Tetrahedron Letters 52 (2011) 6030–6034

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

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

Syntheses of indolo[3,2,1-*d,e*]phenanthridines and isochromeno[3,4-*a*] carbazoles: palladium catalyzed intramolecular arylation via C–H functionalization

Ezhumalai Yamuna [a], Matthias Zeller [b], Karnam Jayarampillai Rajendra Prasad [a,*]

[a] Department of Chemistry, Bharathiar University, Coimbatore 641 046, India
[b] Department of Chemistry, Youngstown State University, One University Plaza, Youngstown, OH 44555, USA

ARTICLE INFO

Article history:
Received 13 May 2011
Revised 30 August 2011
Accepted 4 September 2011
Available online 7 September 2011

Keywords:
Biaryl coupling
Intramolecular cyclization
Palladium catalyst
Indolo[3,2,1-*d,e*]phenanthridines
Isochromeno[3,4-*a*]carbazoles

ABSTRACT

A new synthetic route has been developed for the preparation of indolo[3,2,1-*d,e*]phenanthridines and isochromeno[3,4-*a*]carbazoles via palladium catalyzed intramolecular biaryl coupling reactions. The coupling reactions proceeded smoothly and in high yields under ligand-free conditions with the catalytic system $Pd(OAc)_2/Cs_2CO_3$/TBAB. Under optimized reaction conditions no halogen-reduced products were observed.

The search for new methods for the construction of organic molecules from simple and readily available starting materials is an ongoing challenge for organic chemists. Intramolecular aryl–aryl coupling reactions involving palladium reagents have been used to synthesize many condensed hetero aromatic compounds.[1–6] Out of all of these coupling reactions, palladium-catalyzed cyclization reactions have proven over the last decade to be an extremely powerful and useful tool for the construction of carbon–carbon, as well as carbon–heteroatom bonds.[7] In particular, intramolecular biaryl coupling reactions are of considerable interest due to their utility in the synthesis of many condensed hetero aromatic compounds, such as indoles, quinolines, or carbazoles.[8] Among these carbazoles[9] and their fused derivatives, such as pyrido,[10] pyrrolo,[11] and pyranocarbazoles[12] have received considerable attention from both medicinal as well as synthetic chemists as these compounds display a wide range of biological activities such as anti-cancer,[13] anti-HIV,[14] DNA-intercalator,[15] or anti-microbial.[16]

Although a number of protocols have been developed for the coupling of biaryl moieties, many of them have limited applicability in organic synthesis due to the harshness of reaction conditions, functional group intolerance[17], or high[18] (or even stoichiometric)[19] catalyst loading. Another problem is the use of phosphine and other auxiliary ligands, which are often added to tailor catalyst selectivity or to increase catalyst lifetime, as the removal of the ligands may become problematic in the separation process.[20] Overcoming these hurdles will necessarily require the discovery and development of new or even novel catalytic systems. However, many palladium-catalyzed biaryl-coupling reactions proceed under ligand-free conditions only poorly and give no or only low product yields.[21] These above mentioned observations have prompted us to test one such reaction—a Heck type reaction—under ligand-free conditions to improve the product yield and undertake a study of this reaction to synthesize biologically interesting heterocycles such as indolo[3,2,1-*d,e*]phenanthridines and isochromeno[3,4-*a*]carbazoles.

The Heck precursors 9-(2-bromobenzyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **3a–d** required for our present study were synthesized[22] in 90–95% yields by stirring 2,3,4,9-tetrahydro-1*H*-carbazol-1-ones **1a–e** with 2-bromobenzyl bromide **2** in dry acetone in the presence of KOH. The structures of the compounds **3a** and **3d** were confirmed by X-ray diffraction studies (Figs. 1 and 2, and Supplementary data). When the coupling reaction was carried out with precursor **3a** in the presence of 5 mol % of $Pd(OAc)_2$ as catalyst, Cs_2CO_3 as base, and tetrabutylammonium bromide (TBAB) as an additive in anhydrous DMF as a solvent at 110 °C for 2 h under a nitrogen atmosphere, the 2-methyl-8*H*-indolo[3,2,1-*de*]phenanthridin-10-ol derivative **4a** was obtained in 90% (Scheme 1).[23]

* Corresponding author. Tel.: +91 422 2422311; fax: +91 422 2422387.
E-mail address: prasad_125@yahoo.com (K.J. Rajendra Prasad).

0040-4039/$ - see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2011.09.018

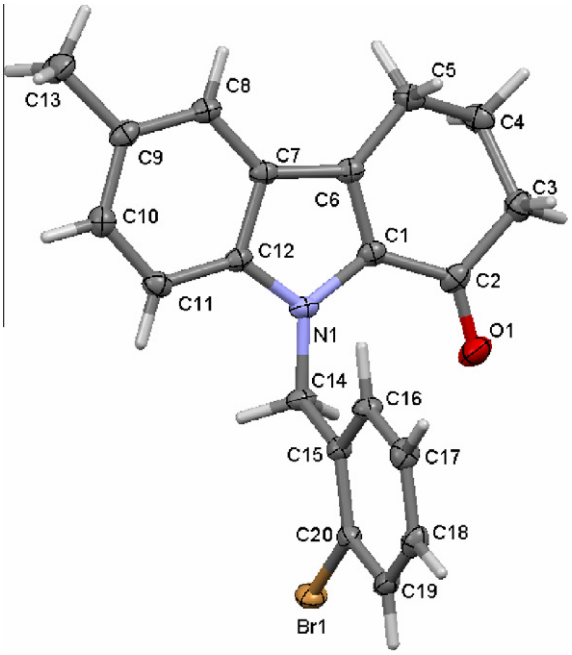


Figure 1. X-ray crystal structure of compound **3a**, thermal ellipsoid probability at 50%.

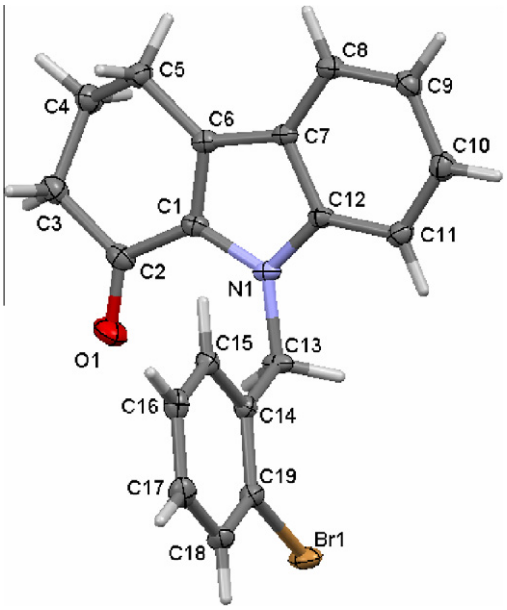
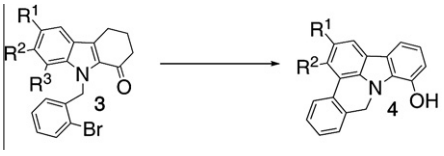


Figure 2. X-ray crystal structure of compound **3d**, thermal ellipsoid probability at 50%.

The best possible conditions for the cyclization were found through a series of experiments using various catalysts, bases, additives and solvents (Table 1). We found that the catalyst, base and solvent have a profound effect on the reaction yield. The use of $PdCl_2$, which is mostly used in Heck type reactions, provides only 30% yield of the cyclized product **4a** (Table 1, entry 3). Here, it is pertinent to note that the additives such as TBAB play an important role in the cyclization. Without any additives the reaction did not occur (entries 1 and 11). The effect of base on the reaction was also investigated. The use of KOAc as a base gave 40% of **4a** in DMF (entry 8). Replacement of KOAc with Cs_2CO_3 was found to be highly effective with the catalyst $Pd(OAc)_2$ (entries 10 and 12) and an excellent yield of the product was obtained in DMF (entry 13). Other inorganic bases such as K_2CO_3, Ag_2CO_3 and organic bases like Et_3N were explored. The use of Ag_2CO_3 was found to be effective (entry 7). However, with K_2CO_3 and Et_3N, no reaction did occur at all (entries 5 and 6). Among the several aprotic polar solvents examined, DMF gave the highest yields. Other solvents such as DMSO were also found to be effective, but gave lower yields (entries 3, 11, and 12). The reaction also did not occur at or below

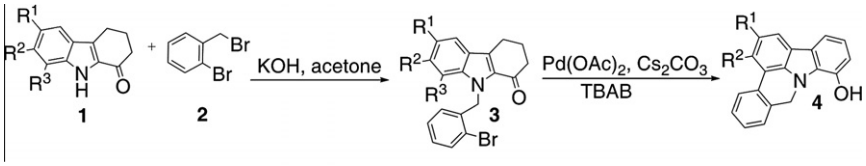
Table 1
Cyclization of 9-(2-bromobenzyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (3) under various conditions



3 a : R^1 =CH_3, R^2, R^3 = H; 4 a : R^1 =CH_3, R^2 = H;
b : R^2 =CH_3, R^1, R^3 = H; b : R^2 =CH_3, R^1= H;
c : R^3 =CH_3, R^1, R^2 = H; d : R^1, R^2 = H
d : R^1, R^2, R^3 = H e : R^1 =Cl , R^2 = H
e : R^1 =Cl , R^2, R^3 = H

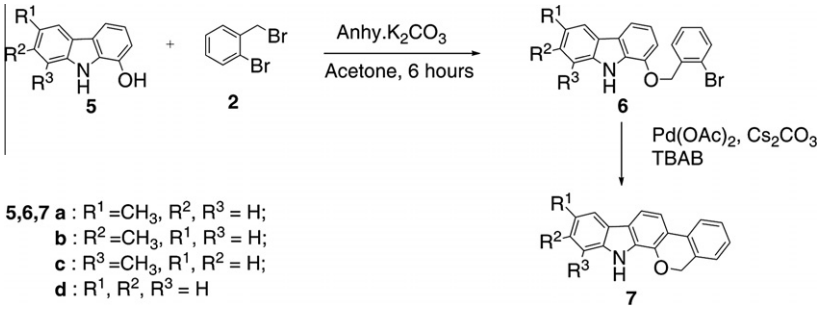
Entry	Reactant	Catalyst 10 mol %	Base 1.5 equiv	Additive 1.5 equiv	Solvent	Yield
1	**3a**	—	Cs_2CO_3	—	DMF	N.R.
3	**3a**	$PdCl_2$	Cs_2CO_3	TBAB	DMSO	20
4	**3a**	$PdCl_2$	Cs_2CO_3	TBAB	DMF	30
5	**3a**	$Pd(OAc)_2$	Et_3N	TBAB	DMF	N.R.
6	**3a**	$Pd(OAc)_2$	K_2CO_3	TBAB	DMF	N.R.
7	**3a**	$Pd(OAc)_2$	Ag_2CO_3	TBAB	DMF	38
8	**3a**	$Pd(OAc)_2$	KOAc	TBAB	DMF	40
10	**3a**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMA	54
11	**3a**	$Pd(OAc)_2$	Cs_2CO_3	—	DMSO	N.R.
12	**3a**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMSO	67
13	**3a**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	90
14	**3b**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	92
15	**3c**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	N.R.
16	**3d**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	93
17	**3e**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	94

N.R.—No Reaction.



1,3 **a** : R^1 =CH_3, R^2, R^3 = H; 4 **a** : R^1 =CH_3, R^2 = H;
b : R^2 =CH_3, R^1, R^3 = H; **b** : R^2 =CH_3, R^1= H;
c : R^3 =CH_3, R^1, R^2 = H; **d** : R^1, R^2 = H
d : R^1, R^2, R^3 = H **e** : R^1 =Cl , R^2 = H
e : R^1 =Cl , R^2, R^3 = H

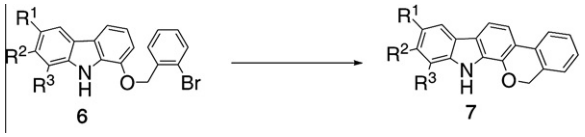
Scheme 1. Synthesis of 8*H*-indolo[3,2,1-*de*]phenanthridin-10-ol.



Scheme 2. Synthesis of 2, 13-dihydroisochromeno[3,4-*a*]carbazole.

85 °C. In order to examine the versatility of this intramolecular biaryl coupling reaction, a series of 8*H*-indolo[3,2,1-*de*]phenanthridin-10-ols **4a,b,d,e** were synthesized under the optimized conditions. Details of all reaction conditions that were checked are given in Table 1.

Table 2
Cyclization of 1-(2-bromobenzyloxy)-6-methyl-9*H*-carbazole 6 under various conditions



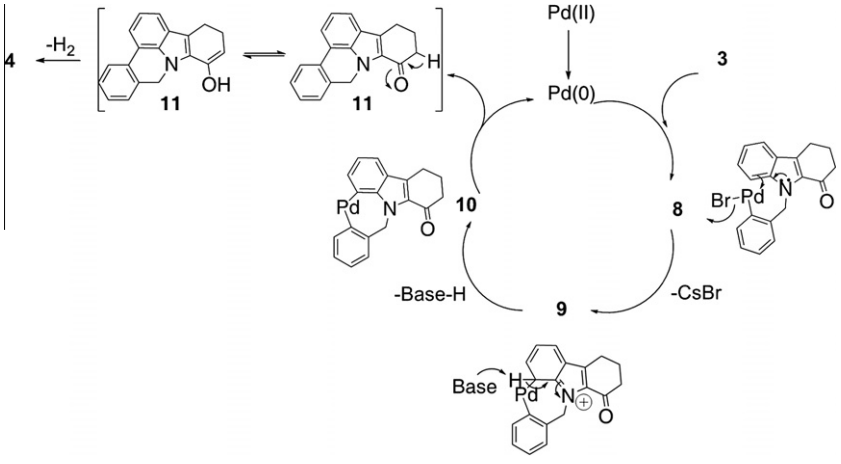
6,7 a : R^1 =CH_3, R^2, R^3 = H;
b : R^2 =CH_3, R^1, R^3 = H;
c : R^3 =CH_3, R^1, R^2 = H;
d : R^1, R^2, R^3 = H

Entry	Reactant	Catalyst (10 mol %)	Base (1.5 equiv)	Additive (1.5 equiv)	Solvent	Yield (%)
1	**6a**	$PdCl_2$	Ag_2CO_3	—	DMSO	20
2	**6a**	$PdCl_2$	Ag_2CO_3	TBAB	DMA	23
3	**6a**	$PdCl_2$	Ag_2CO_3	TBAB	DMF	30
4	**6a**	$Pd(OAc)_2$	KOAc	TBAB	DMA	34
5	**6a**	$Pd(OAc)_2$	K_2CO_3	TBAB	DMA	N.R.
6	**6a**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMA	50
7	**6a**	$Pd(OAc)_2$	Ag_2CO_3	TBAB	DMSO	N.R.
8	**6a**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	85
9	**6b**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	80
10	**6c**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	81
11	**6d**	$Pd(OAc)_2$	Cs_2CO_3	TBAB	DMF	82

The starting materials 1-hydroxy carbazoles **5a–d** for another series of coupling reactions were easily prepared[24] by the reaction of 2,3,4,9-tetrahydro-carbazol-1-ones **1a–d** upon reduction with Pd/C. Treatment of 1-hydroxy carbazoles **5** with 2-bromobenzyl-bromide **2** in acetone in the presence of anhydrous K_2CO_3 under refluxing conditions afforded the corresponding O-substituted products **6** in high yield (Scheme 2).[25] The actual coupling reaction was first tested for 1-(2-bromo-benzyloxy)-6-methyl-9*H*-carbazole **6a**. The use of bases such as Ag_2CO_3, KOAc or K_2CO_3 in DMA gave only low yields of **7a** (entries 2, 4, and 5). Our next attempt to initiate the cyclization of 6a in presence of $Pd(OAc)_2$, Cs_2CO_3 as the base, TBAB as an additive in DMA as the solvent gave the cyclized product 10-methyl-2,13-dihydroisochromeno[3,4-*a*]carbazole **7a** in 60% yield (Table 2, entry 6). All attempts to optimize the reactions conditions using $PdCl_2$ gave lower yields. Therefore, we decided to focus the optimization attempts on the $Pd(OAc)_2$ system.

A study of the influence of various solvents (DMF, DMSO, and DMA) suggested that DMF is the best choice. No reaction was found to occur below 90 °C. Switching to the mild base Cs_2CO_3 in these reactions gave the desired cyclized product **7a**. The best results were achieved using Cs_2CO_3 as the base, $Pd(OAc)_2$ as the catalyst, TBAB as an additive and DMF as a solvent at 110 °C. After 4 h of reaction time this procedure provided a 85% yield of the cyclized product **7a** (entry 8).[26] The results for all compounds **7a–d** are summarized in Table 2.

From a mechanistic point of view, the cyclization most likely proceeds through oxidative addition of Pd(0) to the 1-(2-bromobenzyloxy)-9*H*-carbazole **6** to give a σ-aryl palladium intermediate. Electrophilic attack on the aromatic ring leads to the biaryl palladium species, which after reductive elimination of palladium affords the cyclized products **7**.



Scheme 3. A catalytic cycle for the formation of **4**.

A similar catalytic cycle for the formation of the product **4** from the substrate **3** is outlined in Scheme 3. Abstraction of halide by Cs_2CO_3 leads to cationic intermediate **9** presumably stabilized by the nitrogen atom of the tetrahydrocarbazole moiety. Cs_2CO_3 abstraction of a proton from **9** leads to the intermediate **11**. On subsequent enolization and dehydrogenation, the product **4** was obtained. It has been observed that the biaryl coupling reactions proceeded smoothly under our optimized reaction conditions and gave good yields of the cyclized products under ligand-free conditions. No halogen-reduced product was observed at all. The use of Cs_2CO_3 as base seems to completely inhibit the formation of this undesired reduced product and thus dramatically improves the yield of the desired product **4**.

In conclusion, we have developed a convenient and high yielding method for the synthesis of indolo[3,2,1-*d,e*]phenanthridines and isochromeno[3,4-*a*]carbazoles, present in many biologically active alkaloids, by palladium-catalyzed intramolecular Heck reaction under ligand-free conditions. The method is new, mild and highly effective for the cyclization of biaryl systems, and afforded the cyclized products in high yields. The method is likely to be applicable for many other ring systems and hetero atomic species.

Acknowledgments

Our sincere thanks go to the Director, ISO Quality Assurance Cell, IICT, Hyderabad, and SAIF, IIT Madras, Chennai and the Chairman, NMR Research Centre, IISc, Bangalore, for providing access to their Mass and NMR spectral facilities. The diffractometer was funded by NSF grant 0087210, by the Ohio Board of Regents grant CAP-491, and by Youngstown State University.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.09.018.

References and notes

1. Tsuji, J. *Palladium Reagents and Catalysts*; John Wiley & Sons: New York, 2004. p 176.
2. Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry*; Oxford: Pergamon, 2000.
3. Dyker, G. *Chem. Ber.* **1997**, *130*, 1567.
4. Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359.
5. Miura, M.; Nomura, M. *Top. Curr. Chem.* **2002**, *219*, 212.
6. Echavarren, A. M.; Gomez-Lor, B.; Gonzalez, J.; De Frutos, O. *Synlett* **2003**, 585.
7. (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Tetrahedron* **2005**, *61*, 11771; (b) Li, C. *Chem. Rev.* **2005**, *105*, 3095; (c) Lebsack, A. D.; Link, J. T.; Overman, L. E.; Stearns, B. A. *J. Am. Chem. Soc.* **2002**, *124*, 9008; (d) Huang, Q.; Fazio, A.; Dia, G.; Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2004**, *126*, 7460; (e) Gracon, S.; Vassiliou, S.; Cavicchioli, M.; Hartmann, B.; Monteiro, N.; Balme, G. *J. Org. Chem.* **2001**, *66*, 4069; (f) Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633; (g) Majumdar, K. C.; Chattopadhyay, B.; Shina, B. *Tetrahedron Lett.* **2008**, *49*, 1319.
8. (a) Shi, Z.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 7895; (b) Wollikar, S. A.; Neuenswander, B.; Lushington, G. H.; Larock, R. C. *J. Comb. Chem.* **2009**, *11*, 875; (c) Harayama, T.; Sato, T.; Hori, A.; Abe, H.; Takeuchi, Y. *Synlett* **2003**, 1141; (d) Liu, Z.; Larock, R. C. *Tetrahedron* **2007**, *63*, 347; (e) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115.
9. (a) Knolker, H.-J.; Reddy, K. R. In Cordell, G. A., Ed.; The Alkaloids Chemistry and Biology; Academic Press, Elsevier: London, 2008; Vol. 65, p 1; (b) Choi, T. A.; Czerwonka, R.; Forke, R.; Jagar, A.; Knoll, J.; Krahl, M. P.; Krause, T.; Reddy, K. R.; Franzblau, S. G.; Knolker, H.-J. *Med. Chem. Res.* **2008**, *17*, 374; (c) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303; (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127; (e) Gallagher, P. T. In *Science of Synthesis*, Thieme: Stuttgart, 2000; Vol. 10, p. 693.; (f) Omura, S.; Sasaki, Y.; Iwai, Y.; Takeshima, H. *J. Antibiot.* **1995**, *48*, 535; (g) Moody, C. J. *Synlett* **1994**, 681; (h) Bergman, J.; Pelcman, B. *Pure Appl. Chem.* **1990**, *62*, 1967.
10. (a) Bourderioux, A.; Kassis, P.; Merour, J.-Y.; Routier, S. *Tetrahedron* **2008**, *64*, 11012; (b) Rivalle, C.; Francoise, W.; Tambourin, P.; Jean, L. M.; Bisagni, E.; Chermann, C. J. *J. Med. Chem.* **1983**, *26*, 181; (c) Cornel, V. M. *J. Org. Chem.* **2000**, *65*, 2267; (d) Hirata, K.; Ito, C.; Furukawa, H.; Itoigawa, M.; Cosentino, L. M.; Lee, K.-H. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 119.
11. Tsuchimoto, T.; Matsubayashi, H.; Kaneko, M.; Nagase, Y.; Miyamura, T.; Shirakawa, E. *J. Am. Chem. Soc.* **2008**, *130*, 15823.
12. (a) Meesala, R.; Nagarajan, R. *Tetrahedron* **2009**, *65*, 6050; (b) Chattopadhyay, S. K.; Ghosh, D.; Biswas, T. *Synlett* **2006**, 3358; (c) Terzidis, M.; Tsoleridis, C. A.; Stephanidou-stephanatou, J. *Tetrahedron Lett.* **2005**, *46*, 7239; (d) Vandana, T.; Rajendra Prasad, K. J. *Indian J. Chem.* **2005**, *44B*, 819.
13. (a) Henon, H.; Conchon, E.; Bernadette, M.; Samior, G.; Roy, M.; Prudhomme, M. *Anti-can. Agen. Med. Chem.* **2008**, *8*, 577; (b) Hudkins, R. L.; Johnson, N. W.; Angeles, T. S.; Gessner, G. W.; Mallamo, J. P. *J. Med. Chem.* **2007**, *50*, 433; (c) Wells, G. J.; Bihovsky, R.; Hudkins, R. L.; Ator, M. A.; Husten, J. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1151; (d) Tran-Thi, H. A.; Nguyen-Thi, T.; Michel, S.; Tillequin, F.; Koch, M.; Pfeiffer, B.; Pierre, A.; Trinh-Van-Dufat, H. *Chem. Pharm. Bull.* **2004**, *52*, 540; (e) Cornel, V. M. *J. Org. Chem.* **2002**, *67*, 2387; (f) Stiborova, M.; Rupertova, M. S.; Dohalska, L. B.; Wiessler, M.; Frei, E. *Chem. Res. Toxicol.* **2003**, *16*, 38; (g) Thompson, D.; Miller, C.; McCarthy, F. O. *Biochemistry* **2008**, *47*, 10333; (h) Ricci, C. G.; Netz, P. A. *J. Chem. Inf. Model* **2009**, *49*, 1925.
14. (a) Wang, J.; Zheng, Y.; Efferth, T.; Wang, R.; Shen, Y.; Hao, X. *Phytochemistry* **2005**, *66*, 697.
15. (a) Wang, J. C. *Annu. Rev. Biochem.* **1996**, *65*, 635; (b) Monks, N. R.; Blankey, D. C.; East, S. J.; Dowell, R. I.; Caluete, J. A.; Curtin, N. J.; Arris, C. E.; Newell, D. R. *Eur. J. Cancer* **2002**, *11*, 1543; (c) LePez, J. B.; DzXuong, N.; Gosse, C.; Paolett, C. *Proc. Natl. Acad. Sci. U.S.A.* **1974**, *71*, 5078.
16. (a) Pachera, T.; Bacher, M.; Hoferb, O.; Gregera, H. *Phytochemistry* **2001**, *58*, 129; (b) Randelia, B. E.; Patel, B. P. J. *Experienta* **1982**, *38*, 529; (c) Al-Trawneh, S. A.; Zahra, J. A.; Kamal, M. R.; El-Abadelah, M. M.; Zani, F.; Incerti, M.; Cavazzoni, A.; Alfieri, R. R.; Petronini, P. G.; Vicini, P. *Bioorg. Med. Chem.* **2010**, *18*, 5873.
17. Ames, D. E.; Opalko, A. *Tetrahedron* **1984**, *40*, 1919.
18. (a) Kitamura, M.; Ohmori, K.; Kawase, T.; Suzuki, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 1229; (b) Hosoya, T.; Takashiro, E.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1994**, *116*, 1004; (c) Cuny, G. D. *Tetrahedron Lett.* **2003**, *44*, 8149; (d) Qabaja, G.; Jones, G. B. *J. Org. Chem.* **2000**, *65*, 7187; (e) Rice, J. E.; Cai, Z.-W.; He, Z.-M.; LaVaoie, E. J. *J. Org. Chem.* **1995**, *60*, 8101.
19. Futagami, S.; Ohashi, Y.; Imura, K.; Hosoya, T.; Ohmori, K.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **2000**, *41*, 1063.
20. (a) Harayama, T.; Yasuda, H. *Heterocycles* **1997**, *46*, 61; (b) Brigmann, G.; Pabst, T.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M.; Rycroft, D. S.; Connolly, J. D. *J. Am. Chem. Soc.* **2000**, *122*, 9127; (c) Harayama, T.; Akiyama, T.; Akamatsu, H.; Kawano, K.; Abe, H.; Takeuchi, Y. *Synthesis* **2001**, 444; (d) Wiegand, S.; Schafer, H. J. *Tetrahedron* **1995**, *51*, 5341.
21. Hennings, D. D.; Iwasa, S.; Rawal, V. H. *J. Org. Chem.* **1997**, *62*, 2.
22. *General procedure for the synthesis of 9-(2-bromobenzyl)-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3**)*:
To a solution of respective 2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**1**, 1 mmol) and acetone (15 mL), powdered KOH was added in ice cold condition. After few minutes 2-bromobenzylbromide (1 mmol) was added to the solution with vigorous stirring and the reaction mixture was stirred for 3 h. Benzene (75 mL) was added to the reaction mixture and insoluble materials were removed by filtration. The benzene solution was washed with saturated NaCl solution and dried over sodium sulfate. Then, the solvent is evaporated to get the respective 9-(2-bromobenzyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**).
*9-(2-bromobenzyl)-6-methyl-2,3,4,9-tetrahydro-1H-carbazol-1-one (**3a**)*
Pale yellow solid (0.349 g, 95%); mp: 265 °C; IR (KBr) 3441, 2923, 1657, 1535 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.23–2.26 (m, 2H, C_3–2H), 2.45 (s, 3H, CH_3), 2.64 (t, 2H, *J* = 6.0 Hz, 2-2H), 3.05 (t, 2H, *J* = 6.0 Hz, 4-2H), 5.85 (s, 2H, N–CH_2), 6.30 (d d, 1H, *J* = 6.7 Hz, *J* = 2.4 Hz, 6′-H), 7.03 (d t, 2H, *J* = 6.7 Hz, *J* = 2.4 Hz, 4′- & 5′-H), 7.08 (d, 1H, *J* = 8.6 Hz, 8-H), 7.17 (d d, 1H, *J* = 8.6 Hz, *J* = 1.2 Hz, 7-H), 7.47 (d, 1H, *J* = 1.2 Hz, 5-H), 7.57 (d d, 1H, *J* = 6.7 Hz, *J* = 2.4 Hz, 3′-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 21.39, 21.92, 24.77, 39.88, 48.34, 110.52, 120.68, 121.86, 125.26, 126.88, 127.60, 128.13, 129.13, 129.48, 130.01, 130.20, 132.57, 137.57, 137.88, 191.81; MS, *m*/*z* (%): 370 (M+2, 97), 368 (M^+, 100), 352 (15), 273 (26), 183 (12), 113 (10); Anal. Calcd for $C_{20}H_{18}BrNO$: C, 65.23; H, 4.93; N, 3.80%. Found: C, 65.26; H, 4.97; N, 3.85%.
23. *General procedure for the synthesis of 8H-indolo[3,2,1-de]phenanthridin-10-ol (**4**)*:
To a mixture of 9-(2-bromobenzyl)-2,3,4,9-tetrahydro-1*H*-carbazol-1-one (**3**, 1 mmol), Bu_4NBr (1.5 equiv), and Cs_2CO_3 (1.5 equiv) in anhydrous DMF (8 mL) was added $Pd(OAc)_2$ (10 mol %) placed in a pre-heated oil bath at 110 °C for 2 h. After completion of the reaction, the mixture was cooled and diluted with water. This was extracted with EtOAc. The combined organic extracts were washed with aq 1 N HCl, water, brine solution and dried (anhyd Na_2SO_4). The solvent was removed by distillation and the crude product was purified by column chromatography over silica gel using pet. ether as an eluant to give the final compound **4**.
*2-Methyl-8H-indolo[3,2,1-de]phenanthridin-10-ol (**4a**)*
White solid (0.256 g, 90%); mp: 223 °C; IR (KBr) 3428, 2923, 1657, 1537 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.70 (s, 3H, CH_3), 6.43 (d d, 2H, *J* = 9.5 Hz, N–CH_2), 7.13 (d, 1H, *J* = 8.0 Hz, 11-H), 7.40 (t, 1H, *J* = 8.0 Hz, 12-H), 7.50 (d, 1H, *J* = 7.5 Hz, 7-H), 7.71 (t, 1H, *J* = 7.5 Hz, 6-H), 7.89 (s, 1H, 3-H), 7.92 (t, 1H, *J* = 7.5 Hz, 5-H), 8.04 (s, 1H, 1-H), 8.37 (d, 1H, *J* = 8.0 Hz, 4-H), 8.70 (d, 1H, *J* = 8.0 Hz, 13-H), 12.35 (s, 1H, 10-OH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 21.98, 48.33, 111.28, 116.55, 117.22, 121.06, 122.06, 122.28, 125.60, 125.99, 126.65, 127.88, 128.36, 129.68, 131.62, 133.56, 133.93, 134.98, 146.72, 160.57; MS, *m*/*z* (%): 285 (M^+, 100), 271 (15), 254 (14), 164 (9), 113 (12); Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91%. Found: C, 84.21; H, 5.33; N, 4.95 %.
24. Shanmugasundaram, K.; Rajendra Prasad, K. J. *Heterocycles* **1999**, *51*, 2163.
25. *General procedure for the synthesis of 1-(2-bromo-benzyloxy)-9H-carbazole (**6**)*:
A mixture of the respective 1-hydroxycarbazoles (**5**, 1 mmol), 2-

bromobenzylbromide (1 mmol) and dried K_2CO_3 in acetone was refluxed in a steam bath for 3 h. The reaction mixture was monitored by TLC. After completion of the reaction the excess solvent was removed and dissolved in ice water and neutralized with ice cold 1:1 HCl. The solid separated was filtered, washed with water and dried. Then, it was purified by column chromatography over silica gel using petroleum ether and ethyl acetate (99:1) to get the respective 1-(2-bromo-benzyloxy)-9*H*-carbazole (**6**).

1-(2-Bromo-benzyloxy)-6-methyl-9H-carbazole (6a):

White solid (0.307 g, 84%); mp: 252 °C; IR (KBr) 3429, 2920, 1675, 1574 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ (ppm) 2.52 (s, 3H, CH_3), 5.33 (s, 2H, O–CH_2), 6.93 (d, 1H, *J* = 8.0 Hz, 6′-H), 7.11 (t, 1H, *J* = 8.0 Hz, 3-H), 7.21 (d t, 1H, *J* = 8.0 Hz, 4′-H), 7.23 (d, 1H, *J* = 7.6 Hz, 7-H), 7.32-7.36 (m, 2H, 5′& 8-H), 7.58 (d, 1H, *J* = 7.6 Hz, 2-H), 7.62 (d d, 1H, *J* = 8.0 Hz, *J* = 1.2 Hz, 3′-H), 7.67 (d, 1H, *J* = 7.6 Hz, 4-H), 7.84 (s, 1H, 5-H), 8.20 (bs, 1H, 9-H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 21.46, 66.99, 107.40, 110.60, 113.38, 119.50, 120.46, 122.91, 123.83, 124.52, 127.21, 127.63, 128.76, 129.36, 129.55, 130.33, 132.84, 136.27, 137.50, 144.45; MS, *m*/*z* (%): 368 (M+2, 97), 366 (M^+, 100), 350 (29), 271 (18), 165 (10), 113 (9); Anal. Calcd for $C_{20}H_{16}BrNO$: C, 65.59; H, 4.40; N, 3.82 %. Found: C, 65.55; H, 4.37; N, 3.86%.

26. *General procedure for the synthesis of 2,13-dihydroisochromeno[3,4-a]carbazole (**7**)*:

To a mixture of 1-(2-Bromo-benzyloxy)-9*H*-carbazole (1 mmol), Bu_4NBr (1.5 equiv) and Cs_2CO_3 (1.5 equiv) in anhydrous DMF (8 mL) was added $Pd(OAc)_2$ (10 mol %) placed in a pre-heated oil bath at 110 °C for 2 h. After completion of the reaction, the mixture was cooled and diluted with water. This was extracted with EtOAc. The combined organic extracts were washed with aq 1 N HCl, water, brine solution and dried (anhyd Na_2SO_4). The solvent was removed by distillation and the crude product was purified by column chromatography over silica gel using pet. ether as the eluent to give the final compound **7**.

10-methyl-2,13-dihydroisochromeno[3,4-a]carbazole (7a):

White solid (0.242 g, 85%); mp: 259 °C; IR (KBr) 3432, 2920, 1623, 1577 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.56 (s, 3H, CH_3), 5.31 (s, 2H, O–CH_2), 7.21 (d, 1H, *J* = 7.5 Hz, 3-H), 7.29 (d t, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, 4-H), 7.42 (d, 1H, *J* = 8.0 Hz, 11-H), 7.43 (d t, 1H, *J* = 7.5 Hz, *J* = 1.5 Hz, 5-H), 7.47 (d, 1H, *J* = 8.0 Hz, 12-H), 7.63 (d, 1H, *J* = 8.0 Hz, 7-H), 7.77 (d, 1H, *J* = 8.0 Hz, 6-H), 7.81 (d, 1H, *J* = 8.0 Hz, 8-H), 8.09 (s, 1H, 9-H), 8.28 (bs, 1H, 13-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 21.53, 66.71, 106.59, 110.59, 111.93, 113.31, 119.93, 120.48, 122.88, 124.66, 126.31, 127.38, 128.71, 129.12, 129.41, 129.63, 130.19, 136.28, 136.86, 142.68; MS, *m*/*z* (%): 285 (M^+, 100), 270 (25), 218 (16), 164 (12), 113 (11); Anal. Calcd for $C_{20}H_{15}NO$: C, 84.19; H, 5.30; N, 4.91 %. Found: C, 84.22; H, 5.35; N, 4.95 %.