Tetrahedron Letters 54 (2013) 3694–3696

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Microwave assisted palladium-catalyzed synthesis of phthalazinones and pyridopyridazinones

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ARTICLE INFO

Article history:
Received 9 April 2013
Revised 30 April 2013
Accepted 3 May 2013
Available online 13 May 2013

Keywords:
Carbonylation
Phthalazinones
Pyridopyridazinones
Microwave synthesis

ABSTRACT

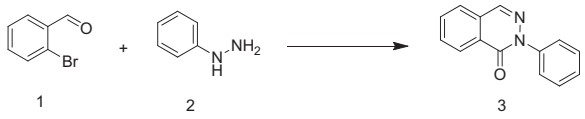
Microwave assisted palladium-catalyzed efficient synthesis of phthalazinones and pyridopyridazinones from *O*-bromoarylaldehydes, $Mo(CO)_6$, and arylhydrazines is described. This methodology avoids the use of toxic CO gas and can be carried out even on a small scale.

The significance and widespread use of the phthalazinone[1] and pyridopyridazinones[2] framework in many drugs of natural and synthetic origin, have led to interest in their synthesis. There is a continuing interest in the development of new synthetic methodologies for the preparation of phthalazinones[3] and pyridopyridazinones.[4] These methods are encouraging; however, there is still a need for an original methodology that avoids the use of highly toxic CO gas and allows for an efficient assembly of the phthalazinone and pyridopyridazinone cores from readily available materials in high yields.

Inspired by the emergence of molybdenum hexacarbonyl[5] as an alternate source of toxic CO gas under palladium catalyzed carbonylation, we designed a straightforward method to prepare phthalazinones and pyridopyridazinones by condensation of O-bromoarylaldehydes with arylhydrazines and subsequent carbonylation reaction. We herein describe a general and efficient palladium-catalyzed synthesis of phthalazinones and pyridopyridazinones from commercially available O-bromoarylaldehydes, $Mo(CO)_6$, and arylhydrazines.

The carbonylation of 2-bromobenzaldehyde with phenylhydrazine, $Mo(CO)_6$, and Cs_2CO_3 in dioxane at 140 °C under thermal heating was investigated as a model reaction in the presence of $Pd(OAc)_2$ and di-1-adamantyl-*n*-butylphosphine ($BuPAd_2$) which has been proved to be a useful catalyst system for various carbonylation reactions. Under this reaction condition, we observed the formation of product **3**[3k] in good yield (58%). With the successful result of this reaction, we studied the scope of this reaction under microwave irradiation (Biotage® Initiator) at 140 °C for 1 h and obtained similar results (Scheme 1).[7]

The smooth conversion of 2-bromobenzaldehyde **2** to 2-phenylphthalazin-1(2*H*)-one **3** under thermal and microwave conditions encouraged us to investigate this reaction under similar



Scheme 1. Reagents and conditions: $Mo(CO)_6$, $Pd(OAc)_2$, di-1-adamantyl-*n*-butylphosphine Cs_2CO_3, dioxane, 140 °C, 16 h, 58% yield or microwave, 140 °C, 1 h, 60% yield.

Table 1
Optimization of reaction conditions in microwave

Entry	Ligand	Base	Solvent	Yield[a] (%)
1	$BuPAd_2$	Cs_2CO_3	THF	38
2	$BuPAd_2$	Cs_2CO_3	DMF	32
3	$BuPAd_2$	Cs_2CO_3	DME	34
4	$BuPAd_2$	K_2CO_3	Dioxane	—
5	$BuPAd_2$	Na_2CO_3	Dioxane	—
6	dppf	Cs_2CO_3	Dioxane	26
7	X-phos	Cs_2CO_3	Dioxane	38
8	Xantphos	Cs_2CO_3	Dioxane	41
9	BINAP	Cs_2CO_3	Dioxane	45
10	PPh_3	Cs_2CO_3	Dioxane	22

[a] Isolated yields obtained using 1.0 mmol of 2-bromobenzaldehyde, 0.9–1.0 mmol of phenylhydrazine, 3.0 mmol of base, 2.50 mmol of $Mo(CO)_6$, 0.1 mmol of $Pd(OAc)_2$ and 0.2 mmol of ligand at 140 °C for 1 h under microwave irradiation.

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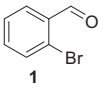
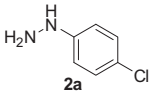
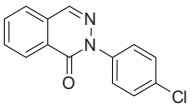
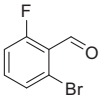
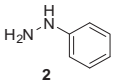
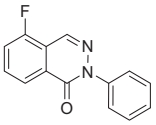
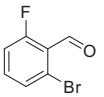
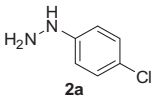
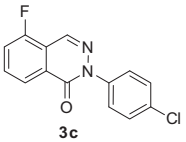
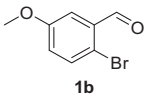
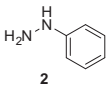
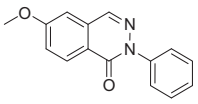
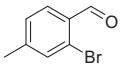
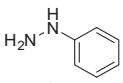
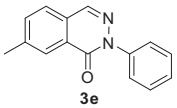
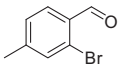
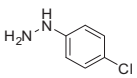
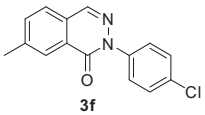
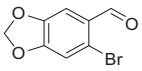
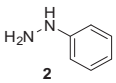
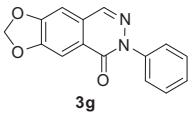
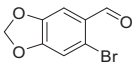
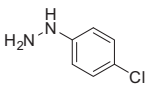
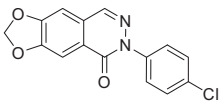
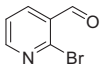
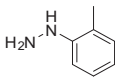
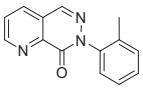
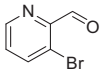
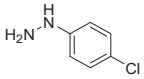
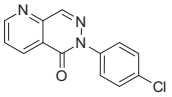
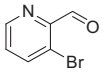
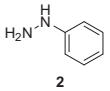
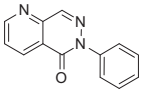
http://dx.doi.org/10.1016/j.tetlet.2013.05.006

Table 2
Microwave assisted synthesis of substituted phthalazinones (**3a**–**3h**)

Entry	Substrate 1	Substrate 2	Product 3	Isolated yield[a] (%)
1	 **1**	 **2a**	 **3a**	72[b]
2	 **1a**	 **2**	 **3b**	65
3	 **1a**	 **2a**	 **3c**	69
4	 **1b**	 **2**	 **3d**	64[b]
5	 **1c**	 **2**	 **3e**	62[b]
6	 **1c**	 **2a**	 **3f**	66
7	 **1d**	 **2**	 **3g**	63[b]
8	 **1d**	 **2a**	 **3h**	75

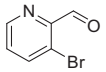
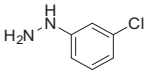
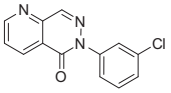
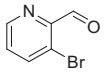
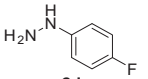
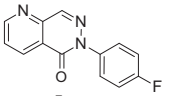
[a] Isolated yields obtained using 1.0 mmol of aldehyde, 0.9–1.0 mmol of hydrazine, 3.0 mmol of Cs_2CO_3, 2.50 mmol of $Mo(CO)_6$, 0.1 mmol of $Pd(OAc)_2$ and 0.2 mmol of $BuPAd_2$ in dioxane at 140 °C for 1 h under microwave irradiation.
[b] Ref. 3k.

Table 3
Microwave assisted synthesis of substituted pyridopyridazinones (**5a**–**5e**)

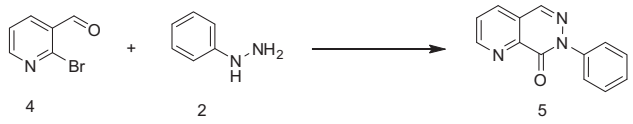
Entry	Substrate 4	Substrate 2	Product 5	Isolated yield[a] (%)
1	 **4**	 **2b**	 **5a**	40
2	 **4a**	 **2a**	 **5b**	67
3	 **4a**	 **2**	 **5c**	65

(*continued on next page*)

Table 3 (*continued*)

Entry	Substrate 4	Substrate 2	Product 5	Isolated yield[a] (%)
4	 **4a**	 **2c**	 **5d**	63
5	 **4a**	 **2d**	 **5e**	62

[a] Isolated yields obtained using 1.0 mmol of aldehyde, 0.9–1.0 mmol of hydrazine, 3.0 mmol of Cs_2CO_3, 2.50 mmol of $Mo(CO)_6$, 0.1 mmol of $Pd(OAc)_2$ and 0.2 mmol of $BuPAd_2$ in dioxane at 140 °C for 1 h under microwave irradiation.



Scheme 2. Reagents and conditions: $Mo(CO)_6$, $Pd(OAc)_2$, di-1-adamantyl-*n*-butylphosphine, Cs_2CO_3, dioxane, microwave, 140 °C, 1 h, 71% yield.

conditions on substrate **1** and **2** as shown in Table 1 and observed better yield with the original condition (Cs_2CO_3 as base, $BuPAd_2$ as ligand in dioxane at 140 °C for 1 h under microwave irradiation).

With the successful results of these investigations we studied the scope of this reaction on various substrates (Table 2). As shown in Table 2, diverse phthalazinones were isolated in moderate to good yields (62–75%).

To expand the scope of this methodology, we investigated the synthesis of pyridopyridazinones. Under this reaction condition, 2-bromopyridine-3-aldehyde (**4**) and phenylhydrazine (**2**) led to the smooth formation of product **5**[6] in 71% yield (Scheme 2).

The extent of this reaction was further examined with O-bromopyridine aldehydes and various arylhydrazines for the synthesis of substituted pyridopyridazinones. As shown in Table 3, various pyridopyridazinones were isolated in moderate to good yields (40–67%).

In conclusion, phthalazinones and pyridopyridazinones have been successfully synthesized from O-bromoarylaldehydes and arylhydrazines using $Mo(CO)_6$ as an alternative to the toxic CO gas. This methodology is simple, efficient, and environmentally friendly which can be carried out even on a small scale under thermal and/or microwave irradiation.

Acknowledgments

We are thankful to Jubilant Chemsys management for providing financial support and analytical facilities for the execution of this research work.

Supplementary data

Supplementary data (synthesized compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.006.

References and notes

1. (a) Nakajima, M.; Ohyama, K.; Nakamura, S.; Shimada, N.; Yamazaki, H.; Yokoi, T. *Drug Metab. Dispos.* **1999**, *27*, 792–797; (b) Prime, M. E.; Courtney, S. M.; Brookfield, F. A.; Marston, R. W.; Walker, V.; Warne, J.; Boyd, A. E.; Kairies, N. A.; Von der Saal, W.; Limberg, A.; Georges, G.; Engh, R. A.; Goller, B.; Rueger, P.; Rueth, M. *J. Med. Chem.* **2011**, *54*, 312–319. and references cited therein.
2. Epsztajn, J.; Brzezifiski, J. Z.; Czech, K. *Monatsh. Chem.* **1993**, *124*, 549–558. and references cited therein.
3. (a) Csámpai, A.; Körmendy, K.; Sohár, P.; Ruff, F. *Tetrahedron* **1989**, *45*, 5539–5548; (b) Sutherland, J. B.; Freeman, J. P.; Williams, A. J. *Appl. Microbiol. Biotechnol.* **1998**, *49*, 445–449; (c) Haider, N.; Käferböck, J. K.; Mátyus, P. *Heterocycles* **1999**, *51*, 2703–2710; (d) Morgan, D. O.; Ollis, W. D.; Stanforth, S. P. *Tetrahedron* **2000**, *56*, 5523–5534; (e) Franck, P.; Hostyn, S.; Dajka-Halász, B.; Polonka-Bálint, A.; Monsieurs, K.; Mátyus, P.; Maes, B. U. W. *Tetrahedron* **2008**, *64*, 6030–6037; (f) El Nezhawy, A. O. H.; Gaballah, S. T.; Radwan, M. A. A. *Tetrahedron Lett.* **2009**, *50*, 6646–6650; (g) Outerbridge, V. M.; Landge, S. M.; Tamaki, H.; Török, B. *Synthesis* **2009**, 1801–1806; (h) Zare, L.; Mahmoodi, N. O.; Yahyazadeh, A.; Mamaghani, M.; Tabatabaeian, K. *Chin. Chem. Lett.* **2010**, *21*, 538–541; (i) Li, W.; Li, H.; Li, Z. *Tetrahedron Lett.* **2010**, *51*, 5448–5450; (j) Poli, D.; Catarzi, D.; Colotta, V.; Varano, F.; Filacchioni, G.; Daniele, S.; Trincavelli, L.; Martini, C.; Paoletta, S.; Moro, S. *J. Med. Chem.* **2011**, *54*, 2102–2113; (k) Wu, X.-F.; Neumann, H.; Neumann, S.; Beller, M. *Chem. Eur. J.* **2012**, *18*, 8596–8599. and references cited therein.
4. Brzezmski, J. Z.; Bzowski, H. B.; Epsztajn, J. *Tetrahedron* **1996**, *52*, 3261–3272. and references cited therein.
5. Odell, L. R.; Russo, F.; Larhed, M. *Synlett* **2012**, 685–698. and references cited therein.
6. Sako, M. Science of Synthesis In *Houben Weyl Methods of Molecular Transformations Category 2*; Yamamoto, Y., Ed.; Georg Thieme: Stuttgart–New York, 2004; Vol. 16, pp 1109–1153.
7. *General experimental procedure*: To a solution of 2-bromobenzaldehyde (**1**) (1.00 mmol) and phenylhydrazine (**2**) (1.00 mmol) in anhydrous 1,4-dioxane (2 mL) was added cesium carbonate (3.00 mmol) in a 2–5 mL capacity microwave vial. The mixture was stirred and degassed with argon gas for 5 min. To this mixture were added $Pd(OAc)_2$ (0.10 mmol) and di-1-adamantyl-*n*-butylphosphine (0.20 mmol) under argon atmosphere, and purged with argon gas for 2 min and then molybdenum hexacarbonyl (2.50 mmol) was added and the vial was sealed and irradiated in microwave at 140 °C for 1 h. The vial was cooled to room temperature over a period of 10 min and filtered through Celite pad, washed with ethyl acetate (10 mL). The combined filtrate was concentrated in vacuo and the obtained residue was purified by flash column chromatography over 4 g SNAP cartridge by eluting with gradient of 20–40% ethyl acetate in hexane to afford 2-phenylphthalazin-1(2*H*)-one (**3**) (60%).