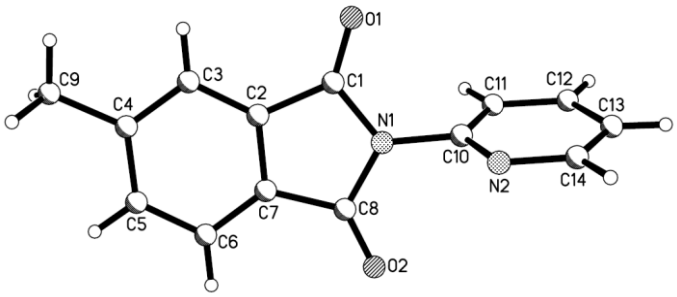
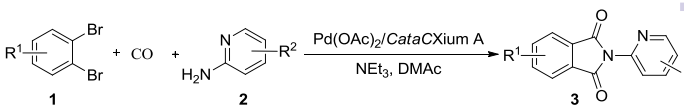


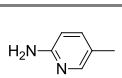
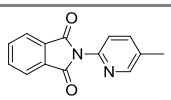
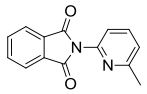
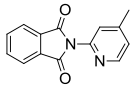
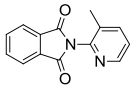
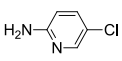
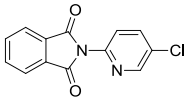
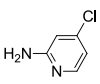
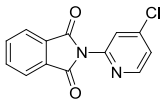
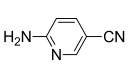
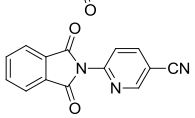
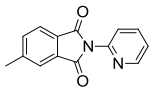
Figure 2. Molecular structure of 5-methyl-2-(pyridin-2-yl)isoindoline-1,3-dione. Displacement ellipsoids correspond to 50% probability.

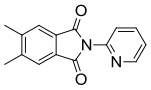
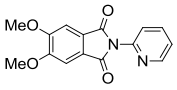
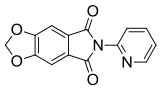
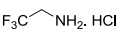
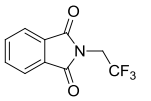
In order to make this procedure useful for synthesis of biological compounds containing phthalimide groups, for the first time we have applied our developed synthetic protocol reaction conditions to synthesise thalidomide which was resulted in excellent yield (87%; Scheme 1). In addition to this, we also made to synthesise various biological *N*-substituted phthalimides from different naturally occurring amines such as tryptamine and tyramine. The reactions were achieved with ease whereby these two naturally occurring amines were quite eligible in providing good to excellent yields of the expected products (Scheme 2).

Table 2. Carbonylative reactions of *o*-dibromobenzenes with amines.[a]

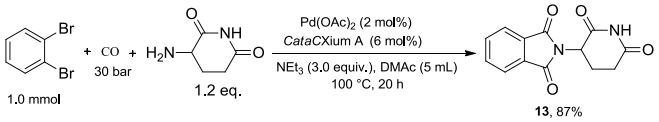


1 2 3

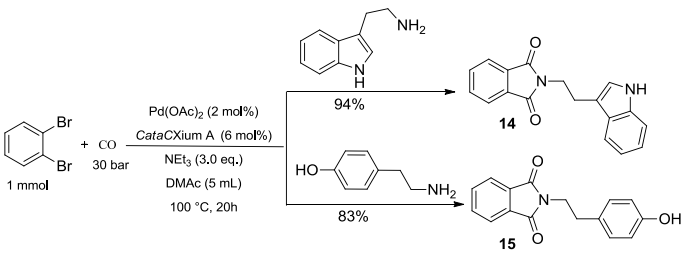
Entry	Amine **2**	Product **3**	Yield[b]
1			84%
2			82%
3			74%
4			83%
5			73%
6			65%
7			67%
8			77%

9			72%
10			61%
11			69%
12			88%[c]

Reaction conditions: *o*-Dibromobenzene (1 mmol), amine (1.1 equiv.), $Pd(OAc)_2$ (2 mol%), *CataC*Xium A (6 mol%), NEt_3 (3 equiv.), 30 bar CO, DMAc (5 mL), 100 °C, 20 h. [b] Isolated yield. [c] 30 h.



Scheme 1. Synthesis of thalidomide.



Scheme 2. Synthesis of phthalimides with naturally occurring amines.

In conclusion, we have demonstrated that *N*-pyridyl phthalimides and its derivatives can be synthesized directly from *o*-dibromobenzenes. A wide range of different amino pyridines and naturally occurring amines as well as a variety of miscellaneous *o*-dibromobenzenes can be applied as substrates, and the corresponding phthalimides were obtained in moderate to excellent yields. This facile and versatile procedure offers to synthesize valuable thalidomide and could also be applied to other drug molecules like pomalidomide, etc.

General information

Reactions were run under an argon/N_2 atmosphere with exclusion of moisture from reagents and autoclaves. All substrates were purchased from Sigma–Aldrich, 3-Aminopiperidine-2, 6-dione from Fluorochem and were used as received. Solvents were dried from molecular sieves and kept under argon. NMR spectra were recorded on the Bruker AV 300 spectrometers. All chemical shifts (δ) are reported in parts per million (ppm) and coupling constants (*J*) in Hz. All chemical shifts are reported relative to tetramethylsilane (δ 0.0 for ^{1}H NMR in DMSO-d_6, $CDCl_3$) and *d*-solvent peaks (δ 77.00 for ^{13}C NMR, chloroform and for DMSO-d_6, δ 40.00), respectively. All measurements were carried out at room temperature unless otherwise stated. Mass spectra were recorded on an AMD 402/3 or a HP 5989A mass selective detector. Gas chromatographic analysis was performed on an Agilent HP-5890 instrument with an FID detector and an HP-5 capillary column (poly(dimethylsiloxane) with 5% phenyl groups, 30 m, 0.32 mm i.d., 0.25 mm film thickness) with argon as the carrier gas.

Experimental section

The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for six 4 mL Wheaton vials. $Pd(OAc)_2$, (4.49 mg, 2.0 mol%), *CataC*Xium A (21,48 mg, 6.0 mol%), amino pyridine (1.1 mmol), and a magnetic stir bar were placed in each vials, which were then capped with a septum equipped with an inlet needle and flushed with argon. Then NEt_3 (3 mmol, 3.0 equiv.), *o*-dibromobenzene (1.0 mmol) and DMAc (5 mL) were added to the vial *via* syringe. The vials were placed in an autoclave, which was then purged several times with argon. Subsequently it was filled with 30 bars of CO at room temperature and heated at 100 °C for 20 h. After the reaction the autoclave was cooled to room temperature and vented to discharge N_2. The product was extracted with ethyl acetate (5×3 mL). The organic layers were washed with brine, dried over Na_2SO_4, and evaporated to yield the crude reaction mixture. The purification occurred by flash chromatography on silica gel (eluent: heptane/EtOAc 50:50).

Acknowledgements:
We thank the state of Mecklenburg-Vorpommern and the Bundesministerium für Bildung und Forschung (BMBF) for financial support. We also thank Dr. W. Baumann, Dr. C. Fischer, and S. Buchholz (LIKAT) for analytical support.

Notes and references*:*

[+] These authors contributed equally to this work.
Leibniz-Institut für Katalyse an der Universität Rostock, Albert-Einstein-Straße 29a, 18059 Rostock (Germany)
E-Mail: xiao-feng.wu@catalysis.de

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

[1] a) M. K. Hargreaves, J. G. Pritchard, H. R. Dave, *Chem. Rev.* 1970, **70**, 439-469; b) Y. Kamitori, M. Hojo, R. Masuda, T. Kimura, T. Yoshida, *J. Org. Chem.* 1986, **51**, 1427-1431; c) K. Rad-Moghadam, L. Kheyrkhah, *Synth. Commun.* 2009, **39**, 2108-2115; d) X. Collin, J. Robert, G. Wielgosz, G. Le Baut, C. Bobin-Dubigeon, N. Grimaud, J. Petit, *Eur. J. Med. Chem.* 2001, **36**, 639–649; e) H. Teisseire, G. Vernet, *Pestic. Biochem. Physiol*. 2001, **69**, 112–117; f) F. B. Miguel, D. Gema, S. Beatriz, R. Cynthia, R. Simmon, B. Teresa, *Eur. J. Med. Chem.* 2002, **37**, 541–551; g) A. A. Abdel-Hafez, *Arch. Pharm. Res.* 2004, **27**, 495–501; e) C. Shinji, T. Nakamura, S. Maeda, M. Yoshida, Y. Hashimoto, H. Miyachi, *Bioorg. Med. Chem. Lett*. 2005, **15**, 4427–4431; h) J. Ungwitayatorn, C. Wiwat, C. Matayatsuk, J. Pimthon, S. Piyaviriyakul, *Chin. J. Chem.* 2008, **26**, 379–387; i) U. Sharma, P. Kumar, N. Kumar, B. Singh, *Mini-Rev. Med. Chem.* 2010, **10**, 678–704.

[2] a) A. Schoenberg, I. Bartolet, R. F. Heck, *J. Org. Chem*. 1974, **39**, 318–326; b) A. Schoenberg, R. F. Heck, *J. Org. Chem*. 1974, **39**, 3327–3331; c) A. Schoenberg, R. F. Heck, *J. Am. Chem. Soc*. 1974, **96**, 7761-7764.

[3] a) A. Brennführer, H. Neumann, M. Beller, *Angew. Chem. Int. Ed*. 2009, **48**, 4114–4133; b) X. -F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev*. 2011, **40**, 4986–5009; c) X. -F. Wu, H. Neumann, M. Beller, *Chem. Rev*. 2013, **113**, 1–35; d) X. -F. Wu, H. Neumann, M. Beller, *ChemSusChem* 2013, **6**, 229–241; e) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed*. 2011, **50**, 10788–10799; f) C. F. J. Barnard, *Organometallics* 2008, **27**, 5402–5422.

[4] a) A. Da Settimo, G. Primofiore, F. Da Settimo, F. Simorini, C. La Motta, A. Martinelli, E. Boldrini, *Eur. J. Med. Chem.* 1996, **31**, 49-58. b) N. B. Mehta, A. P. Phillips, F. F. Lui, R. E. Brooks, *J. Org. Chem*. 1960, **25**, 1012-1015; c) S. M. Capitosti, T. P. Hansen, M. L. Brown, *Org. Lett.*, 2003, **5**, 2865-2867; d) S. Y. Yeung, S. Kampmann, K. A. Stubbs, B. W. Skelton, B. J. Kaskow, L. J. Abraham, S. G. Stewart, *Med. Chem. Commun.*, 2011, **2**, 1073-1078; e) G. W. Muller, W. E. Konnecke, A. M. Smith, V. D. Khetani, *Org. Process Res. Dev.*, 1999, **3**, 139-140.

[5] a) R. J. Perry, S. R. Turner, *J. Org. Chem.* 1991, **56**, 6573–6579; b) H. Cao, H. Alper, *Org. Lett.* 2010, **12**, 4126–4129; c) M. Mori, K. Chiba, N. Ohta, Y. Ban, *Heterocycles* 1979, **13**, 329–332; d) A. Takács, P. Ács, L.Kollár, *Tetrahedron* 2008, **64**, 983–987.

[6] a) M. V. Khedkar, S. R. Khan, D. N. Sawant, D. B. Bagal, B. M. Bhanage, *Adv. Synth. Catal*. 2011, **353**, 3415–3422; b) D. N. Sawant, Y. S. Wagh, K. D. Bhatte, B. M. Bhanage, *Eur. J. Org. Chem*. 2011, 6719-6724.

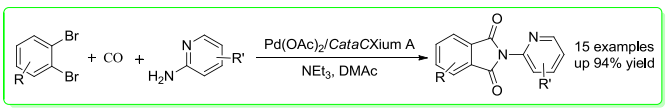
[7] X. -F. Wu, S. Oschatz, M. Sharif, A. Flader, L. Krey, M. Beller, P. Langer, *Adv. Synth. Catal*. 2013, **355**, 3581-3585.

[8] M. Reist, P. -A. Carrupt, E. Francotte, B. Testa, *Chem. Res. Toxicol.* 1998, **11**, 1521–1528.

[9] E. P. Sampaio, E. N. Sarno, R. Gallily, Z. A. Cohn, G. J. Kaplan, *Exp. Med*. 1991, **173**, 699-703.

[10] a) R. A. Van Hogezand. H. W. Verspaget, J. Scand. *Gastroenterol*. 1997, 32 (Suppl. 223), 105-107; b) M. J. Elliott, M. Feldmann, R. N. Maini, *Int. J. Immunopharmacol*. 1995, **17**, 141-145.

[11] For selected examples, see reference 1d, a) X. Collin, J. M. Robert, S. Robert-Piessard, G. Le Baut, C. Bobin-Dubigeon, L. Vernhet, F. Lang, J. Y. Petit, *Pharm. Pharmacol. Commun.*, 1998, **4**, 27–31; b) J. M. Robert, S. Robert-Piessard, J. Courant, G. Le Baut, B. Robert, F. Lang, J.Y. Petit, N. Grimaud, L. Welin, *Eur. J. Med. Chem.* 1995, **3**, 915–924.



A convenient and mild procedure for double carbonylation of *o*-dibromobenzene with various 2-amino pyridines and naturally occurring amines has been developed. *N*-Substituted phthalimides were produced in good to excellent yields. Furthermore, thalidomide was produced in excellent yield under these conditions.