Tetrahedron Letters 51 (2010) 3372–3375

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Palladium-mediated reductive Mizoroki–Heck cyclization strategy for the regioselective formation of dibenzoazocinone framework

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ARTICLE INFO

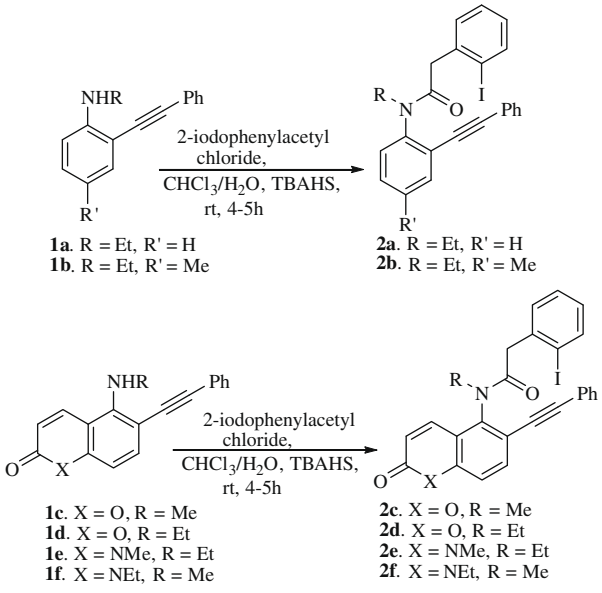
Article history:
Received 25 March 2010
Revised 16 April 2010
Accepted 20 April 2010
Available online 24 April 2010

Keywords:
Dibenzoazocinone
Reductive Mizoroki–Heck cyclization
$Pd(PPh_3)_4$
Mixed solvent
2-Iodophenylacetic acid

ABSTRACT

The synthesis of dibenzoazocine framework through palladium-mediated reductive Mizoroki–Heck cyclization has been described. The procedure is simple, straightforward, and regioselective.

Nitrogen heterocycles are among the most useful compounds and their utility has been widely demonstrated in the chemistry of natural products, material sciences, and in pharmaceutical chemistry.[1] Their synthesis has attracted considerable attention due to their importance as building blocks for many therapeutically useful materials, as well as a wide range of potential biological activity of both synthetic and naturally occurring derivatives. The eight-membered nitrogen-containing framework is found in several alkaloids such as manzamine A,[2,3] keramamine-A.[4] Some N-substituted dibenzoazocine derivatives are found to exhibit hypotensive properties.[5] A number of approaches for the synthesis of nitrogen-containing heterocycles have been developed, most of them lead to the formation of five- and six-membered ring systems. However, the construction of eight- and nine-membered heterocycles is limited.[6] The main reason is that their formations are often inhibited due to entropy factors and transannular interaction.[7] Tetrahydrobenzo[*d*]azocine derivatives have been synthesized by Larock et al. via palladium-catalyzed heteroannulation of allenes.[8] However, this procedure renders the compounds as mixtures of *E*/*Z* isomers of the *exo*-cyclic double bond. Transition metal-catalyzed reactions were used for generating dibenzoazocinone scaffolds.[9] Thus the Mizoroki–Heck reaction of olefins proved to be high yielding and reliable. Though this approach regioselectively leads to eight-membered rings, a problem with the geometry and location of the resulting double bond still exists, due to unselective elimination of palladium-hydrogen species at the final step of the Mizoroki–Heck reaction. Donets and Eycken[10] recently developed a microwave-assisted cyclization procedure to synthesize extended alkyl chain containing dibenzoazocinone framework. However, the procedure is low yielding and applied for only two-



Scheme 1. Synthesis of precursors **2a–f**.

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doi:10.1016/j.tetlet.2010.04.084

Table 1
Optimization of the reductive Mizoroki–Heck reaction[a]

Entry	Catalyst	Solvent (v/v)	Time (h)	Temp (°C)	Yield[b] (%)
1[c]	**$Pd(PPh_3)_4$**	**DMF/H_2O (7:3)**	**0.5**	**100**	**60**
2	$Pd(PPh_3)_4$	DMF	0.5	100	—
3	$Pd(PPh_3)_4$	DMF/H_2O (1: 1)	0.5	100	30
4	$Pd(PPh_3)_4$	DMF/H_2O (7:3)	0.5	140	20
5	$Pd(PPh_3)_4$	DMF/H_2O (7:3)	1.5	100	DP[d]
6	$Pd(OAc)_2$	DMF/H_2O (7:3)	0.5	100	—
7	$Pd(PPh_3)_2Cl_2$	DMF/H_2O (7:3)	0.5	100	—
8	$Pd(PPh_3)_4$	DME/H_2O (7:3)	0.5	100	20
9	$Pd(PPh_3)_4$	CH_3CN/H_2O(7:3)	0.5	100	15
10	$Pd(PPh_3)_4$	THF/H_2O (7:3)	0.5	100	15

[a] In all cases HCOONa was used as reducing agent.
[b] Isolated yield.
[c] Optimized reaction condition.
[d] DP = Decomposed product.

electron-donating substrates. Our continued interest in the palladium-mediated synthesis of heterocycles[11] has prompted us to undertake the present study to synthesize dibenzoazocinone framework based on palladium-mediated intramolecular reductive Mizoroki–Heck cyclization.

The precursors **2a–f** for our present study were synthesized in good to moderate yields by the reaction of either *N*-methyl or *N*-ethyl *o*-substituted amines **1a–f** with 2'-iodophenylacetyl chloride (which was in turn prepared by refluxing 2'-iodophenylacetic acid with thionyl chloride) as depicted in Scheme 1. The *o*-substituted *N*-methyl or *N*-ethyl amines were prepared from *N*-methyl or *N*-ethyl amines by bromination and subsequent Sonogashira cross coupling with phenyl acetylene.

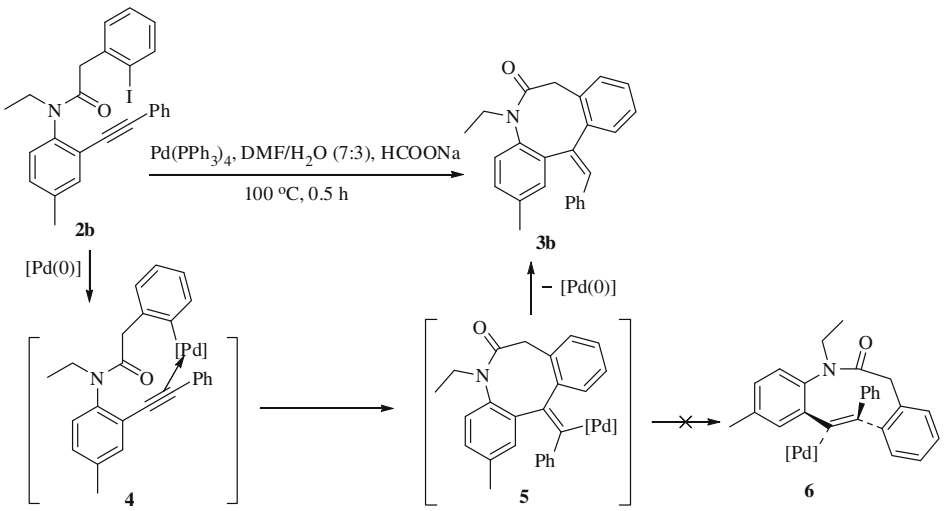
The optimal conditions for the reductive Mizoroki–Heck cyclization were established with the amide **2b**. The reaction was run under the conventional heating condition at 100 °C in a mixture of solvents (DMF/water in 7:3 volume) in the presence of tetrakis (triphenylphosphine) palladium(0) (10 mol %) as a catalyst and sodium formate as a reducing agent. We found that temperature plays an important role in the cyclization. As the temperature was increased from 100 °C, extensive decomposition of the starting materials occurred leading to lowering of the yield (10–20%) of cyclized products. On the other hand, decreasing the temperature from the optimal temperature results in the recovery of the starting materials. The cyclization process is extremely time dependent. The reaction was run for about 30 min. The increase in the reaction time resulted in the decomposition of both the product and the unreacted starting material. Under the optimal condition (DMF/water in 7:3, $Pd(PPh_3)_4$, HCOONa, reflux at 100 °C for 30 min.) the amide **2b** was regioselectively cyclized to afford 8-*exo* product **3b** in 60% yield along with the unreacted starting material. Even at this optimal condition some decomposition occurred. The catalysts like $Pd(OAc)_2$, $Pd(PPh_3)_2Cl_2$ were found to be ineffective. Solvents like acetonitrile, DME, THF with water gave low yields of the cyclized product. The reaction failed in the absence of water due to the ineffectiveness of the reducing agent in organic solvent (Table 1).

The regioselective formation of 8-*exo*-cyclized product during the course of the reaction can be rationalized by a mechanism similar to the one proposed by Donets and Eycken.[10] An aryl palladium Π-complex **4** generated initially from **2b** is transformed readily into a σ-vinyl palladium complex **5** via simultaneous *syn*-addition to the triple bond. *endo*-Cyclization via a hypothetical intermediate **6** is unfavorable due to high strain exerted by the trans-geometry around the double bond in the nine-membered intermediate.[10] The σ-vinyl complex readily gets reduced to regenerate the Pd(0) catalyst with a reducing agent present in the reaction mixture. *syn*-Addition of palladium to the triple bond during the Mizoroki–Heck reaction implies exclusive formation of azocinone compounds possessing *Z* configuration of the *exo*-cyclic double bond (Scheme 2).

All the other substrates **2a**, **2c–f** were treated similarly to produce the 8-*exo* cyclized products in 42–65% yields (Table 2).

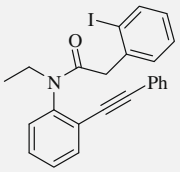
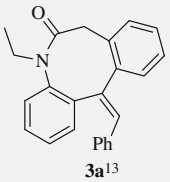
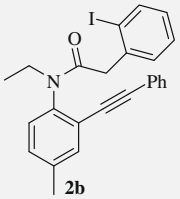
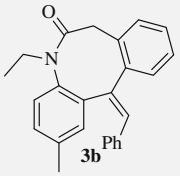
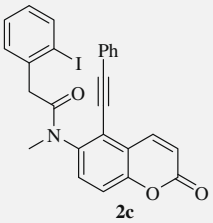
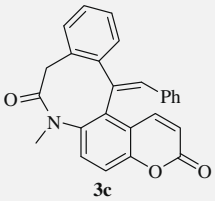
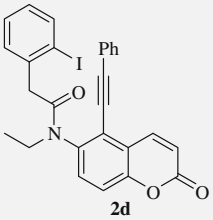
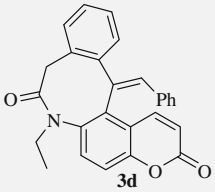
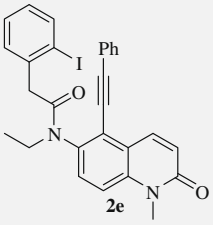
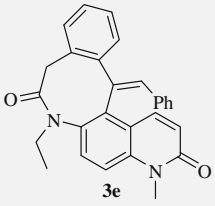
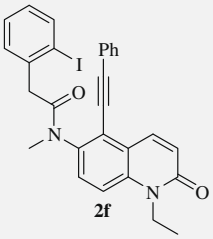
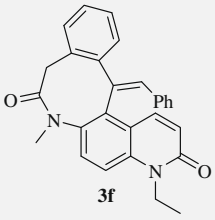
Donets and Eycken[10] reported the dibenzoazocinone framework via microwave-assisted cyclization. The procedure is low yielding and applied only to two-electron-donating substrates. Recently we have also synthesized[9] different dibenzoazocine and azocinone frameworks through palladium-mediated Mizoroki–Heck cyclization strategy. However, this process led to the formation of nine-membered cyclized products and bond migration products along with expected 8-*exo* cyclized products. Another drawback of such a process is that either the reaction failed or produced very low yield of the cyclized products in the case of substrates containing an electron-donating group attached to the amide nitrogen.

In conclusion, we have achieved an efficient and straightforward method for the construction of potentially bioactive dibenzoazocinone framework via palladium-mediated reductive Mizoroki–Heck cyclization. In this method the 8-*exo*-cyclization products have been obtained in a regioselective manner. The protocol is equally effective for both electron-donating and electron-withdrawing substrates.



Scheme 2. Reagents, conditions, and plausible mechanism of the reaction.

Table 2
Summarized results of the reductive Mizoroki–Heck reaction (see below-mentioned reference for further information).

Entry	Substrate	Time (min)	Product	Yield
1	 **2a**[12]	30	 **3a**[13]	65
2	 **2b**	30	 **3b**	60
3	 **2c**	30	 **3c**	55
4	 **2d**	30	 **3d**	56
5	 **2e**	30	 **3e**	45
6	 **2f**	30	 **3f**	42

Acknowledgments

We thank the DST (New Delhi) and the CSIR (New Delhi) for financial assistance. T.G. and S.C. are grateful to the CSIR (New Delhi) for their research fellowships.

References and notes

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12. *General procedure for the preparation of the amide* **2a**:
A mixture of 2'-iodophenylacetic acid (500 mg, 1.9 mmol) and $SOCl_2$ (5 ml) was stirred at 100 °C for 3 h. After evaporation, the residue was dissolved in $CHCl_3$ (20 mL). A solution of amine **1a** (421 mg, 1.9 mmol) in $CHCl_3$ (20 mL) and tetrabutylammonium hydrogensulfate (catalytic amount) were added to the stirred solution of the acid chloride. To this reaction mixture an aqueous solution of K_2CO_3 (526 mg, 3.8 mmol) was added slowly. After stirring for 4.5 h at room temperature, the solution was washed with 5% HCl (2 × 20 mL) and then with 5% aqueous NaOH (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography over silica-gel using pet. ether–ethylacetate (9:1) as an eluent. *Compound* **2a:** Gummy, yield = 75%, IR (KBr): 2216, 1662, 1592. cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.72 (d, 1H, *J* = 7.6 Hz), 7.65–7.66 (m, 1H), 7.52–7.53 (m, 2H), 7.36–7.39 (m, 4H), 7.16–7.26 (m, 4H), 6.83 (t, 1H, *J* = 7.2 Hz), 3.98–4.06 (m, 1H), 3.69–3.78 (m, 1H), 3.61 (d, 1H, *J* = 16.4 Hz), 3.55 (d, 1H, *J* = 16.4 Hz), 1.17 (t, 3H, *J* = 7.2 Hz). Anal. Calcd for $C_{24}H_{20}INO$: C, 61.95; H, 4.33; N, 3.01. Found: C, 61.86; H, 4.18; N, 2.83.
General procedure for the reductive Mizoroki–Heck cyclization of compound **2a**:
A mixture of the compound **2a** (100 mg, 0.21 mmol), HCOONa (21.9 mg, 0.32 mmol), $Pd(PPh_3)_4$ (7.4 mg, 6.4×10^{-3} mmol) in DMF/H_2O (10 mL, 7:3) was heated with continuous stirring at 100 °C for 30 min. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and water (5 mL) was added. This was then extracted with $CHCl_3$ (3 × 15 mL). The $CHCl_3$ extract was washed with water (2 × 10 mL) followed by brine (10 mL). The organic layer was dried (Na_2SO_4). Evaporation of $CHCl_3$ furnished a crude mass. This was purified by column chromatography over silica-gel. Elution of the column with pet. ether–ethyl acetate (9:1) afforded the product **3a**. *Compound* **3a:** White solid, yield = 65%, mp 126–128 °C, IR (KBr): 1651, 1592 cm^{-1}, ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.54 (dd, 1H, *J* = 1.2 Hz, 7.6 Hz), 7.35–7.48 (m, 3H), 7.27–7.34 (m, 3H), 7.04–7.23 (m, 4H), 6.78–6.81 (m, 2H), 6.78 (s, 1H), 3.61–3.65 (m, 1H), 3.53 (d, 1H, *J* = 14.0 Hz), 3.35 (d, 1H, *J* = 14.0 Hz), 3.02–3.11 (m, 1H), 0.93 (t, 3H, *J* = 7.2 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C = 169.5, 142.0, 141.0, 139.3, 136.4, 135.4, 133.6, 131.1, 131.2, 130.9, 129.1, 129.0, 128.5, 128.3, 128.2, 128.1, 127.6, 127.5, 125.1, 43.7, 42.6, 14.1. MS (EI): *m/z* = 339 [M^+]. Anal. Calcd for $C_{24}H_{21}NO$: C, 82.92; H, 6.24; N, 4.13. Found: C, 82.74; H, 6.18; N, 4.06.