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Synthesis of 8-aryl substituted benzo[*a*]phenanthridine derivatives by consecutive three component tandem reaction and 6-*endo* carbocyclization☆

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ABSTRACT

A concise construction of benzo[*a*]phenanthridines involving multicomponent tandem reaction/carbocyclization in a sequential format is described. The reaction proceeds initially via formation of a 4-aryl-3-arylethynyl-isoquinoline from 2-bromobenzaldehyde/*tert*-butylamine/1,3-diyne in a three component format followed by a second ring closure either via gold/silver catalyzed intramolecular hydroarylation or via iodo-catalyzed regioselective 6-*endo*-dig electrophilic cyclization. The salient feature of the strategy involves a three component reaction followed by transformation of the resulting product in to polyheterocycles with increased structural complexity in two steps.

1. Introduction

Multicomponent tandem reactions remain one of the most powerful approaches for the one pot transformation of three or more reactants into new products.[1] They have been used widely for the synthesis of natural products and heterocyclic structures of therapeutic interest.[1b,2] In an attempt to introduce further structural complexity in the multicomponent tandem reaction products, *post*-multicomponent transformations are being combined with multicomponent reactions either in tandem or in a sequential format. This in turn, provides greater flexibility, novelty, and efficiency for the rapid access to annulated polyheterocycles.[3] In recent years, terminal and internal alkynes have been extensively used as versatile building blocks in multicomponent formats that have led to the synthesis of structurally diverse five-, six-, seven-, and eight-membered heterocycles of therapeutic importance.[4] However, the above applications predominantly remained limited to terminal/internal alkynes only and report involving 1,3-diynes as reactants in a multicomponent format is scarce.[5] We envisaged that the use of 1,3-diyne as one of the reactants in a multicomponent format may initially undergo annulation to furnish a functionalized heterocycle with an alkynyl handle attached to it, which can then be subjected to *post*-multicomponent transformation for enhancing the structural diversity following the alkyne activation to enforce a second annulation.

In view of our ongoing interest in the synthesis of annulated polyheterocycles involving alkynes as one of the reactants in one pot/three component tandem formats,[6] we proposed to extend the studies to 1,3-diynes in a three component format by initially synthesizing functionalized isoquinolines followed by their conversion to afford tetracyclic scaffold benzophenanthridine and its analogues.

Benzophenanathridines are one of the widely distributed alkaloids and associated with DNA-chain intercalating ability and potent antitumor and antiinfectious activities.[7] A careful survey of the literature revealed multistep synthetic strategies for this class of compounds associated with low yields and poor generality[8] and to the best of our knowledge there is no report dealing with multicomponent format-based protocols. In this communication, we report sequenced three component tandem reaction and 6-*endo* carbocyclization reactions for the concise construction of benzo[*a*]phenanthridines by treating 2-bromobenzaldehyde with *tert*-butylamine and 1,3-diynes.

2. Results and discussion

In the first instance we explored the formation of functionalized isoquinolines using 1,3-diyne in a three component format. For this, we initially studied the condensation of the preformed imines with 1,3-diynes to afford functionalized isoquinolines.[9] Accordingly, we screened a variety of Pd-catalyzed conditions for the condensation

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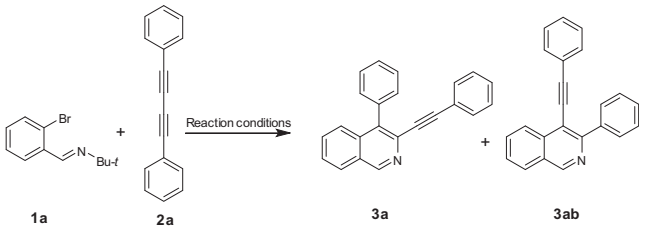
of preformed (2-bromo-benzylidene)-*tert*-butylamine **1a** with 1,3-diyne **2a** and the results have been summarized in Table 1. The reactions were generally performed in the presence of a variety of Pd-complex, LiCl, and a base by heating at 120 °C in DMF from 22 to 42 h. For most of the Pd-catalyzed conditions examined, we obtained formation of isoquinoline as a mixture of two isomers **3a** and **3ab** with the former being obtained as a major isomer. In general, use of strong bases was found to be detrimental (entry 2, 3, 6, and 9), whereas use of mild base furnished **3a** in comparatively higher yields (entry 1, 4, 7, 10). The highest isolated yields for the isomer **3a** was obtained either by employing $Pd(PPh_3)_4/LiCl/K_2CO_3$ in DMF under heating for 25 h (70%; entry 4) or by employing $Pd(PPh_3)_4/TPP/Na_2CO_3$ in DMF under heating for 22 h (68%; entry 7). For our studies, we selected $Pd(PPh_3)_4/LiCl/K_2CO_3$ as the method of choice for our further studies.

Table 1
Screening of reaction conditions for the formation isoquinoline derivative **3a** from the preformed (2-bromo-benzylidene)-*tert*-butylamine **1a** and 1,3-diyne **2a**



1a 2a 3a 3ab

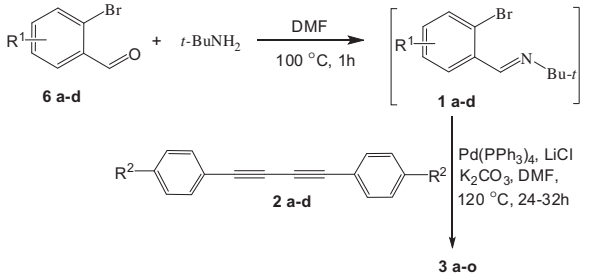
Entry	Pd-catalyst	Base	Time (h)	Yield (%)[a] **3a**/**3ab**
1	$Pd(OAc)_2$	Na_2CO_3	32	62:13
2	$Pd(dppf)_2Cl_2/LiCl$	KOAc	36	47:25
3	$Pd(PPh_3)_4/LiCl$	KOAc	42	56:18
4	$Pd(PPh_3)_4/LiCl$	K_2CO_3	25	70:12
5	$Pd(dppf)_2Cl_2$	K_2CO_3	32	48:19
6	$Pd(PPh_3)_4$	Cs_2CO_3	36	42:16
7	$Pd(PPh_3)_4/TPP$	Na_2CO_3	22	68:11
8	$Pd(PPh_3)_4/TPP$	K_2CO_3	24	<10
9	$Pd(PPh_3)_4/TPP$	KOAc	24	<10
10	$Pd(OAc)_2/TPP$	Na_2CO_3	24	65:14

[a] Imine **1a** (1.0 mmol, 0.239 g) and bis alkyne **2a** (1.2 mmol, 0.286 g), 5 mL of DMF, Pd catalyst (0.05 mmol), TPP (0.1 mmol, 0.027 g) or LiCl (1.0 mmol, 0.041 g), and base (2.0 mmol) heated at 120 °C.

Once the conditions for the synthesis of functionalized isoquinoline **3a** was established, we embarked with the development of a three component tandem format for its synthesis. For this, we treated 2-bromobenzaldehyde **6a** with *tert*-butylamine in DMF for 1 h followed by addition of 1,3-diyne **2a** in the presence of the optimized reaction condition $Pd(PPh_3)_4/LiCl/K_2CO_3$ at 120 °C for 25 h. After work up, the product **3a** was isolated in 65% yield, which was marginally less than 70% yield obtained when preformed imine **1a** was treated with 1,3-diyne **2a** (entry 4; Table 1). Next, the scope and limitation of our methodology was established by treating a series of 1,3-diynes (**2a**–**d**) with 2-bromobenzadehydes (**6a**–**d**) in the presence of *tert*-butylamine in a three component tandem format and the results have been summarized in Table 2. In all cases, the substrates underwent annulation to afford 11 isoquinoline derivatives (**3a**–**o**) in 58–70% yield. In general, the three component tandem synthesis to isoquinoline was not sensitive to electronic substitution present on 1,3-diynes and 2-bromobenzaldehydes.

After successfully establishing the reaction condition for the synthesis of functionalized isoquinolines **3**, we next screened the reaction conditions for enforcing the second cyclization using 6-*endo* carbocyclization route in these two isomers. In the first instance we proposed to effect this via 6-*endo*-dig carbocyclization

Table 2
Three component tandem synthesis of isoquinoline derivatives **3a**–**o** in one-pot



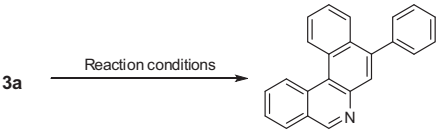
6 a-d 1 a-d 2 a-d 3 a-o

entry	R^1	R^2	Time	Compound no (% yield)[a]
1	H	H	25	**3a** (65)
2	H	CH_3	28	**3b** (64)
3	H	^{t}Bu	25	**3c** (66)
4	H	OCH_3	26	**3d** (65)
5	5-OCH_3	H	28	**3e** (68)
6	5-OCH_3	CH_3	30	**3f** (65)
7	5-OCH_3	^{t}Bu	26	**3g** (66)
8	5-OCH_3	OCH_3	24	**3h** (64)
9	4,5-di OCH_3	H	25	**3i** (70)
10	4,5-di OCH_3	CH_3	30	**3j** (65)
11	4,5-di OCH_3	^{t}Bu	26	**3k** (68)
12	5-F	H	24	**3l** (62)
13	5-F	CH_3	32	**3m** (60)
14	5-F	^{t}Bu	28	**3n** (58)
15	5-F	OCH_3	26	**3o** (61)

[a] Reaction condition: 5 mL of DMF, 1.0 mmol of **6**, 1.5 mmol of ^{t}BuNH$_2$ were placed in a 4 dram vial heated at 100 °C for 1 h followed by the addition of 1.2 mmol of **2**, 0.05 mmol of $Pd(PPh_3)_4$, 1.0 mmol of LiCl, and 2.0 mmol of K_2CO_3 and were heated at 120 °C for indicated time.

following the activation of the alkyne moiety with transition metals.[4e,9,10] The annulation of alkyne containing intramolecular nucleophilic centers via activation of the alkyne moiety has been documented[11] as the most efficient strategy for the straight forward and rapid access to heterocyclic scaffolds. Accordingly, we initiated our studies by examining the ability of the isoquinoline intermediates **3a** and **3ab** to undergo intramolecular hydroarylation by employing a variety of transition metal catalysts in different solvents and the results have been summarized in Table 3. After extensive screening of a metal catalysts, such as CuI (entry 1), $AuCl_3$

Table 3
Optimization of reaction conditions for the conversion of **3a** to **4a**



4a

Entry	Solvent	Catalyst(s)	Yield (%)[a]
1	Toluene	CuI	NR
2	Toluene	$AuCl_3$	NR
3	Toluene	$Cu(OTf)_2$	NR
4	Toluene	$Zn(OTf)_2$	NR
5	Toluene	$AgSbF_6$	NR
6	Toluene	$AuClPPh_3$	NR
7	Toluene	$AgSbF_6/AuClPPh_3$	65[b]
8	DCE	$AgSbF_6/AuClPPh_3$	58[b]
9	DME	$AgSbF_6/AuClPPh_3$	17
10	DMF	$AgSbF_6/AuClPPh_3$	NR
11	DMSO	$AgSbF_6/AuClPPh_3$	NR
12	THF	$AgSbF_6/AuClPPh_3$	NR[c]

[a] All reactions were carried out with using 0.5 mmol of **3a** (0.152 g), 0.05 mmol of catalyst(s), and monitored for 24 h at 120 °C. NR=No Reaction.
[b] Reaction completed in 5 h.
[c] Reaction carried out at 60 °C for 24 h.