Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 3606

www.rsc.org/obc

COMMUNICATION

Synthesis of carbazolones and 3-acetylindoles *via* oxidative C–N bond formation through PIFA-mediated annulation of 2-aryl enaminones†

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Received 18th February 2012, Accepted 15th March 2012
DOI: 10.1039/c2ob25348h

A series of carbazolone derivatives and 3-acetylindoles have been achieved *via* PIFA-mediated intramolecular cyclization of 2-aryl enaminones. This process allows the *N*-moiety on the side-chain to be annulated to the benzene ring *via* the metal-free oxidative aromatic C–N bond formation.

The carbazolone unit, which can be categorized as an indole skeleton bearing a specific cyclic ketone, is one of the most important and abundant heterocycles in natural products.[1] Furthermore, substituted carbazolones are key intermediates in the total synthesis of carbazolone alkaloids and drugs. For example, murrayaquinone A (a HIV-integrase inhibitor), ondansetron and alosetron (selective serotonin 5-HT_3 receptor antagonists) can all be accessed from carbazolone derivatives.[2] Accordingly, many varied methods have been reported for the construction of the carbazolone skeleton (Fig. 1).[3] The classic Fisher indole synthesis is a common and important method in this area (Fig. 1, type **a**).[4] Heck-type coupling reactions can also be applied to the synthesis of carbazolones starting from *ortho*-halo aryl enaminones *via* transition metal-catalyzed intramolecular cyclization (Fig. 1, type **b**).[5] Additionally, palladium-mediated cyclization or photocyclization of aryl enaminones are also applicable routes to carbazolones, which realize direct carbon–carbon bond formation (Fig. 1, type **c**).[6] The other approaches include the application of reduction–cyclization of a reductive system of Fe–AcOH to complete the cyclization of 3-hydroxy-2-(2-nitrophenyl)enones (Fig. 1, type **d**),[7] acid-catalyzed cyclization of 1*H*-indole-2-butanoic acid (Fig. 1, type **e**)[8] and oxidation of 2,3,4,9-tetrahydro-1*H*-carbazole (Fig. 1, type **f**).[9]

In this communication, we report an alternative approach for the construction of carbazolones: by joining the *N*-moiety on the side-chain to the phenyl ring *via* oxidative C–N bond formation mediated by hypervalent iodine reagents. This method can also be extended to the synthesis of 3-acetylindoles.

In our previous work, we found that the acyclic enaminone **A** could undergo $PhI(OAc)_2$-mediated intramolecular azirination to give the stable 2*H*-azirine **B**,[10] while the desired indole compound **C** was not formed in this process. However, when the cyclic enaminone **D** was treated with $PhI(OAc)_2$ under identical conditions, the formation of the aromatic C–N bond occurred to give the carbazolone compound **E**. The corresponding 2*H*-azirine **F** was not formed due to its highly strained bridged-ring system.[11] This unexpected finding revealed a complementary route to the construction of the important carbazolone skeleton (Scheme 1).

Although PIDA can provide the desired product in a good yield (Table 1, entry 1), another hypervalent iodine(III) oxidant, *i.e.*, PIFA, was also tested since it is always taken as a more potent hypervalent iodine(III) oxidant than PIDA. It was found that the reaction could go to completion within a much shorter time, affording the desired product in even better yield (Table 1, entry 2). Both CH_2Cl_2 and DCE are desirable solvent for the reaction since no obvious difference was observed (Table 1. entries 2–3). Increasing the dosage of PIFA to 1.5 equivalents decreased the yield due to the formation of some unidentified by-products (Table 1, entry 4). Attempts to further improve the yield by adding $BF_3{\cdot}Et_2O$ as Lewis acid or TFA as a protonic catalyst was not successful since the reaction gave more complicated mixtures, even at 0 °C (Table 1, entries 5–6). Our further studies showed that other solvents including CH_3CN, toluene,

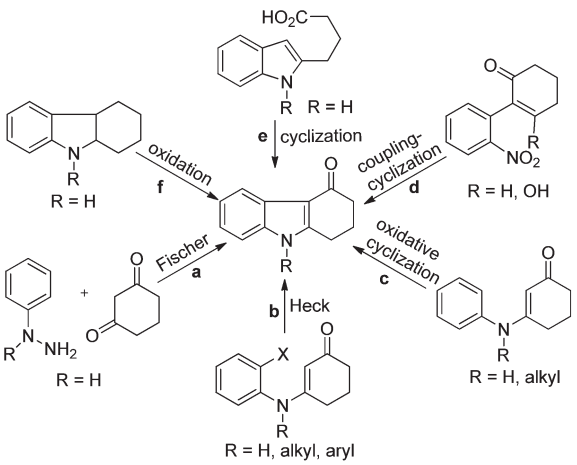

Fig. 1 General synthetic routes to the carbazolone motif.

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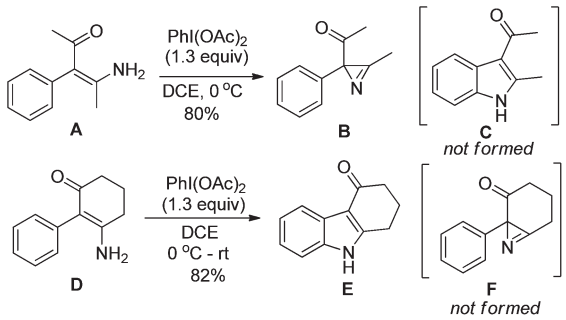
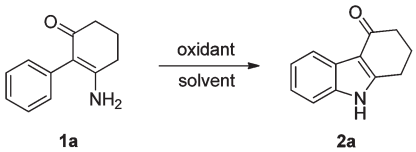
†Electronic supplementary information (ESI) available: NMR data. See DOI: 10.1039/c2ob25348h



Scheme 1 The two different reaction routes when acyclic and cyclic enaminones were treated with PIDA.

Table 1 Optimization of reaction conditions for the oxidative coupling of enaminones **1a**[a]



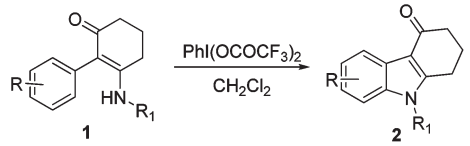
Entry	Oxidant	Solvent	Time (h)	Yields (%)[b]
1	PIDA (1.2 equiv)	DCE	4	80
2	PIFA (1.2 equiv)	DCE	0.5	88
3	PIFA (1.2 equiv)	CH_2Cl_2	0.5	90
4	PIFA (1.5 equiv)	CH_2Cl_2	0.5	83
5[c]	PIFA (1.2 equiv)	CH_2Cl_2	0.5	45
6[d]	PIFA (1.2 equiv)	CH_2Cl_2	0.5	32
7	PIFA (1.2 equiv)	CH_3CN	4	75
8	PIFA (1.2 equiv)	Toluene	4	67
9	PIFA (1.2 equiv)	THF	4	52
10	PIFA (1.2 equiv)	DMSO	4	41
11	PIFA (1.2 equiv)	DMF	4	ND[e]

[a] All the reactions were carried out at rt unless otherwise stated. [b] Isolated yields after silica gel chromatography. [c] $BF_3{\cdot}Et_2O$ (0.2 equiv.) was added as additive, at 0 °C. [d] TFA (0.2 equiv.) was added as additive, at 0 °C. [e] **2a** was not detected.

THF and DMSO gave inferior yields, while no desired product was obtained when DMF was used as the solvent (Table 1, entries 7–11).

Under the optimal reaction conditions (Table 1, entry 3), various substituted 2-arylenaminones were examined to explore the scope of this oxidative system. The results showed that substrates bearing both electron-donating and electron-withdrawing groups can be well tolerated in the process. The presence of a methyl group in the substrate does not influence the yield (Table 2, entry 2). However, when strong electron-donating groups were introduced, the yield was greatly decreased due to the formation of some unidentified by-products. However, by carrying out the reaction at 0 °C, the electron-rich enaminone **1c**, with two methoxy groups substituted on the phenyl ring, can afford the single regio-isomer **2c** in an acceptable yield (Table 2, entry 3). In the case of *meta*-substituted substrates bearing either an F or CF_3 group (Table 2, entries 4–5), two regioisomeric indole products were formed in each case.

Table 2 Synthesis of carbazolone derivatives **2** by PIFA[a]



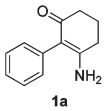
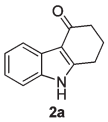
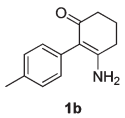
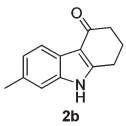
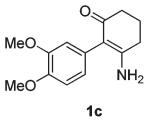
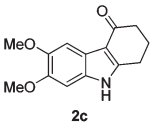
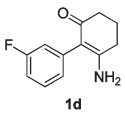
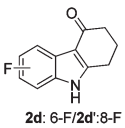
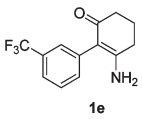
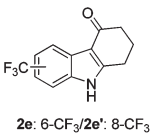
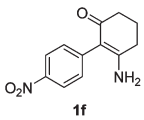
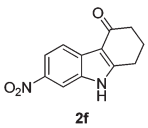
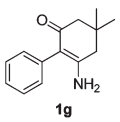
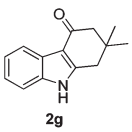
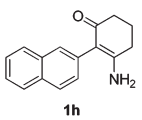
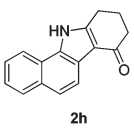
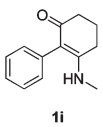
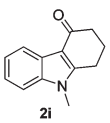
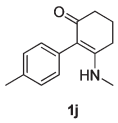
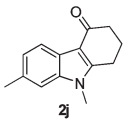
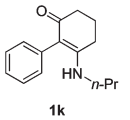
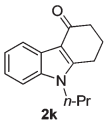
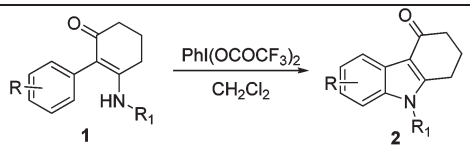
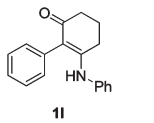
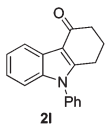
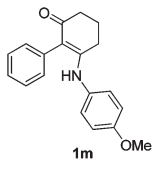
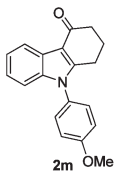
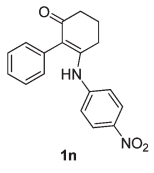
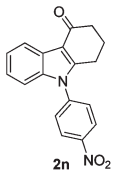
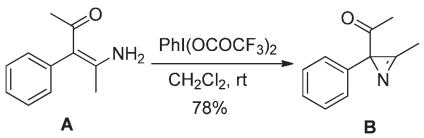
Entry	Substrate **1**	Product **2**	Yield (%)[b]
1	 **1a**	 **2a**	90
2	 **1b**	 **2b**	90
3[c]	 **1c**	 **2c**	67
4	 **1d**	 **2d**: 6-F/**2d′**:8-F	87 (**2d**/**2d′** = 3/1)
5	 **1e**	 **2e**: 6-CF_3/**2e′**: 8-CF_3	90 (**2e**/**2e′** = 1.2/1)
6	 **1f**	 **2f**	79
7	 **1g**	 **2g**	87
8	 **1h**	 **2h**	84
9	 **1i**	 **2i**	82
10	 **1j**	 **2j**	74
11	 **1k**	 **2k**	64

Table 2 *(Contd.)*



Entry	Substrate **1**	Product **2**	Yield (%)[b]
12			73
13			76
14			70

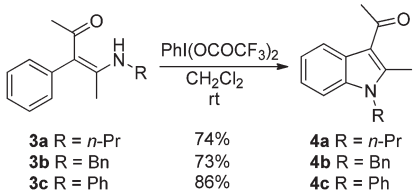
[a] Reaction conditions: **1** (1.0 equiv) and PIFA (1.2 equiv) in CH_2Cl_2 at rt. [b] Yield of isolated product. [c] The reaction was carried out at 0 °C.



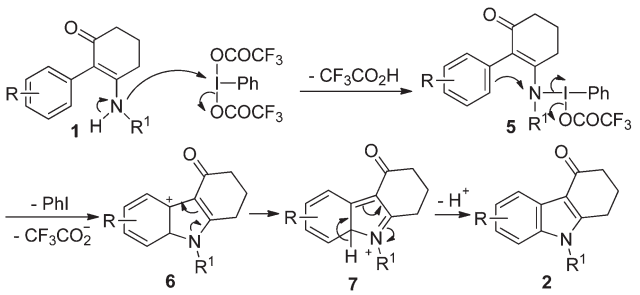
Scheme 2 Formation of azirine **B** when acyclic enaminone **A** was treated with PIFA.

Notably, when a strong electron-withdrawing NO_2 group was introduced, the corresponding enaminone substrate **1f** could also lead conveniently to the desired product **2f** in good yield (Table 2, entry 6). Changing the phenyl ring into a naphthyl ring, or installing the alkyl groups to the cyclic enaminone moiety in the substrate did not influence the reaction and the desired cyclized products can be reached, respectively (Table 2, entries 7–8). Furthermore, this methodology also allows for both *N*-alkyl and *N*-aryl substitution (Table 2, entries 9–14), thus providing an alternative route to N-substituted carbazolones, which are always obtained *via* *N*-alkylation or metal-catalyzed *N*-arylation of N-unsubstituted carbazolones.[12]

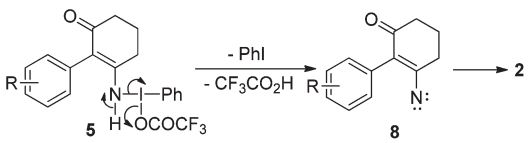
Encouraged by the above results, we also studied the reaction of acyclic enaminone under the same conditions. The treatment of **A** with PIFA in CH_2Cl_2 was found to give 2*H*-azirine compounds **B** (Scheme 2), the result of which indicated that PIDA and PIFA showed no difference in this conversion. Delightedly, when N-substituted acyclic enaminones were used, the oxidative C–N bond formation occurred to give either the *N*-alkyl or *N*-aryl 3-acyl indole compounds in good yields (Scheme 3).[13]



Scheme 3 Synthesis of 3-acetylindole **4** when N-substituted enaminone **3** was treated with PIFA.



Scheme 4 Possible mechanism for PIFA-mediated cyclization.



Scheme 5 An alternative mechanism *via* a nitrene intermediate.

A plausible mechanistic sequence is proposed in Scheme 4. Firstly, the *N*-iodo intermediate **5** is expected to be formed directly from the intermolecular reaction of enaminone **1** and PIFA by losing one molecule of trifluoroacetic acid. Next, when R^1 represents alkyl or aryl groups, a concerted process involving the electrophilic attack of the N-center on the phenyl ring *via* simultaneous release of PhI and CF_3CO_2H occurs in intermediate **5** to afford the Wheland intermediate **6**. Considering that the corresponding intermediate **6** from substrate **1f**, in which the phenyl ring is greatly deactivated by the NO_2 group, is unstable, we propose that the carbon cation **6** can be stabilized by the lone pair on nitrogen through conjugation to give the iminium salt **7**. Finally, the rapid elimination of a proton from **7** regenerates the aromatic system of the phenyl ring to afford the title carbazolone **2**.

Alternatively, when R in cyclic enaminones represents H, it may also adopt the other pathway involving the formation of nitrene intermediate **8** from intermediate **5**, followed by insertion into the Ar–H σ bond or π participation from the aromatic ring to give the title **2** (Scheme 5).[14]

In summary, we have described an alternative approach to carbazolone and 3-acetylindoles derivatives mediated by PIFA from enaminones. This method features mild reaction conditions, simplicity of workup and the construction of carbazolone and indole backbone by a metal-free oxidative annulation of the N-atom on the side chain to the sp^2-carbon on benzene ring at the last synthetic step.

Acknowledgements

Y.D. acknowledges the National Natural Science Foundation of China (#21072148) and Cultivation Foundation (B) for Young Faculty of Tianjin University (TJU-YFF-08B68) for financial support.

Notes and references

1 (*a*) S. Masanori and Y. Fumio, *Nat. Prod. Rep.*, 2004, **21**, 278; (*b*) K. Tomomi and H. Kazuhiro, *Nat. Prod. Rep.*, 2005, **22**, 73; (*c*) C. V. Z. Michael, L. J. Michael and D. P. Alberto, *J. Med. Chem.*, 2005, **48**, 3141.
2 (*a*) H. J. Knolker, *Top. Curr. Chem.*, 2005, **244**, 115; (*b*) Z. Bouaziz, P. Nebois, A. Poumaroux and H. Fillion, *Heterocycles*, 2000, **52**, 977; (*c*) H. J. Knoelker and K. R. Reddy, *Heterocycles*, 2003, **60**, 1049; (*d*) S. W. Yang and G. A. Cordell, *J. Nat. Prod.*, 1997, **60**, 44.
3 (*a*) J. C. Gramain, H. P. Husson and Y. Troin, *J. Org. Chem.*, 1985, **50**, 5517; (*b*) D. Desmaele and Angelo, *J. Org. Chem.*, 1994, **59**, 2292; (*c*) Y. K. Ramtohul and A. Chartrand, *Org. Lett.*, 2007, **9**, 1029; (*d*) J. J. Neumann, S. Rakshit, T. Droege, F. Glorius and S. Wuertz, *Chem.–Eur. J.*, 2011, **17**, 7298; (*e*) S. D. Edmondson, A. Mastracchio and E. R. Parmee, *Org. Lett.*, 2000, **2**, 1109; (*f*) K. Mills, K. A. Ibtisam, A. S. Fowzia and J. A. Joule, *J. Chem. Soc., Perkin Trans. 1*, 1981, 636; (*g*) P. Kazmierczak and L. Skulski, *Synthesis*, 1998, 1721; (*h*) P. Kazmierczak, L. Skulski and L. Kraszkiewicz, *Molecules*, 2001, **6**, 881.
4 (*a*) X. Li and R. Vince, *Bioorg. Med. Chem.*, 2006, **14**, 2942; (*b*) L. V. Kudzma, *Synthesis*, 2003, **11**, 1661.
5 (*a*) M. C. Willis, G. N. Brace and I. P. Holmes, *Angew. Chem., Int. Ed.*, 2005, **44**, 403; (*b*) L. Ackermann, *Org. Lett.*, 2005, **7**, 439; (*c*) S. Yan, H. Wu, N. Wu and Y. Jiang, *Synlett*, 2007, **17**, 2699; (*d*) U. S. Sorensen and E. P. Villar, *Helv. Chim. Acta*, 2004, **87**, 82; (*e*) B. Li, S. Yang and Z. Shi, *Synlett*, 2008, **7**, 949; (*f*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173; (*g*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174.
6 (*a*) B. Weng, R. Liu and J. H. Li, *Synthesis*, 2010, **17**, 2926; (*b*) D. Sissouma, S. C. Collet and A. Y. Guingant, *Synlett*, 2004, **14**, 2612; (*c*) Y. Blache, M. E. S. Troin, M. Hichour, V. Benezech, O. Chavignon, J. C. Gramain, J. C. Teulade and J. P. Chapar, *Tetrahedron*, 1999, **55**, 1959; (*d*) S. Wurtz, S. Rakshit and J. J. Neumann, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230; (*e*) M. Watanabe, T. Yamamoto and M. Nishiyama, *Angew. Chem., Int. Ed.*, 2003, **42**, 4257; (*f*) C. Tietcheu, C. Garcia and D. Gardette, *J. Heterocycl. Chem.*, 2002, **39**, 965.
7 D. Janreddy, V. Kavala, J. W. J. Bosco and C. W. Kuo, *Eur. J. Org. Chem.*, 2011, 2360.
8 R. A. Bunce and B. Nammalwar, *J. Heterocycl. Chem.*, 2009, **46**, 172.
9 Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, 1977, **42**, 1213.
10 X. Li, Y. Du, Z. Liang, X. Li, Y. Pan and K. Zhao, *Org. Lett.*, 2009, **11**, 2643.
11 K. Banert and B. Meier, *Angew. Chem., Int. Ed.*, 2006, **45**, 4015.
12 (*a*) T. E. Barta, A. F. Barabasz and B. E. Foley, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3078; (*b*) R. Giuseppe, M. Luisa and P. Valeria, *Bioorg. Med. Chem.*, 2006, **14**, 5211.
13 Y. Du, R. Liu, G. Linn and K. Zhao, *Org. Lett.*, 2006, **8**, 5919.
14 D. F. Taber and W. Tian, *J. Am. Chem. Soc.*, 2006, **128**, 1058.