Palladium-Mediated Reductive Heck Cyclization for the Formation of Dibenzoazepinone Framework

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Received 15 September 2009

Abstract: The dibenzoazepinone framework has been synthesized through a palladium-mediated Sonogashira cross-coupling followed by a reductive Heck cyclization. The reactions are simple, straightforward, and have been carried out under ligand-free conditions.

Key words: dibenzoazepinone, reductive Heck, Sonogashira cross coupling, $Pd(PPh_3)_4$

Palladium-mediated reactions are the most developed methods for the construction of carbon–carbon and carbon–heteroatom bonds.[1] Among the many intramolecular processes provided by palladium catalyst in heterocyclic chemistry, the Heck reaction is particularly valuable for the formation of rings of various sizes. Most often this type of reaction is used for the formation of five- and six-membered rings.[2] However, there is a growing number of reports in recent years that demonstrate the synthetic utility of the intramolecular Heck reaction for the assembly of medium-sized rings ($n \geq 7$).[3,4] In most cases, the substrates contain a suitably placed substituent to affect arylation, leading to exclusive formation of *exo*[3] or *endo*[4] products. In the absence of such stereodirecting groups, the outcome can be unpredictable, often leading to mixtures of products. Ways of controlling the regioselectivity of this cyclization are rarely studied.[5]

Dibenzoazepinone framework is widespread among natural compounds and important pharmaceuticals. Considerable efforts have been made toward the synthesis of oxacarbazepine,[6] (Figure 1) the active ingredient of Trileptal, LY411575[7] (Figure 1) a γ-secretase inhibitor and N-substituted Darenzepine[8] as selective $\alpha_v\beta_3$ antagonists.

Most often the construction of the medium-sized ring of dibenzoazepinone framework is achieved via intramolecular Friedel–Crafts alkylation. However, this method demands an excess of Lewis acid and lacks flexibility for variation of substituent. Alternatively, ring closure is accomplished upon formation of the C–N bond via intramolecular reductive amination. In this particular paper we have elaborated a new pathway towards the synthesis of dibenzoazepinone framework based on palladium-mediated intramolecular reductive Heck cyclization.

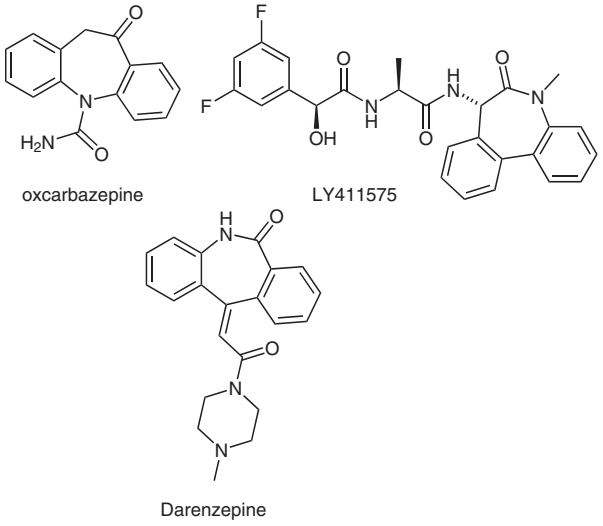
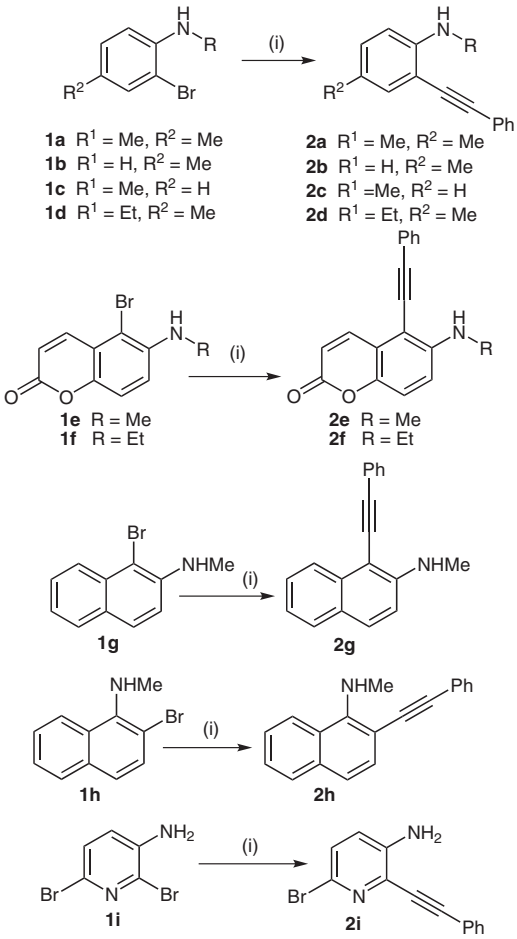


Figure 1

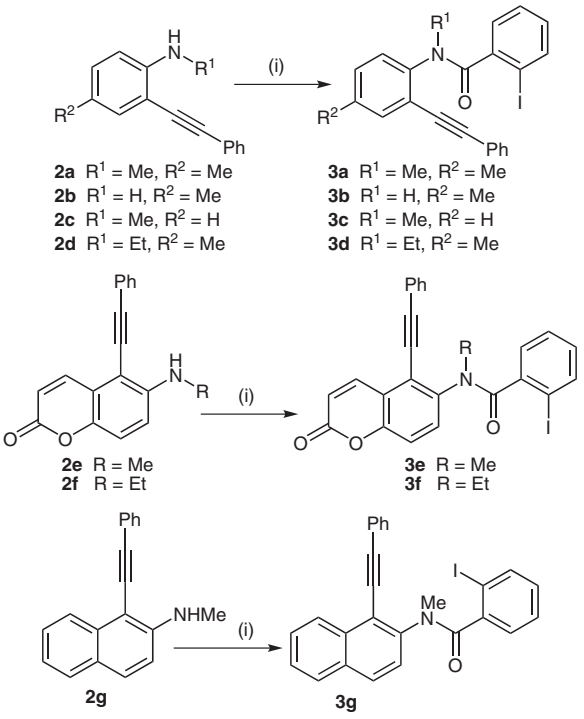
The required precursors for the reductive Heck cyclization were synthesized in three steps: bromination of the amines, Sonogashira coupling of the bromo derivatives with phenylacetylene, and subsequent amide-formation reaction with iodobenzoylchloride. The brominations of amines were carried out with *N*-bromosuccinimide in acetonitrile at room temperature. The Sonogashira coupling of all the bromo derivatives were carried out with phenylacetylene using $Pd(PPh_3)_2Cl_2$ as catalyst and CuI as the co-catalyst in anhydrous DMF containing triethylamine under heating for four to six hours (Scheme 1).

The subsequent amide formation reactions of substrate **2a–f,g** were carried out with 2-iodobenzoylchloride (which was in turn prepared by refluxing 2-iodobenzoic acid with thionyl chloride) under phase-transfer-catalysis conditions using tetrabutylammonium hydrogen sulfate (TBAHS) as a catalyst and potassium carbonate as a base (Scheme 2). However, attempts of amide formation using all the reported protocols failed in the case of substrates **2h,i**. Perhaps due to steric hindrance for the former (**2h**) and the presence of the pyridine nitrogen for the latter (**2i**). Our first attempt to find optimal conditions for the reductive Heck reaction (Table 1) was carried out with the amide **3f**. The reaction was run under conventional heating (at 120 °C) in the presence of 3 mol% of $Pd(PPh_3)_4$ as the catalyst and sodium formate as the reducing agent.

SYNLETT 2009, No. 19, pp 3127–3130
Advanced online publication: 15.10.2009
DOI: 10.1055/s-0029-1218298; Art ID: G30409ST



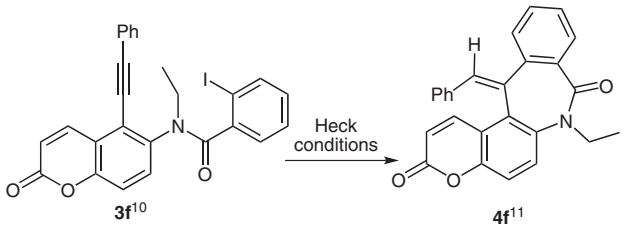
Scheme 1 *Reagents and conditions*: (i) phenylacetylene, dry DMF, Et_3N, $Pd(PPh_3)_2Cl_2$, CuI, heat, 120 °C, 4–6 h.



Scheme 2 *Reagents and conditions*: (i) 2-iodobenzoyl chloride, $CHCl_3$–H_2O, TBAHS, K_2CO_3.

The optimal solvent system for the cyclization was found to be a DMF–water mixture. Under these optimized conditions we obtained 7-*exo*-cyclized product **4f** regioselectively and in 85% yield. The structure of the obtained compound **4f** was fully confirmed from its X-ray crystal structure.[9] The reaction failed in the absence of water probably due to ineffectiveness of the reducing agent under anhydrous conditions.

Table 1 Optimization of the Reaction Conditions[10,11]



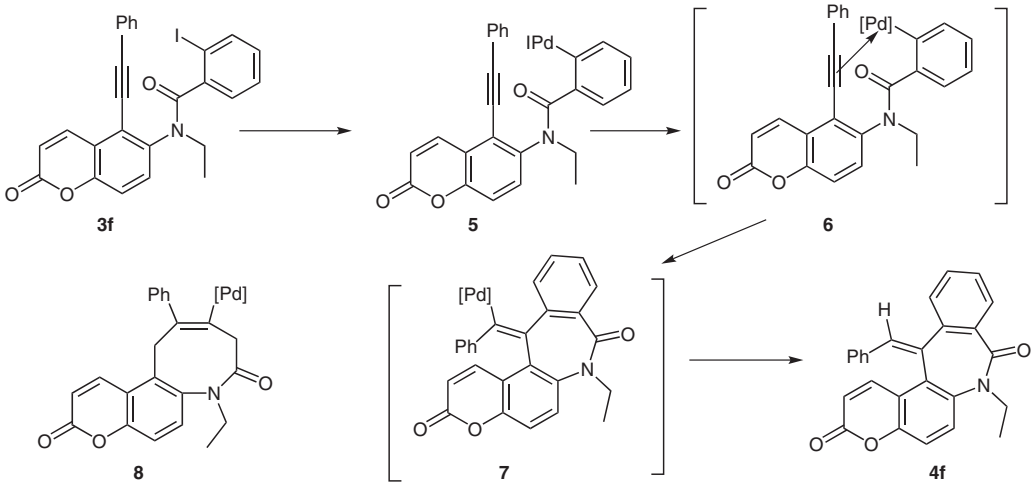
Entry	Solvent	Catalyst[a]	Base[b]	Temp (°C)[c]	Yield of **4f** (%)
1	DMF–H_2O (7:3)	$Pd(PPh_3)_4$	–	120	85
2	MeCN–H_2O (7:3)	$Pd(PPh_3)_4$	–	80	45
3	DMF	$Pd(PPh_3)_4$	–	120	n.r.
4	DME–H_2O (7:3)	$Pd(PPh_3)_4$	–	120	35
5	DMF–H_2O (7:3)	$Pd(PPh_3)_4$	K_2CO_3	120	n.r.
6	DMF–H_2O (7:3)	$Pd(OAc)_2$	–	120	n.r.
7	DMF	$Pd(OAc)_2$	Cs_2CO_3	120	n.r.
8	DMF–H_2O (7:3)	$Pd(PPh_3)_4$	–	150	45
9	DMF–H_2O (7:3)	$Pd(PPh_3)_2Cl_2$	–	120	n.r.

[a] All the reactions were carried out using 3 mol% of catalyst.
[b] All the reactions were carried out for 4 h.
[c] Sodium formate used as a reducing agent for entries 1–4, 6, and 8.

Catalysts like $Pd(OAc)_2$ and $Pd(PPh_3)_2Cl_2$ were found to be ineffective. Solvents like acetonitrile or DME with water resulted in the formation of a small amount of cyclized product along with unidentified products. Addition of a base like K_2CO_3 or Cs_2CO_3 caused decomposition of the starting material. Increasing the temperature led to decomposition of the cyclized products.

The regioselective formation of *exo*-cyclized products during reductive Heck cyclization can be rationalized via a probable mechanism as depicted in Scheme 3.

Initially generated aryl palladium π-complex **6** is transformed into σ-vinyl palladium complex **7** via simultaneous *syn* addition to the triple bond. The *endo* cyclization via a hypothetical intermediate **8** is fairly unlikely due to high strain exerted by the *trans* geometry around the double bond in the eight-membered ring. The Pd(0) catalyst is regenerated by the reducing agent present in the reaction mixture.



Scheme 3 Probable mechanism of the cyclization

Table 2 Results of Reductive Heck Cyclization

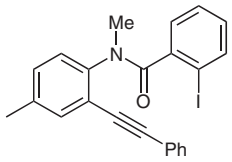
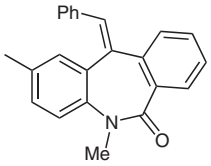
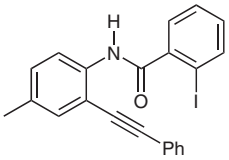
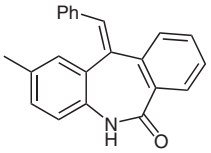
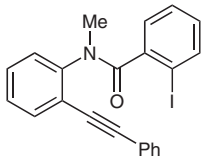
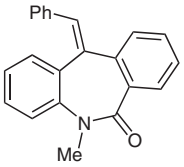
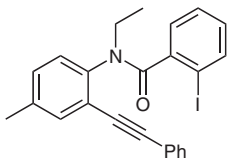
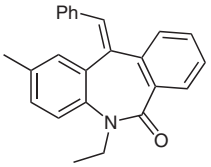
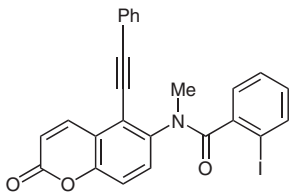
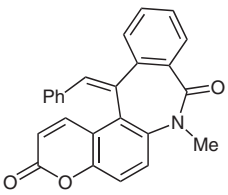
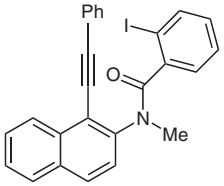
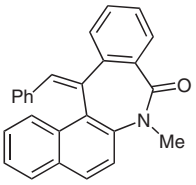
Substrate	Time (h)	Product	Yield (%)
 **3a**	4.2	 **4a**	90
 **3b**	4.5	 **4b**	87
 **3c**	4.1	 **4c**	85
 **3d**	4.3	 **4d**	75
 **3e**	4.2	 **4e**	80

Table 2 Results of Reductive Heck Cyclization (continued)

Substrate	Time (h)	Product	Yield (%)
 **3g**	5	 **4g**	65

To explore general applicability of this strategy for the synthesis of medium-sized rings we applied this protocol to other amides **3a**–**e**,**g**, and in all cases we obtained the desired *exo*-cyclized products in 65–90% yields (Table 2).

In summary, we have developed an efficient new protocol for the synthesis of dibenzoazepinone framework. The medium-sized ring is constructed by applying reductive intramolecular Heck cyclization, which occurs regioselectively.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the DST (New Delhi) for financial assistance. Two of us are grateful (S.C., T.G.) to the CSIR (New Delhi) for fellowships.

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(9) CCDC 747690 contains supplementary crystallographic data for the structure **4f**.

(10) **General Procedure for the Formation of Amide 3f**

A mixture of 2-iodobenzoic acid[12] (500 mg, 2.01 mmol) and $SOCl_2$ was stirred at 100 °C for 3 h. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2 (20 mL). A solution of amine **2f** (583 mg, 2.01 mmol) in CH_2Cl_2 (20 mL) and TBAHS (cat. amount) was added to the stirred solution of acid chloride. To this reaction mixture an aq solution of K_2CO_3 (556 mg, 4.03 mmol) was added slowly. After stirring for 5 h at r.t., the solution was washed with 5% HCl (2 × 20 mL) and then with 5% aq NaOH (2 × 20 mL). The organic layer was dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was purified by column chromatography over silica gel using PE–EtOAc (7:3) as an eluent.

Compound **3f**: white solid, yield 78%, mp 176–178 °C. IR (KBr): ν_{max} = 2212, 1738, 1651, 1565 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.08 (t, 3 H, *J* = 7.2 Hz), 3.56–3.68 (m, 1 H), 4.49–4.61 (m, 1 H), 6.48 (d, 1 H, *J* = 9.6 Hz), 6.82–6.83 (m, 1 H), 7.03–7.11 (m, 1 H), 7.21–7.26 (m, 2 H), 7.45–7.47 (m, 3 H), 7.56–7.70 (m, 4 H), 8.15 (d, 1 H, *J* = 9.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.8, 43.7, 82.1, 93.6, 117.0, 117.6, 121.5, 126.7, 127.0, 127.6, 128.7, 128.8, 129.9, 130.1, 131.7, 131.9, 132.6, 139.8, 141.3, 141.9, 153.0, 159.6, 169.7. HRMS: *m/z* found for $C_{26}H_{18}INO_3$: 542.1890 [M^+ + Na]. Anal. Calcd for $C_{26}H_{18}INO_3$: C, 60.13; H, 3.49; N, 2.70. Found: C, 60.33; H, 3.29; N, 2.93.

(11) **General Procedure for Reductive Heck Cyclization of Compound 3f**

A mixture of compound **3f**[12] (100 mg, 0.19 mmol), HCOONa (19.6 mg, 0.29 mmol), $Pd(PPh_3)_4$ (6.6 mg, 5.7×10^{-3} mmol) in DMF–H_2O (10 mL, 7:3) was heated with continuous stirring at 120 °C for 4.2 h. After completion of the reaction as monitored by TLC, the reaction mixture was cooled and H_2O (5 ml) was added. This was then extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extract was washed with H_2O (3 × 10 mL) followed by brine (10 mL). The organic layer was dried (Na_2SO_4). Evaporation of CH_2Cl_2 furnished a crude mass, which was purified by column chromatography over silica gel. Elution of the column with PE–EtOAc (3:1) afforded product **4f**.

Compound **4f**: white solid, yield 85%, mp 198–200 °C. IR (KBr): ν_{max} = 1724, 1633 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.19–1.27 (m, 3 H), 3.74–3.81 (m, 1 H), 4.69–4.76 (m, 1 H), 6.18 (d, 1 H, *J* = 9.8 Hz), 6.98 (s, 1 H), 7.08–7.09 (m, 2 H), 7.19–7.20 (m, 3 H), 7.28–7.31 (m, 2 H), 7.38–7.41 (m, 1 H), 7.45–7.49 (m, 1 H), 7.57 (d, 1 H, *J* = 9.0 Hz), 7.63 (d, 1 H, *J* = 9.8 Hz), 7.89 (dd, 1 H, *J* = 0.8, 7.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 44.3, 114.3, 116.9, 117.3, 124.9, 127.8, 128.4, 128.5, 128.8, 128.9, 130.9, 131.7, 131.9, 132.2, 132.4, 132.8, 134.6, 135.4, 136.4, 140.5, 145.04, 152.2, 159.9, 167.6. HRMS: *m/z* calcd for $C_{26}H_{19}NO_3$: 394.1438 [M^+ + H]; found: 394.1406 [M^+ + H]. Anal. Calcd for $C_{26}H_{19}NO_3$: C, 79.37; H, 4.87; N, 3.56. Found: C, 79.58; H, 5.04; N, 3.75.

(12) 2-Bromobenzoic acid can also be used to give the corrosponding 2-bromo derivative **3** which also undergoes reductive Heck cyclization to afford **4f** (yield 80%).