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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

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ABSTRACT

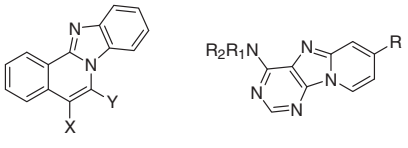
An efficient route for the synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogues has been developed via the palladium-catalyzed cyclization/C–H activation of *N*-allyl and *N*-methallyl derivatives of benzimidazoles.

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, antiulcer, antihypertension, and cardiotonic 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 Bu_3SnH-mediated 6-*exo-trig* cyclization of σ-aryl radicals generated from 1-allyl-2-(ω-bromoaryl)benzimidazoles[7] 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), H_2O_2 (30%, 4 mmol, 0.4 mL), and $NH_4Ce(NO_3)_6$ (0.1 mmol, 0.0548 g) at 50 °C for 10 min[10] 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 %), PPh_3 (0.25 equiv), Cs_2CO_3 (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: jkray@chem.iitkgp.ernet.in (J.K. Ray).

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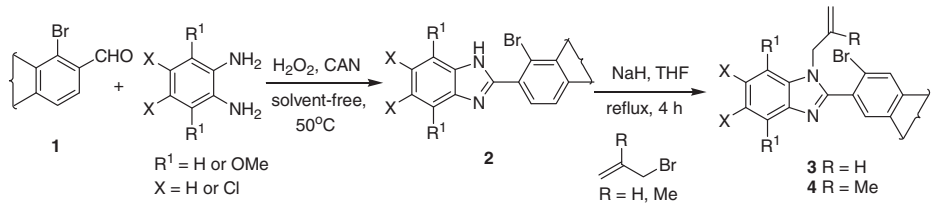
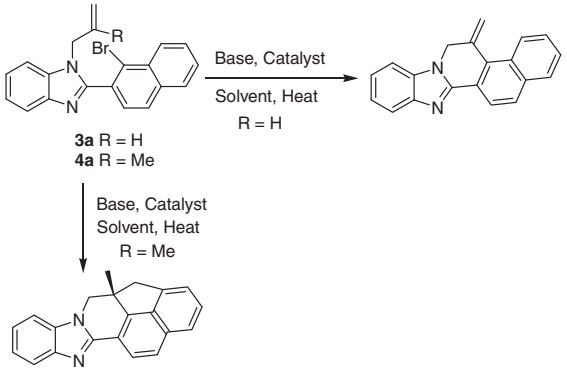


Scheme 1. Preparation of *N*-allyl and *N*-methallyl derivatives of benzimidazoles.

Table 1
Optimization of the reaction condition by using different types of catalysts, bases, and solvents[a]



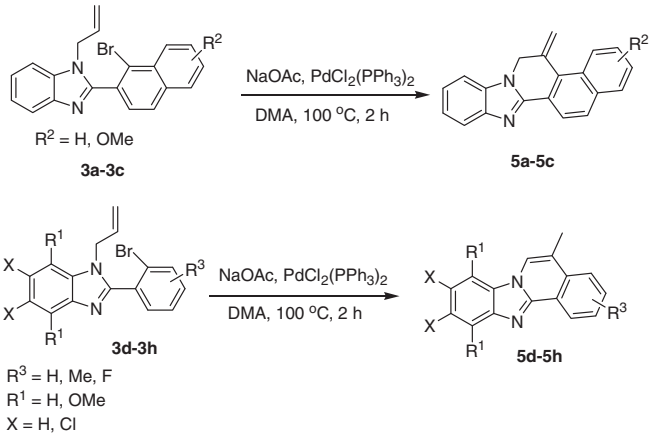
Entry	Catalyst	Base	Solvent	Yield (%)	
				5a	**6a**
1	$PdCl_2(PPh_3)_2$	NaOAc	DMA	87	85
2	$Pd(PPh_3)_4$	NaOAc	DMA	56	50
3	$PdCl_2$	NaOAc	DMA	NR[b]	NR[b]
4	$Pd(OAc)_2$	Cs_2CO_3	DMF	58	55
5	$PdCl_2(PPh_3)_2$	Et_3N	CH_3CN	15	15
6	$PdCl_2(PPh_3)_2$	NaOAc	CH_3CN	30	26
7	$PdCl_2(PPh_3)_2$	Na_2CO_3	DMA	52	45
8	$PdCl_2(PPh_3)_2$	NaOAc	$PhCH_3$	Decomp.[b]	Decomp.[b]

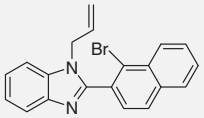
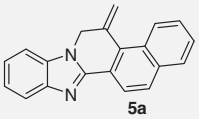
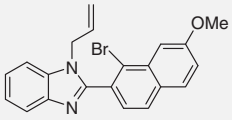
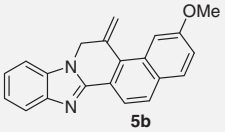
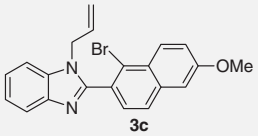
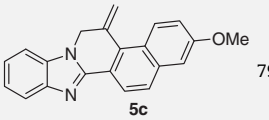
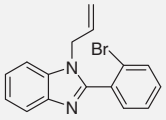
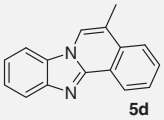
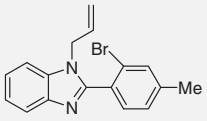
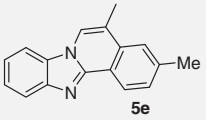
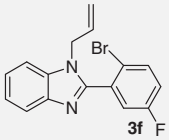
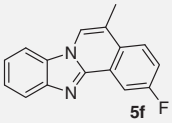
Decomp.: decomposition of starting material.
[a] Reaction conditions: substrate **3a** or **4a** (1 mmol), catalyst (10 mol %), base (1.2 mmol), and solvent (5 mL) at 100–110 °C for 2 h.
[b] NR: no reaction.

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 $PdCl_2$ catalyst no cyclized product was isolated (Table 1, entry 3). **3a** and **4a** on treatment with $PdCl_2(PPh_3)_2$ (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, [$PdCl_2(PPh_3)_2$ (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 yields[11] 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).

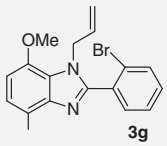
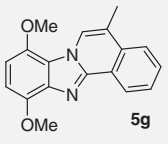
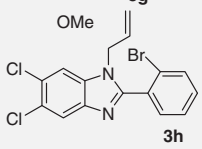
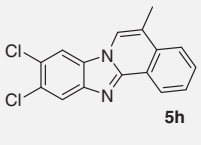
Table 2
Pd(0)-catalyzed intramolecular reaction of N-allylated benzoimidazole derivatives[a]



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	 **3g**	 **5g**	81
8	 **3h**	 **5h**	80

[a] Reagents and conditions: **3a–3h** (1 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), NaOAc (1.2 equiv), DMA (5 mL), 100–110 °C.

On the other hand N-methallylated derivatives **4a–4e** with same Heck reaction conditions afforded highly condensed analogs of benzimidazo[2,1-*a*]isoquinoline **6a–6e** (Table 3) in good yields[11] via 6-*exo*-*trig* cyclization followed by C–H activation.

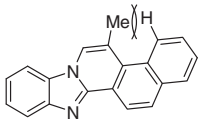


Figure 2. Steric interaction between methyl group and peri hydrogen of naphthyl ring.

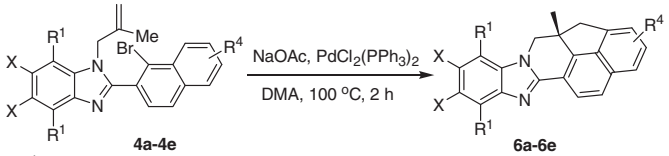
A plausible rationale for the formation of the products (**6a–6e**) is shown in Scheme 2.

Initially an alkenyl palladium (II) intermediate was generated by oxidative addition of Pd(0) to the sp^2 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).

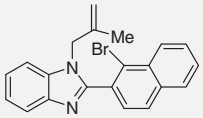
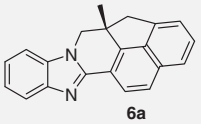
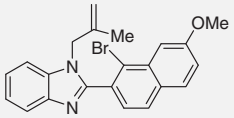
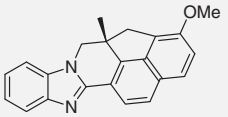
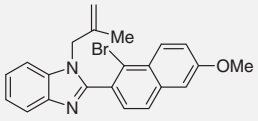
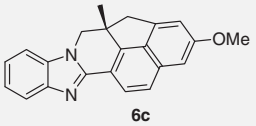
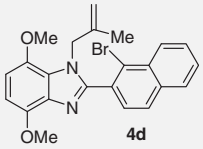
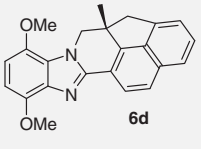
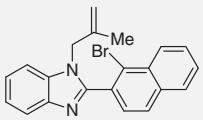
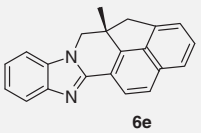
In conclusion, we have developed a general methodology for the synthesis of benzimidazo[2,1-*a*]isoquinoline and its highly condensed analogs by Pd(0)-catalyzed cyclization/C–H activation. This

Table 3
Pd(0)-catalyzed intramolecular reaction of N-methallylated benzoimidazole derivatives[a]

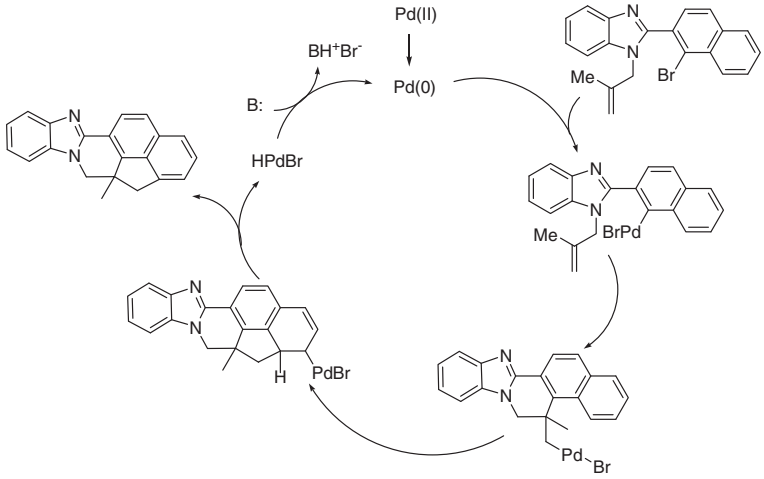


4a-4e **6a-6e**

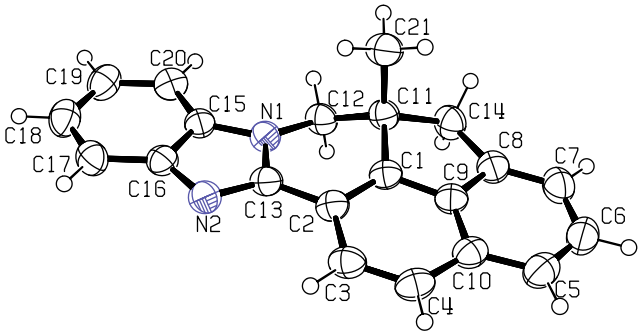
R^4 = H, OMe
R^1 = H, OMe
X = H, Cl

Entry	Substrate	Product	Yield (%)
1	 **4a**	 **6a**	85
2	 **4b**	 **6b**	78
3	 **4c**	 **6c**	75
4	 **4d**	 **6d**	76
5	 **4e**	 **6e**	80

[a] Reagents and conditions: **4a–4e** (1 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), NaOAc (1.2 equiv), DMA (5 mL), 100–110 °C.



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

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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

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11. General procedure for the synthesis of benzimidazo[2,1-*a*]isoquinolines and its condensed analogs.
Compounds **3** or **4** (1 equiv), $PdCl_2(PPh_3)_2$ (10 mol %), NaOAc (1.2 equiv), and DMA (5 mL) were placed in a two-necked round-bottomed flask. After degassing with N_2, the mixture was heated at 100–110 °C for 2 h. After cooling, the reaction mixture was diluted with saturated NH_4Cl solution, extracted with EtOAc (30 mL × 3), and the combined organics dried (Na_2SO_4). The solvent was evaporated and the crude product was purified by column chromatography.
Spectral data of representative compounds.
Compound **5a**: yellow liquid, ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{20}H_{15}N_2$ $[M^+{+}H]$: 283.1235, found: 283.1231.
Compound **5e**: pale yellow solid, mp 132 °C, ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{17}H_{15}N_2$ $[M^+{+}H]$: 247.1235, found: 247.1231.
Compound **6b**: white solid, mp 170 °C, ^1H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 $C_{22}H_{19}N_2O$ $[M^+{+}H]$: 327.1497, found: 327.1492.
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