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One-pot concise syntheses of benzimidazo[2,1-*a*]isoquinolines by a microwave-accelerated tandem process

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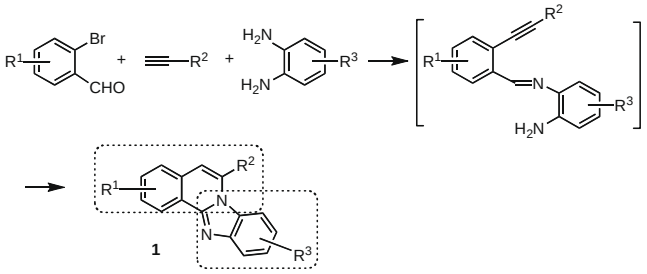
ABSTRACT

Direct, efficient syntheses of the benzimidazo[2,1-*a*]isoquinoline ring system have been achieved with 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines by a 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.

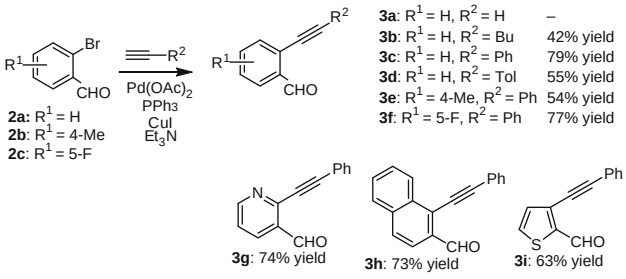
Synthesis of the benzimidazo[2,1-*a*]isoquinoline ring system has attracted a great deal of attention because of its biological activities associated with the hybrid structure of isoquinoline[1] and benzimidazole.[2] Although some approaches to the ring system have been reported,[3] one of the most efficient methodologies involves direct formation of the isoquinoline ring by metal-catalyzed cyclization of alkynylbenzene derivatives. We have recently reported the formation of 1,2-dihydroisoquinoline derivatives by In(OTf)$_3$-catalyzed tandem cyclization of *ortho*-alkynylarylimines,[4] in which the starting alkynylbenzene derivatives were obtained by a Sonogashira coupling from the corresponding aryl halides. Herein, we report an efficient methodology for the construction of the benzimidazo[2,1-*a*]isoquinoline ring system from 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines via a microwave-accelerated tandem process[5] in which a copper- and ligand-free Sonogashira coupling, 5-*endo* cyclization, oxidative aromatization, and 6-*endo* cyclization can be performed in a single synthetic operation (Scheme 1).

Prior to the investigation of the tandem strategy, we decided to tune the reaction conditions for each step, and we first examined the Sonogashira coupling reaction using *o*-bromobenzaldehyde derivatives **2**. *O*-Alkynyl aromatic aldehydes **3** were obtained in 42–79% yields, indicating the tolerance of an aldehyde group in the coupling conditions (Scheme 2).

Since the Sonogashira coupling proceeded well, we next examined the second annulation step, in which an isoquinoline ring and an imidazole ring can be formed in a tandem fashion starting from 2-ethynylbenzaldehydes **3** and 1,2-phenylenediamines **4**. Attempted cyclization using the protocol described by Dyker, who used nitrobenzene both as an oxidizing agent and as a solvent,[3a] resulted in lower yield of **1a** (Table 1, run 1). Recently, metal-catalyzed cyclization of *o*-alkynylarylimines has been reported as a direct method for the synthesis of isoquinolines.[4,6] We therefore screened a range of metal-catalyst systems including In(OTf)$_3$, Pd(OAc)$_2$/CuI, and Pd(OAc)$_2$ at 120 °C (runs 2–4). Among them, Pd(OAc)$_2$ afforded the best result under aerobic conditions. Since the lower yields obtained for **1a** may be attributed to decomposition of the products due to prolonged heating, we decided to



Scheme 1. Tandem approach to the synthesis of benzimidazo[2,1-*a*]-isoquinolines **1**.



Scheme 2. Syntheses of *o*-alkynyl aromatic aldehydes.

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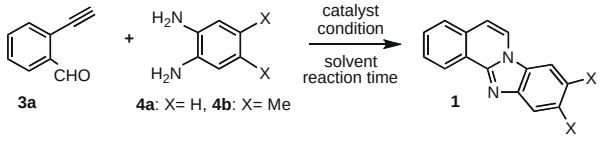
Table 1
Stepwise reaction of **3a** with **4**



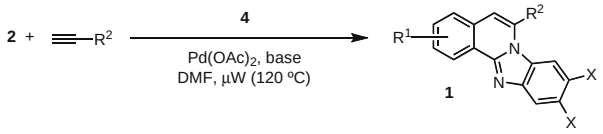
Run	Catalyst	Mol (%)	4	Condition	Solvent	Time (h)	1	Yield (%)
1[a]	—	—	**4a**	Heat[c]	$PhNO_2$	24	**1a**	41
2[b]	$In(OTf)_3$	10	**4a**	Heat[c]	DMF	24	**1a**	26
3[b]	$Pd(OAc)_2$, CuI	2	**4a**	Heat[c]	DMF	13	**1a**	27
4[b]	$Pd(OAc)_2$	2	**4a**	Heat[c]	DMF	10	**1a**	60
5[b]	$Pd(OAc)_2$	2	**4a**	μW[d]	DMF	5	**1a**	68
6[b]	$Pd(OAc)_2$	2	**4b**	μW[d]	DMF	5	**1b**	64

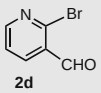
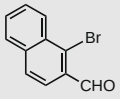
[a] Under nitrogen atmosphere.
[b] Under aerobic conditions.
[c] Oil bath temperature of 120 °C. Compound **3a** (concentration of 0.5 M).
[d] Microwave irradiation at 120 °C. Compound **3a** (concentration of 2.0 M).

conduct the reaction under microwave irradiation with the intention of minimizing the quantity of solvents and accelerating the reaction. In fact, the reaction was greatly accelerated with microwave irradiation and was completed in 5 h to give **1a** in improved yield (run 5). This microwave irradiation reaction with dimethyl derivative **4b** also gave **1b** in moderate yield (run 6).

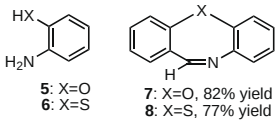
Having in hand the optimized conditions for each step, we next examined a one-pot synthetic strategy that would allow direct formation of the benzimidazo[2,1-*a*]isoquinoline ring system. In an attempt to improve the reaction conditions, we found that the

Table 2
One-pot preparation of benzimidazo[2,1-*a*]isoquinoline **1** under microwave irradiation



Run	2	R^1	R^2	4	Base	Time (h)	1	Yield[a] (%)
1	**2a**	H	Ph	**4a**	Et_3N	5.0	**1e**	68
2	**2a**	H	Ph	**4a**	Cs_2CO_3	3.0	**1e**	70
2	**2a**	H	Ph	**4a**	Cs_2CO_3	3.0	**1e**	70
3	**2a**	H	Ph	**4a**	Bu_4NOAc	0.5	**1e**	80
4	**2a**	H	Bu	**4a**	Bu_4NOAc	0.5	**1c**	77
5	**2a**	H	Bu	**4b**	Bu_4NOAc	0.5	**1d**	70
6	**2a**	H	Ph	**4b**	Bu_4NOAc	1.0	**1f**	76
7	**2a**	H	*p*-Tol	**4a**	Bu_4NOAc	0.5	**1g**	78
8	**2b**	4-Me	Ph	**4a**	Bu_4NOAc	0.5	**1h**	81
9	**2b**	4-Me	Ph	**4b**	Bu_4NOAc	0.5	**1i**	83
10	**2c**	5-F	Ph	**4a**	Bu_4NOAc	0.5	**1j**	79
11	 **2d**		Ph	**4a**	Bu_4NOAc	1.0	**1k**	73
12	 **2e**		Ph	**4b**	Bu_4NOAc	1.0	**1l**	79
13	 **2f**		Ph	**4a**	Bu_4NOAc	0.5	**1m**	77

[a] Conditions: Aldehyde **2** (0.5 mmol), alkyne (0.55 mmol), 1,2-diamine **4** (0.55 mmol), $Pd(OAc)_2$ (0.01 mmol), and Bu_4NOAc (1.0 mmol) were dissolved in DMF (100 μl), (concentration of 5.0 M). Microwave irradiation (120 °C, 200 W).



Scheme 3.

one-pot reaction of compounds **2a**, phenylacetylene, and 1,2-phenylenediamine **4a** can proceed smoothly even in the absence of CuI and PPh_3 to give **1e** in 68% yield under microwave irradiation (Table 2, run 1).[7,8] Furthermore, both Cs_2CO_3 and tetrabutylammonium acetate (Bu_4NOAc) were effective as bases, the latter being more effective, allowing for complete conversion to **1e** within 0.5 h (runs 2 and 3). Bu_4NOAc might facilitate the reduction of $Pd(OAc)_2$ to a catalytically active Pd(0) species (Pd nanoparticle).[9] To determine the general utility of this procedure, we applied these improved conditions to other aldehydes **2**, terminal alkynes, and 1,2-phenylenediamines **4**. Change in the electronic nature of substituents on the aromatic rings of the aldehydes and on alkynes did not affect the efficiency of the reaction, giving the expected hybrid compounds **1** in moderate yields in the presence of DMF (concentration of 5 M) after 0.5–1.0 h at 120 °C and 200 watts (W) (runs 4–13).

Finally, we briefly examined the reactions using aminophenol **5** and aminothiophenol **6** to see whether heteroatoms other than nitrogen can participate in the tandem reaction. When compounds **5** and **6** were treated with phenylacetylene and 1,2-phenylenediamine under similar reaction conditions, only dibenzoxazepine **7** and dibenzothiazepine **8** were obtained in 82% and 77% yields, respectively (Scheme 3).

In summary, we have demonstrated a new and concise method for one-pot construction of benzimidazo[2,1-*a*]isoquinolines starting from 2-bromoarylaldehydes, terminal alkynes, and 1,2-phenylenediamines by a microwave-promoted tandem process that involves imine formation, copper-ligand-free Sonogashira reaction, 5-*endo-trig* cyclization, oxidative aromatization, and 6-*endo-dig* cyclization reaction.

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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.2009.04.126.

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