RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A straight forward synthesis of 4-aryl substituted 2-quinolones *via* Heck reaction†

Sumanta Gupta,[¶] Bhaskar Ganguly[¶] and Sajal Das*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A variety of aryl halides have been successfully coupled with different olefins *via* Heck reaction in presence of active stimulant (Pd-NHC). An efficient one pot protocol for the easy access of structurally diverse 4-aryl-2-quinolones *via* domino Heck/cyclization reaction has been developed.

Introduction

The scaffold, 2-quinolone is present in several natural products and a wide variety of biologically active compounds.[1] These are well known for therapeutic values.[2] Besides that 2-quinolones also serve as crucial intermediates in numerous synthetic transformations. For example, these can readily be transformed into 2- (pseudo)/haloquinolines[3] which could act as a key material for accessing structurally diverse compounds.[4] Substituted 4-aryl-2-quinolone, tipifarnib is known to act as an anticancer agent.[5] In addition, several synthesized products in this series are under clinical trial.[6] Various strategies, both metal free [7] and metal[8,9] catalyzed, are available in literature to access 2-quinolone structural motifs. However, the metal-catalyzed protocol proved to be a powerful and practical route for the synthesis of substituted 2-quinolones. Much attention has been paid for the palladium catalyzed synthesis of 2-quinolones. The domino Heck/Buchwald-Hartwig reaction of *o*-bromocinnamide with iodoarenes,[8b] cyclization of 3,3-diarylacrylamides followed by intramolecular C-H amination,[8c] carbonylative annulations of alkynes with anilines in presence of gaseous CO, are frequently used techniques.[8d,8e] Very recently, Inamoto *et. al.*[8f] reported the synthesis of 4-aryl-2-quinolones *via* the Pd-catalyzed sequential Heck reaction and intramolecular C-H amidation. Another alternative procedure, the oxidative carbonylation of 2-vinylanilines was developed by Alper's group.[8g] The ring closing metathesis (RCM) reaction of *N*-phenylacrylamide,[9a] iridium catalyzed annulations of *N*-arylcarbamoyl chloride,[9b] copper catalyzed cyclization of 3,3-diarylacrylamides through C-H functionalization/C-N bond formation[9c] and nickel catalyzed cycloaddition of *o*-cyanophenylbenzamides with alkenes[9d] have also been reported to use for the synthesis of functionalized 2-quinolones.

In Pd-catalyzed synthesis of 4-aryl-2-quinolones, cinnamides are most commonly used starting compounds (fig-1, b-d). However, Cacchi's group for the first time described the synthesis of 4-aryl-2-quinolones from methyl *β*-(*o*- acetamidophenyl) acrylate instead of cinnamides (fig. 1a).[8h] But in this case, the amino group has to be protected before the reaction, otherwise it solely results in the unsubstituted 2-quinolone.

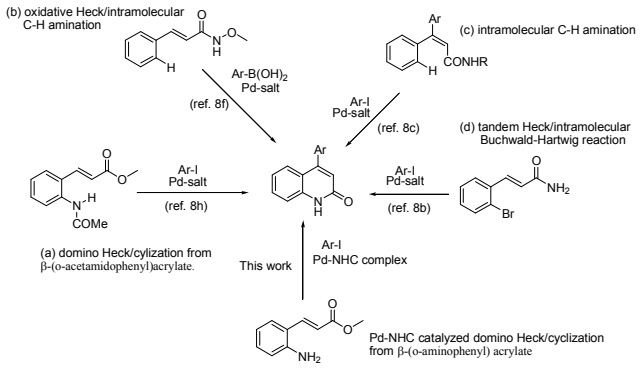


Figure-1: Synthesis of 4-aryl-2-quinolones via palladium catalyzed process.

In light of these successful precedents, we anticipated that the Pd -catalyzed Heck reaction of *β*-(*o*- aminophenyl) acrylate with arylhalide followed by the intramolecular cyclization would be an efficient protocol for easy access of structurally diverse 4-aryl-2-quinolones.

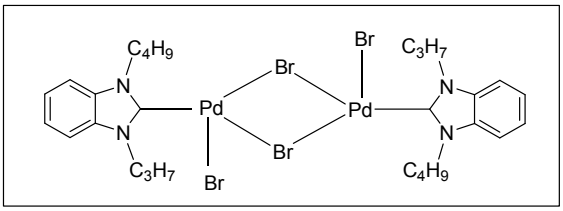


Figure-2: Pd-NHC

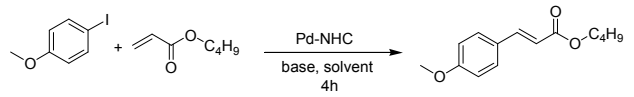
Very recently, we have demonstrated the benzimidazole based palladium-*N*-heterocyclic carbene (Pd-NHC) (Figure-2) that effectively catalyzes the C-C cross-coupling reaction with a broad variety of substrates.[10] In light of these achievements, herein we address the details of Pd-NHC catalyzed Heck reaction and one-pot efficient protocol for the synthesis of 4-aryl-2-quinolones.

Result and Discussion

We began our study to find the suitable condition for Heck cross-coupling reaction using our newly developed Pd-NHC

catalyst. 4-iodoanisole and n-butyl acrylate were selected as the model coupling partners to screen the best reaction condition.

Table-1: Optimization studies of reaction condition in Heck coupling between 4-iodoanisole and n-butyl acrylate.[a]



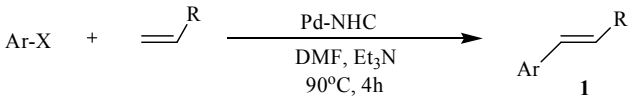
Entry	Solvent	Base	Temperature	Pd-NHC(mol%)	Yield(%)[b]
1	DMSO/H_2O	K_2CO_3	90°C	2	71
2	Acetone/H_2O	K_2CO_3	70°C	2	66
3	EtOH/H_2O	K_2CO_3	90°C	2	39
4[c]	H_2O	K_2CO_3	90°C	2	69
6	**DMF**	**Et_3N**	**90°C**	**1**	**91**
7	DMSO	Et_3N	90°C	1	81
8	DMF	K_2CO_3	90°C	1	83

[a]Reaction conditions: 4-iodoanisole (1 mmol), n-butylacrylate (1.5 mmol), base (2 mmol); [b]Isolated yield after column chromatography; [c]2 mmol TBAB was added.

The detailed optimization results in respect of solvents and bases are given in Table-1. The results clearly showed that, the reaction responded well both in organic solvents as well as in water. But the combination of DMF as solvent and triethylamine as base, was proved to be the best suited condition in the present study as it led to the desired coupled product in 91% yield upon isolation (Table-1, Entry-6). Notably, 1 mol% of Pd-NHC catalyst was sufficient to catalyze the coupling reaction effectively.

With this optimized condition in hand, we turned our interest to carry out the Heck reaction of different aryl halides with various olefins and the corresponding results are presented in Table-2.

Table-2: Heck coupling of aryl halides with different olefins.[a]

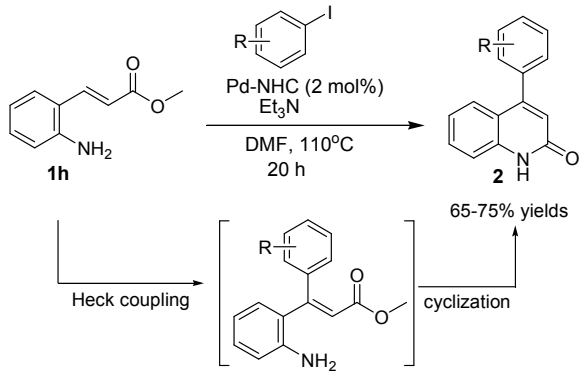


Entry	Ar	R	X	Product	Yield(%)[c]
1	4-OCH_3 -C_6H_5	$CO_2C_4H_9$	I	**1a**	91
2	4-OCH_3 -C_6H_5	CN	I	**1b**	93
3	4-OCH_3 -C_6H_5	Ph	I	**1c**	94
4	4-CH_3 - C_6H_5	$CO_2C_4H_9$	I	**1d**	90
5	2-F -C_6H_5	$CO_2C_2H_5$	I	**1e**	97
6	4-Cl -C_6H_5	Ph	I	**1f**	94
7	2-CH_3 -C_6H_5	CN	I	**1g**	95
8	2-NH_2 -C_6H_5	CO_2CH_3	I	**1h**	95
9	1-Naphthyl	$CO_2C_4H_9$	I	**1i**	98
10	2-OH-C_6H_5	$CO_2C_2H_5$	I	**1j**	93
11	3-CH_3 -C_6H_5	$CO_2C_4H_9$	I	**1k**	96
12	3-OCH_3 -C_6H_5	CO_2CH_3	I	**1l**	98
13[b]	4-OCH_3 -C_6H_5	Ph	Br	**1c**	86
14[b]	4-F-C_6H_5	Ph	Br	**1m**	89
15[b]	4-$COCH_3$ -C_6H_5	Ph	Br	**1n**	76
16[b]	4-CN -C_6H_5	Ph	Br	**1o**	87

[a]Reaction conditions: aryl halides (1 mmol), substituted alkenes (1.5 mmol), Et_3N (2 mmol), Pd-NHC (1 mol%, 0.0096g), DMF, 90°C, 4 h; [b]K_2CO_3 used instead of Et_3N, 130°C, 6 h; [c]Isolated yield after column chromatography.

The results showed that aryl halides bearing electron withdrawing and donating groups worked well under this optimized condition and leading to the corresponding products in excellent yield. Butylacrylate, acrylonitrile as well as styrene were efficiently participaing in cross-coupling reaction with 4-iodoanisole and resulted in the desired coupled products in 91%, 93% and 94% yields (Table-2, Entry-1, 2 and 3) respectively upon isolation. Comparatively sterically hindered aryl halides also underwent the reaction smoothly to furnish the desired coupled products in high yields (Table-2, Entry- 5,7,8,10). On the other hand, aryl moieties containing sensitive functional groups such as –NH2, -OH (Table-2, Entry-8, 10) were resulting in the high yields of the coupled product. No side product was detected in those cases. 1-iodonaphthalene coupled with butylacrylate furnished the desired product in 98% yield (Table-2, Entry-9). 3-substituted aryliodides were subjected to Heck reaction and desired coupled products were obtained in high yields (Table-2, Entry-11 and 12).

After successful completion of the Heck coupling reaction with aryliodides, we then explored the possibility to apply this technique in case of arylbromides. Accordingly, we attempted the Heck reaction between 4-bromoanisole and styrene at our optimized condition but the isolated yield of the desired coupled product was not satisfactory (Table-S1, Entry-1). Then we improved the reaction condition and it was found that at 130°C for 6 h in presence of K_2CO_3, arylbromides were smoothly participating in the coupling reaction. Under this optimized condition various arylbromides were subjected to Heck coupling reaction with styrene (Table-2, Entry-13 to 16). Both the electron rich and electron deficient arylbromides were smoothly coupled with styrene and the corresponding desired coupled products were isolated in high yields (Table-2, Entry-13 to 16). Several sensitive groups such as -CN, -$COCH_3$ remain intact under this reaction condition and results in the high yields of the cross coupled products.



Scheme 1: Synthesis of 4-aryl-2-quinolone.

After that we turned to our main objective *i.e.* the synthesis of 4-aryl-2-quinolones (Scheme-1). Synthesis of 4-aryl-2-quinolones from the Heck coupled product methyl *β*-(*o*-

aminophenyl) acrylate (**1h**) is a two step process *viz.* Heck cross coupling and cyclization reaction. We attempted to carry out both the reaction in one pot. After completion of Heck reaction between 2-iodoaniline and methyl acrylate, 1.2 equivalent amount of 4-iodoanisole was added into it. Then the resulting reaction mixture was further heated at 90°C and after 20 h only 15% yield of the corresponding cyclized product (**2a**) was obtained. While attempting the cyclization step under the same reaction condition from the pure intermediate (**1h**), we obtained only 36% yield of the cyclized compound (**2a**) upon isolation. Further, we enhanced the reaction temperature and carried out the cyclization step at 100° C and 110°C which resulted in the 4-aryl-2-quinolone (**2a**) in 52% and 75% yield respectively. Very delightfully, we then applied this protocol

Table-3: 4-aryl-2-quinolones **2a-g** produced via Scheme 1[a]

Entry	R	Product	Yield(%)[b]
1	4-OCH_3	**2a**	75
2	4-CH_3	**2b**	72
3	3-CH_3	**2c**	71
4	3-OCH_3	**2d**	64
5	2-OCH_3	**2e**	61
6	2-CH_3	**2f**	67
7	4-Cl	**2g**	65

[a]Reaction conditions: **1h** (1 mmol), aryliodide (1.2 mmol), Et_3N (2 mmol), Pd-NHC (2 mol%, 0.0192g), DMF, 110°C, 20 h; [b]Isolated yield after column chromatography.

with different aryliodides for accessing of structurally diverse 4-aryl-2-quinolones (Table-3).

It was found from the results that aryliodides were efficiently participating in the reaction and resulted in the good yield of the corresponding 4-aryl-2-quinolones. A marginal difference in yield of the final product was observed for electron donating and withdrawing groups present in the aryl moiety. A little drop in yield in case of *o*-OCH_3/-CH_3 might be attributed to the steric effect. Electron deficient 4-chloroiodobenzene productively participating in the reaction to form the desired 4-(4-chlorophenyl) quinolin-2(*1H*)-one (**2g**) in 65% yield and notably chloro atom is well tolerated under this reaction condition.

Conclusions

In summary we have demonstrated an effective Pd-NHC catalyzed Heck coupling. In addition, we have also developed one pot protocol for the synthesis of the valuable 4-aryl-2-quinolone moieties. The process stands good with a range of arylhalides including electron deficient, electron rich as well as sterically hindered entities.

Experimental

General methods

Unless stated otherwise, all reagents such as aryl halides, potassium carbonate, triethylamine, alkenes, and solvents were used as received from commercial suppliers. NMR spectra were recorded on 300 MHz spectrometer at 298 K and calibrations were done on the basis of solvent residual peak. Products were isolated using column chromatography on silica gel (60-120 mesh) and a mixture of petroleum ether (60-80°C)/ethyl acetate was used as an eluent. Reaction progress was monitored by silica gel TLC.

General procedure for Heck reaction

A mixture of aryl halide (1 mmol), alkene (1.5 mmol), base (2 mmol Et_3N for aryliodides and 2 mmol K_2CO_3 for arylbromides), Pd-NHC (1 mol%, 0.0096 g) and 3 mL DMF were taken in a 25 mL round bottom flask and the mixture was placed in a preheated oil bath at 90°C for 4 h (at 130°C for 6 h in case of arylbromides). Then the reaction mixture was diluted with water and extracted with DCM (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography.

General procedure for the synthesis of 4-aryl-2-quinolones (2)

A mixture of **1h** (1 mmol, 0.177 g), aryliodide (1.2 mmol), Et_3N (2 mmol, 0.202 g) and Pd-NHC (2 mol %) were taken in a 25 mL round bottom flask. Then 3 mL DMF was added into it and the mixture was stirred for 20 h at 110°C. After cooling to room temperature, the reaction mixture was diluted with DCM and washed with water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography.

Acknowledgments

We thank the Council of Scientific and Industrial Research, New Delhi for financial support (02(0022)/11/EMR-II). S.G. is thankful to UGC for the award of fellowship.

Notes and references

Department of Chemistry, North Bengal University, Darjeeling, 734013, India. Fax: +91 353 269 9001; Tel: +91 353 277 6381; E-mail: sajal.das@hotmail.com

¶ These authors contributed equally.

† Electronic Supplementary Information (ESI) available: [Spectral analysis, copies of ^1H and ^{13}C spectra of all compounds]. See DOI: 10.1039/b000000x/

1. (a) J. P. Michael, *Nat. Prod. Res.*, 2008, **25**, 166-187; (b) R. Uchida, R Imasato, H. Tomoda, S. Omura, *J. Antibiot.*, 2006, **59**, 652-658; (c) 166-187; (b) R. Uchida, R Imasato, K. Shiomi, H. Tomoda, S. Omura, *Org. Lett.*, 2005, **7**, 5701-5704; (d) N. Fokialakis, P. Magiatis, I. Chinou, S. Mitaku, F. Tillequin, *Chem. Pharm. Bull.*, 2002, **50**, 413-414.

2. (a) G. A. Freeman, C. W. Andrews III, A. L. Hopkins, G. S. Lowell, L. T. Schaller, J. R. Cowan, S. S. Gonzales, G. W. Koszalka, R. J. Hazen, L. R. Boone, G. Rob, R. G. Ferris, K. L. Creech, G. B. Roberts, S. A. Short, K. Weaver, J. David, D. J. Reynolds, J. Milton, J. Ren, D. I. Stuart, D. K. Stammers and J. H. Chan, *J. Med. Chem.*, 2004, **47**, 5923-5936; (b) M. J. Wall, J. Chen, S. Meegalla, S. K. Ballentine, K. J. Wilson, R. L. DesJarlais, C. Schubert, M. A. Chaikin, C. Crysler, I. P. Petrounia, R. R. Donatelli, E. J. Yurkow, L. Boczon, M. Mazzulla, M. R. Player, R. J. Patch, C. L. Manthey, C. Molloy, B. Tomczuk and C. R. Illig, *Bioorg. Med. Chem. Lett.*,

2008, **18**, 2097-2102; (c) J. M. Kraus, C. L. M. J. Verlinde, M. Karimi, G. I. Lepesheva, M. H. Gelb and F. S. Buckner, *J. Med. Chem*., 2009, **52**, 1639-1647.

3. (a) J. R. Goodell, F. Puig-Basagoiti, B. M. Forshey, P.-Y. Shi and D. M. Ferguson, *J. Med. Chem*., 2006, **49**, 2127-2137; (b) M. Anzini, A. Cappelli and S. Vomero, *J. Heterocycl. Chem*., 1991, **28**, 1809-1812; (c) S. Cacchi, A. Carangio, G. Fabrizi, L. Moro and P. Pace, *Synlett*, 1997, 1400-1402.

4. (a) A. Arcadi, S. Cacchi, G. Fabrizi, F. Manna and P. Pace, *Synlett*, 1998, 446-448; (b) A. Godard, J. M. Fourquez, R. Tamion, F. Marsais and G. Queguiner, *Synlett*, 1994, 235-236.

5. E. Van Cutsem, H. van de Velde, P. Karasek, H. Oettle, W. L. Vervenne, A. Szawlowski, P. Schoffski, S. Post, C. Verslype, H. Neumann, H. Safran, Y. Humblet, J. P. Ruixo, Y. Ma and D. von Hoff, *J. Clin. Oncol*., 2004, **22**, 1430-1438.

6. (a) J. M. Kraus, C. L. M. J. Verlinde, M. Karimi, G. I. Lepesheva, M. H. Gelb and F. S. Buckner, *J. Med. Chem*., 2009, **52**, 1639-1647; (b) D. S. Hong, S. M. Sebti, R. A. Newman, M. A. Blaskovich, L. Ye, R. F. Gagel, S. Moulder, J. J. Wheler, A. Naing, N. M. Tannir, C. S. Ng, S. I. Sherman, A. K. E. Naggar, R. Khan, J. Trent, J. J. Wright and R. Kurzrock, *Clin. Cancer Res*., 2009, **15**, 7061-7068; (c) B. C. Capell, M. Olive, M. R. Erdos, K. Cao, D. A. Faddah, U. L. Tavarez, K. N. Conneely, X. Qu, H. San, S. K. Ganesh, X. Chen, H. Avallone, F. D. Kolodgie, R. Virmani, E. G. Nabel and F. S. Collins, *Proc. Natl. Acad. Sci. U.S.A*., 2008, **105**, 15902-15907; (d) B. M. Andresen, M. Couturier, B. Cronin, M. D'Occhio, M. D. Ewing, M. Guinn, J. M. Hawkins, V. J. Jasys, S. D. LaGreca, J. P. Lyssikatos, G. Moraski, K. Ng, J. W. Raggon, A. M. Stewart, D. L. Tickner, J. L. Tucker, F. J. Urban, E. Vazquez and L. Wei, *Org. Process Res. Dev*., 2004, **8**, 643-650; (e) M. Venet, D. End and P. Angibaud, *Curr. Top. Med. Chem*., 2003, **3**, 1095-1102; (f) J. M. Kraus, H. B. Tatipaka, S. A. McGuffin, N. K. Chennamoneni, M. Karimi, J. Arif, C. L. M. J. Verlinde, F. S. Buckner and M. H. Gelb, *J. Med. Chem*., 2010, **53**, 3887-3898.

7. (a) Y. Kobayashi and T. Harayama, *Org. Lett*., 2009, **11**, 1603-1606; (b) M. S. Reddy, N. Thirupathi and M. H. Babu, *Eur. J. Org. Chem*., 2012, 5803-5809; (c) A. V. Aksenov, A. N. Smirnov, N. A. Aksenov, I. N. Aksenova, L. V. Frolova, A. Kornienko, I. V. Magedov and M. Rubin, *Chem. Commun*., 2013, **49**, 9305-9307; (d) M. Marull, O. Lefebvre and M. Schlosser, *Eur. J. Org. Chem*., 2004, 54-63.; (e) P. R. Angibaud, M. G. Venet, W. Filliers, R. Broeckx, Y. A. Ligny, P. Muller, V. S. Poncelet and D. W. Eng, *Eur. J. Org. Chem*., 2004, 479-486; (f) C.-C. Huang and N.-C. Chang, *Org. Lett*., 2008, **11**, 673-676; (g) W.-T. Gao, W.-D. Hou, M.-R. Zheng and L.-J. Tang, *Synth. Commun*., 2010, **40**, 732-738; (h) K. K. Park and J. J. Lee, *Tetrahedron*, 2004, **60**, 2993-2999.

8. (a) A. C. Tadd, A. Matsuno, M. R. Fielding and M. C. Willis, *Org. Lett*., 2009, **11**, 583-586; (b) G. Battistuzzi, R. Bernini, S. Cacchi, I. D. Salve and G. Fabrizi, *Adv. Synth. Catal*., 2007, **349**, 297-302; (c) K. Inamoto, T. Saito, K. Hiroya and T. Doi, *J. Org. Chem*., 2010, **75**, 3900-3903; (d) D. V. Kadnikov and R. C. Larock, *J. Org. Chem*., 2004, **69**, 6772- 6780; (e) D. V. Kadnikov and R. C. Larock, *J. Organomet. Chem*., 2003, **687**, 425-435; (f) K. Inamoto, J. Kawasaki, K. Hiroya, Y. Kondo and T. Doi, *Chem. Commun*., 2012, **48**, 4332-4334; (g) J. Ferguson, F. Zeng, N. Alwis and H. Alper, *Org. Lett*., 2013, **15**, 1998-2001; (h) R. Bernini, S. Cacchi, G. Fabrizi and A. Sferrazza, *Heterocycles*, 2006, **69**, 99-105.

9. (a) J. Minville, J. Poulin, C. Dufresne and C. F. Sturino, *Tetrahedron Lett*., 2008, **49**, 3677-3681; (b) T. Iwai, T. Fujihara, J. Terao and Y. Tsuji, *J. Am. Chem. Soc*., 2010, **132**, 9602-9603; (c) R. Berrino, S. Cacchi, G. Fabrizi and A. Goggiamani, *J. Org. Chem*., 2012, **77**, 2537-2542; (d) K. Nakai, T. Kurahashi and S. Matsubara, *Org. Lett*., 2013, **15**, 856-859.

10. (a) S. Gupta, B. Basu and S. Das, *Tetrahedron*, 2013, **69**, 122-128; (b) S. Gupta, P. Ghosh, S. Dwivedi and S. Das, *RSC Adv*., 2014, **4**, 6254-6260.

ARTICLE TYPE www.rsc.org/xxxxxx | XXXXXXXX

A straight forward synthesis of 4-aryl substituted 2-quinolones via Heck reaction

Sumanta Gupta, Bhaskar Ganguly and Sajal Das

Pd-*NHC* catalyzed one pot synthesis of 4-aryl-2-quinolones through the Heck reaction followed by cyclization. Additionally an efficient methodology has been developed for Heck reaction with a wide range of arylhalides and olefins.