



Synthesis of substituted benzimidazo[2,1-*a*]isoquinolines and its condensed analogues using Pd(0)-catalyzed cyclization/C–H activation

Sukla Nandi, Shubhankar Samanta, Susovan Jana, Jayanta K. Ray *

Department of Chemistry, Indian Institute of Technology, Kharagpur 721 302, India

ARTICLE INFO

Article history:

Received 2 June 2010

Revised 7 July 2010

Accepted 30 July 2010

Available online 10 August 2010

Keywords:

Benzimidazo[2,1-*a*]isoquinoline

exo-Trig

Palladium-catalyzed cyclization

C–H activation

ABSTRACT

An efficient route for the synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogues has been developed via the palladium-catalyzed cyclization/C–H activation of *N*-allyl and *N*-methallyl derivatives of benzimidazoles.

© 2010 Elsevier Ltd. All rights reserved.

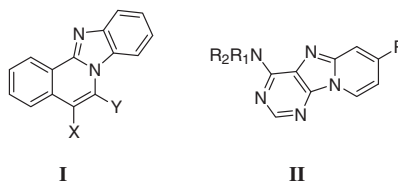
Fused imidazo[1,2-*a*]heterocycles moiety which is a key structural component of bioactive molecules was widely incorporated in the design of multiple biologically active agents and has already been known for its antimicrobial activity along with antiviral, anti-ulcer, antihypertension, and cardiotoxic properties. The synthesis of various benzimidazoles fused with aza-aromatic ring systems, such as benzimidazo[2,1-*a*]isoquinolines (**I**) and pyrido[1,2-*e*]purines (**II**), as anticancer agents,¹ are reported in the literature. On the other hand the benzo[*d*]imidazole subunit has been exclusively used in the design of drugs such as Pimobendan, a dihydropyridazinone-benzo[*d*]imidazole derivative that acts as a calcium sensitizer, as well as a partial inhibitor of PDE-3 and is also effective in both acute and chronic heart failure (Fig. 1).²

There are various methods available for the synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogs.^{3–6} One of the approaches involves Bu₃SnH-mediated 6-*exo-trig* cyclization of σ -aryl radicals generated from 1-allyl-2-(ω -bromoaryl)benzimidazoles⁷ and another approach involves microwave-accelerated tandem process in which a Sonogashira coupling, 5-*endo* cyclization, oxidative aromatization, and 6-*endo* cyclization can be performed in a single synthetic operation using 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines as starting materials.⁸ Among these, palladium-catalyzed cyclization is a very powerful method due to its tolerance of a wide variety of functional groups, thus neatly avoiding protection group chemistry. So in continuation of our efforts on C–C bond formation reaction,⁹ herein we report Pd(0)-catalyzed cyclization/C–H activation for the

synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogs from *N*-allyl and *N*-methallyl derivatives of benzimidazoles.

Attention was first focused on the construction of the starting materials for the cyclization/C–H activation by *N*-allylation and *N*-methallylation of benzoimidazole **3** and **4** (Scheme 1). At first the aromatic bromoaldehydes **1** (1 mmol) were treated with a mixture of 1,2-phenylenediamine (1 mmol), H₂O₂ (30%, 4 mmol, 0.4 mL), and NH₄Ce(NO₃)₆ (0.1 mmol, 0.0548 g) at 50 °C for 10 min¹⁰ to get the benzoimidazole **2**. Benzoimidazoles were converted to *N*-allylated/methallylated products **3** and **4** (for structures, see Tables 2 and 3) by the reaction with allyl bromide/methallyl bromide in the presence of sodium hydride in THF at reflux temperature.

First the intramolecular Heck reaction was performed with *N*-allylated derivatives **3a** in the presence of Pd(OAc)₂ (10 mol %), PPh₃ (0.25 equiv), Cs₂CO₃ (1.2 equiv) in DMF at 95–100 °C which affords substituted benzimidazo[2,1-*a*]isoquinoline derivatives **5a** in 58% yield. Compound **4a** on same reaction condition gave the condensed analog **6a** in 55% yield.



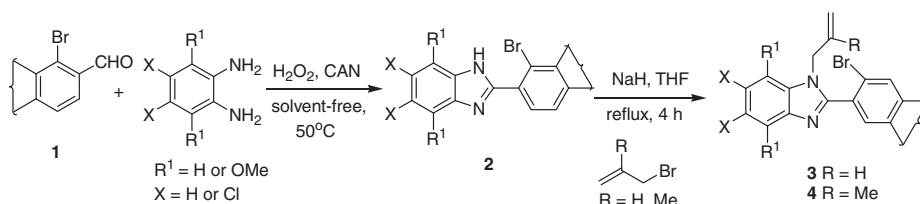
I

II

Figure 1. Some biologically active molecules.

* Corresponding author. Tel.: +91 3222283326; fax: +91 3222282252.

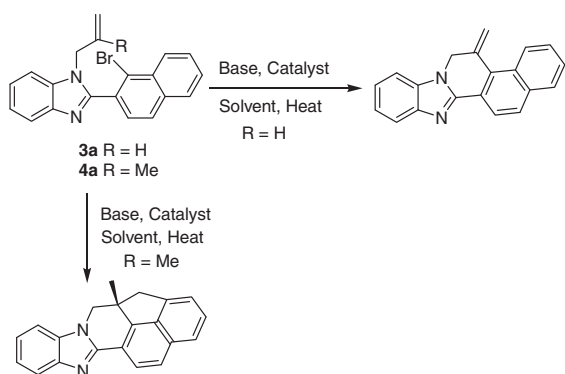
E-mail address: jkraj@chem.iitkgp.ernet.in (J.K. Ray).



Scheme 1. Preparation of *N*-allyl and *N*-methyl derivatives of benzimidazoles.

Table 1

Optimization of the reaction condition by using different types of catalysts, bases, and solvents^a



Entry	Catalyst	Base	Solvent	Yield (%)	
				5a	6a
1	PdCl ₂ (PPh ₃) ₂	NaOAc	DMA	87	85
2	Pd(PPh ₃) ₄	NaOAc	DMA	56	50
3	PdCl ₂	NaOAc	DMA	NR ^b	NR ^b
4	Pd(OAc) ₂	Cs ₂ CO ₃	DMF	58	55
5	PdCl ₂ (PPh ₃) ₂	Et ₃ N	CH ₃ CN	15	15
6	PdCl ₂ (PPh ₃) ₂	NaOAc	CH ₃ CN	30	26
7	PdCl ₂ (PPh ₃) ₂	Na ₂ CO ₃	DMA	52	45
8	PdCl ₂ (PPh ₃) ₂	NaOAc	PhCH ₃	Decomp. ^b	Decomp. ^b

Decomp.: decomposition of starting material.

^a Reaction conditions: substrate **3a** or **4a** (1 mmol), catalyst (10 mol %), base (1.2 mmol), and solvent (5 mL) at 100–110 °C for 2 h.

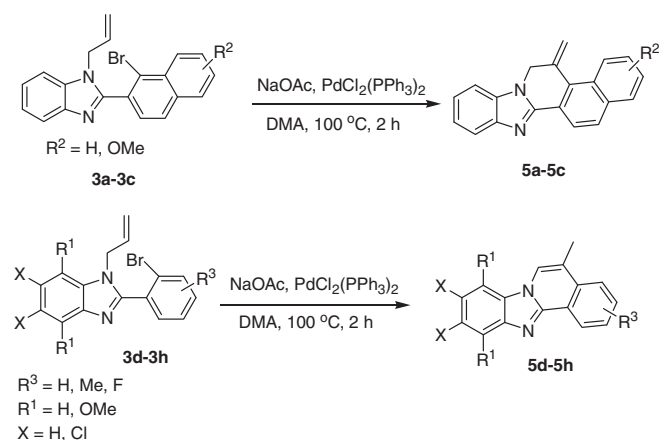
^b NR: no reaction.

Optimization of the reaction condition was done with **3a** and **4a** as the model substrates by changing different types of catalysts, bases, and solvents. When the reaction was carried out in acetonitrile poor yields were obtained (Table 1, entries 5 and 6) and in the case of the PdCl₂ catalyst no cyclized product was isolated (Table 1, entry 3). **3a** and **4a** on treatment with PdCl₂(PPh₃)₂ (10 mol %), NaOAc (1.2 equiv) in DMA at 100–110 °C afforded **5a** and **6a** in 80–90% yield (Table 1, entry 1).

With the optimized reaction conditions, [PdCl₂(PPh₃)₂] (10 mol %) as a catalyst, NaOAc (1.2 equiv) as a base, and DMA as a solvent at 100–110 °C, we examined the generality and substrate scope of this cyclization reaction of substituted *N*-allylated derivatives **3a–3h** to afford substituted benzimidazo[2,1-*a*]isoquinoline derivatives **5a–5h** in good yields¹¹ via 6-*exo-trig* cyclization as shown in Table 2. Here compounds **3a–3c** gave the products with *exo* cyclic double bond but in case of the compounds **3d–3h** isomerised products were obtained. This difference may be due to the steric interaction between the methyl group and the peri hydrogen of naphthyl ring which makes the isomerised products unstable in case of the compounds **3a–3c** (Fig 2).

Table 2

Pd(0)-catalyzed intramolecular reaction of *N*-allylated benzimidazole derivatives^a



Entry	Substrate	Product	Yield (%)
1	3a	5a	87
2	3b	5b	81
3	3c	5c	79
4	3d	5d	90
5	3e	5e	85
6	3f	5f	80

(continued on next page)

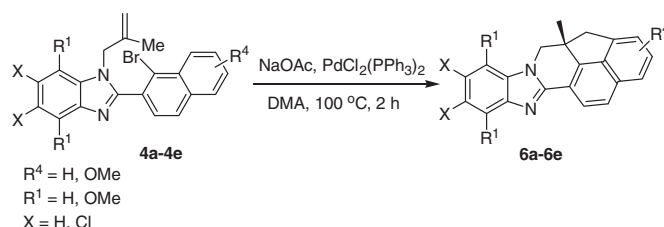
Table 2 (continued)

Entry	Substrate	Product	Yield (%)
7			81
8			80

^a Reagents and conditions: **3a–3h** (1 equiv), PdCl₂(PPh₃)₂ (10 mol %), NaOAc (1.2 equiv), DMA (5 mL), 100–110 °C.

On the other hand N-methylated derivatives **4a–4e** with same Heck reaction conditions afforded highly condensed analogs of benzimidazo[2,1-*a*]isoquinoline **6a–6e** (Table 3) in good yields¹¹ via 6-*exo-trig* cyclization followed by C–H activation.

Table 3
Pd(0)-catalyzed intramolecular reaction of N-methylated benzoimidazole derivatives^a



Entry	Substrate	Product	Yield (%)
1			85
2			78
3			75
4			76
5			80

^a Reagents and conditions: **4a–4e** (1 equiv), PdCl₂(PPh₃)₂ (10 mol %), NaOAc (1.2 equiv), DMA (5 mL), 100–110 °C.

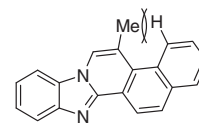


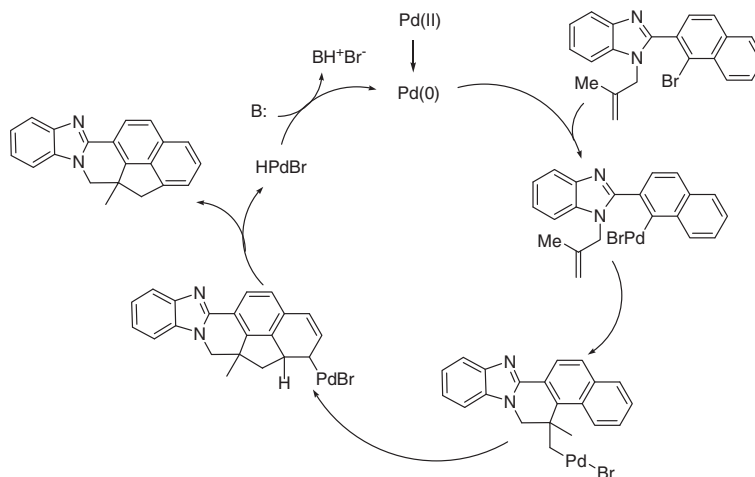
Figure 2. Steric interaction between methyl group and peri hydrogen of naphthyl ring.

A plausible rationale for the formation of the products (**6a–6e**) is shown in Scheme 2.

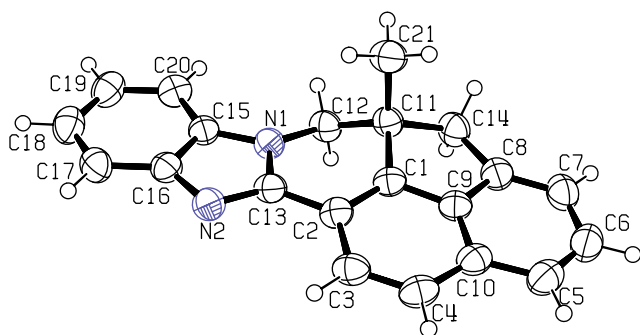
Initially an alkenyl palladium (II) intermediate was generated by oxidative addition of Pd(0) to the sp² C–Br bond which undergoes addition to the inactivated double bond to produce an alkylpalladium which underwent cyclization with the aromatic ring through C–H activation.¹² Since no elimination is possible due to the absence of a β-H in the alkylpalladium intermediates, C–H activation is facilitated.

The ORTEP structure of the condensed analog of benzimidazo[2,1-*a*]isoquinoline **6a** is shown below (Scheme 3).

In conclusion, we have developed a general methodology for the synthesis of benzimidazo[2,1-*a*]isoquinoline and its highly condensed analogs by Pd(0)-catalyzed cyclization/C–H activation. This



Scheme 2. A plausible rationale for the Pd(0)-catalyzed cyclization followed by C–H activation.



Scheme 3. ORTEP structure of condensed analog of benzimidazo[2,1-*a*]isoquinoline **6a**.

methodology can also be used for the synthesis of various types of benzimidazoisoquinolines and benzimidazolequinones natural products which have been reported to exhibit potent biological activity.

Acknowledgements

We thank the CSIR, New Delhi, for the fellowships, the D.S.T. for providing funds for the project, and creating 400 MHz NMR facility under the IRPHA program.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.162.

References and notes

- (a) Deady, L. W.; Loria, P. M.; Rodermann, T. *Aust. J. Chem.* **1998**, *51*, 941; (b) Meng, T.; Zhang, Z.; Hu, D.; Lin, L.; Ding, J.; Wang, X.; Shen, J. *J. Comb. Chem.* **2007**, *9*, 739; (c) Pinguet, F.; Mavel, S.; Galtier, C.; Gueffier, A. *Pharmazie* **1999**, *54*, 876; (d) El-Hawash, S. A. M.; Badawey, E.; Kappe, T. *Pharmazie* **1999**, *54*, 341.
- (a) Navarrete-Vazquez, G.; Hidalgo-Figueroa, S.; Torres-Piedra, M.; Vergara-Galicia, J.; Rivera-Leyva, J. C.; Estrada-Soto, S.; Leon-Rivera, I.; Aguilar-Guardarrama, B.; Rios-Gomez, Y.; Villalobos-Molina, R.; Ibarra-Barajas, M. *Bioorg. Med. Chem.* **2010**, *18*, 3985; (b) Gordon, S. G.; Miller, M. W.; Saunders, A. B. *J. Am. Anim. Hosp. Assoc.* **2006**, *42*, 90.
- (a) Panda, K.; Suresh, J. R.; Ila, H.; Junjappa, H. *J. Org. Chem.* **2003**, *68*, 3498; (b) Katritzky, A. R.; Tymoshenko, D. O.; Monteux, D.; Vvedensky, V.; Nikonov, G.; Cooper, C. B.; Deshpande, M. *J. Org. Chem.* **2000**, *65*, 8059; (c) Hranjec, M.; Kralj, M.; Piantanida, I.; Sedic, M.; Syuman, L.; Pavelic, K. I.; Karminski-Zamola, G. *J. Med. Chem.* **2007**, *50*, 5696.
- (a) Popov, I. I. *Khim. Geterotsikl. Soedin.* **1989**, 1695; (b) Kuzmenko, V. V.; Komissarov, V. N.; Simonov, A. M. *Khim. Geterotsikl. Soedin.* **1981**, 1497; (c) Bergerat, I.; Galous, H.; Rabaron, A.; Combet-Farnoux, C.; Miocque, M. *J. Heterocycl. Chem.* **1985**, *22*, 369; (d) Toth, G.; Kovacs, A.; Balogh, M.; Hermecz, J. *J. Heterocycl. Chem.* **1991**, *28*, 497.
- (a) Cooper, G.; Irwin, W. J. *J. Chem. Soc., Perkin Trans. 1* **1976**, 75; (b) Grimshaw, J.; Trocha-Grimshaw, J. *Tetrahedron Lett.* **1975**, 2601; (c) Benincori, T.; Sannicola, F. *J. Heterocycl. Chem.* **1988**, *25*, 1029; (d) Tkach, I. I.; Luk'yanets, E. A. *Khim. Geterotsikl. Soedin.* **1992**, 1053; *Chem. Abstr.* **1993**, *119*, 28058; (e) Knolker, H.-J.; Boese, R.; Hitzemann, R. *Chem. Ber.* **1990**, *123*, 327; (f) Alajarin, M.; Vidal, A.; Tovar, F. *Tetrahedron Lett.* **2000**, *41*, 7029; (g) Ohta, S.; Yuasa, T.; Narita, Y.; Kawasaki, I.; Minamii, E.; Yamashita, M. *Heterocycles* **1991**, *32*, 1923; (h) Alajarin, M.; Vidal, A.; Tovar, F.; Conesa, C. *Tetrahedron Lett.* **1999**, *40*, 6127.
- Review: Tennant, G., In *The Chemistry of Heterocyclic Compounds*; Weissberger, A., Taylor, E. C., Eds.; Interscience Publishers: New York, 1980; Vol. 40, p 257.
- Moriarty, E.; Aldabbagh, F. *Tetrahedron Lett.* **2009**, *50*, 5251.
- Okamoto, N.; Sakurai, K.; Ishikura, M.; Takeda, K.; Yanada, R. *Tetrahedron Lett.* **2009**, *50*, 4167.
- (a) Samanta, S.; Mohapatra, H.; Jana, R.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 7153; (b) Jana, R.; Chatterjee, I.; Samanta, S.; Ray, J. K. *Org. Lett.* **2008**, *10*, 4795.
- Bahrami, K.; Khodaei, M. M.; Naali, F. *J. Org. Chem.* **2008**, *73*, 6835.
- General procedure for the synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogs.
Compounds **3** or **4** (1 equiv), PdCl₂(PPh₃)₂ (10 mol %), NaOAc (1.2 equiv), and DMA (5 mL) were placed in a two-necked round-bottomed flask. After degassing with N₂, the mixture was heated at 100–110 °C for 2 h. After cooling, the reaction mixture was diluted with saturated NH₄Cl solution, extracted with EtOAc (30 mL × 3), and the combined organics dried (Na₂SO₄). The solvent was evaporated and the crude product was purified by column chromatography.
Spectral data of representative compounds.
Compound 5a: yellow liquid, ¹H NMR (CDCl₃, 200 MHz) δ: 4.95 (s, 2H), 5.85 (s, 2H), 7.27–7.41 (m, 3H), 7.51–7.56 (m, 2H), 7.85–7.92 (m, 3H), 8.39–8.51 (m, 2H); ¹³C NMR (CDCl₃, 200 MHz) δ: 49.33, 109.00, 119.98, 122.35 (2C), 122.71, 123.11, 123.71, 125.96, 126.93, 127.15, 128.99, 129.32, 129.69, 131.34, 134.54, 134.86, 135.12, 143.76, 148.85; HRMS: calcd for C₂₀H₁₅N₂ [M⁺+H]: 283.1235, found: 283.1231.
Compound 5e: pale yellow solid, mp 132 °C, ¹H NMR (CDCl₃, 200 MHz) δ: 2.39 (s, 3H), 2.49 (s, 3H), 7.33 (t, 1H, J = 7 Hz), 7.41–7.48 (m, 3H), 7.64 (d, 1H, J = 8 Hz), 7.74 (s, 1H), 7.95 (d, 1H, J = 8 Hz), 8.66 (d, 1H, J = 8.6 Hz); ¹³C NMR (CDCl₃, 200 MHz) δ: 16.36, 22.08, 109.64, 117.30, 119.08, 119.48, 120.84, 121.31, 123.85, 124.26, 125.07, 129.28, 129.84, 132.30, 140.14, 143.56, 147.16; HRMS: calcd for C₁₇H₁₅N₂ [M⁺+H]: 247.1235, found: 247.1231.
Compound 6b: white solid, mp 170 °C, ¹H NMR (CDCl₃, 200 MHz) δ: 1.31 (s, 3H), 3.30 (d, 1H, J = 16.2 Hz), 3.52 (d, 1H, J = 16.2 Hz), 3.99 (s, 3H), 4.05 (s, 1H), 4.57 (d, 1H, J = 11.8 Hz), 7.22–7.37 (m, 4H), 7.70 (d, 2H, J = 8.6 Hz), 7.82–7.87 (m, 1H), 7.97 (d, 1H, J = 8.6 Hz); ¹³C NMR (CDCl₃, 200 MHz) δ: 26.22, 42.63, 52.91, 56.54, 108.94, 118.10, 118.69, 119.90, 120.58, 122.22, 122.89, 124.66, 125.15, 125.72 (2C), 127.23, 135.38, 136.90, 144.25, 147.85, 148.40, 153.60; HRMS: calcd for C₂₂H₁₉N₂O [M⁺+H]: 327.1497, found: 327.1492.
- (a) Jana, R.; Samanta, S.; Ray, J. K. *Tetrahedron Lett.* **2008**, *49*, 851; (b) Grigg, R.; Sridharan, V.; Sukirthalingam, S. *Tetrahedron Lett.* **1991**, *132*, 3855; (c) Nandi, S.; Ray, J. K. *Tetrahedron Lett.* **2009**, *50*, 6993.