ChemComm



View Article Online

COMMUNICATION



Cite this: DOI: 10.1039/c4cc08911a

Received 7th November 2014, Accepted 20th November 2014

Creation of molecular complexities *via* a new Cu-catalyzed cascade reaction: a direct access to novel 2,2'-spirobiindole derivatives[†]

Bagineni Prasad, Raju Adepu, Atul Kumar Sharma and Manojit Pal*

DOI: 10.1039/c4cc08911a

www.rsc.org/chemcomm

A Cu-mediated unprecedented cascade reaction in the presence of air afforded a conceptually new synthesis of 2,2'-spirobiindole derivatives. This reaction proceeds *via* the rearrangement of several bonds in a cyclopenta[*b*]indole framework including a facial selective intramolecular ring closure. The potential of this method is highlighted in the straightforward and single step synthesis of a paullone like compound.

Creation of new chemical space is one of the prime goals in both academic and industrial organizations as it helps in expanding their IP (intellectual property) portfolio. The chemical transformations that aid this process are in high demand as these reactions generate novel molecules for IP creation and protection. It is therefore desirable to continue to devote efforts to inventing new synthetic methodologies, which is considered to be the most challenging task in organic synthesis.

Cascade reactions involving multiple bond forming events in a single pot are known to play a central role in constructing heterocyclic and carbocyclic structures¹ along with the introduction of the desired degree of complexity required by academic and industrial R & D. Among various cascade reactions² the catalytic versions have emerged as the most active area of research particularly in pursuance of concerns related to chemical hazards, pollution and sustainability. Spiroindole derivatives have attracted particular attention in medicinal/pharmaceutical chemistry because of their numerous pharmacological properties. For example, the spirooxiindole moiety has been found to be a core structure in many synthetic pharmaceuticals^{3a,b} and has become an attractive template for the creation of new IP. Notably, despite their potential usefulness, not much attention has been paid to 2,2'-spirobi[indoline] derivatives,^{3c} perhaps due to their non

accessibility, and consequently as a class they are rather uncommon in the literature. In our efforts towards the identification of novel molecules of potential biological significance, we have recently reported the synthesis of densely functionalized indoles *via* two unique single-step reactions (Scheme 1).⁴ In further continuation of the research, we now wish to report a Cu-mediated unprecedented cascade reaction leading to an array of 2,2'-spirobi[indolin]-3-one based novel and complex derivatives. The degree of molecular complexity generated by this intramolecular cascade reaction in a single-pot is not only remarkable but also attractive from the viewpoint of IP generation (Scheme 2). Thus, cyclopenta[*b*]indoles^{4b} (1) on treatment with CuI in the presence of air afforded a range of spirobi[indolin]-3-one derivatives (2), the preliminary results of which are presented.

We initiated our study by treating **1a** with various catalysts, bases, and solvents in the presence of air and the results are summarized in Table 1. Initially, the reaction was performed using **1a**, $Cu(OAc)_2$ (1 equiv.) and Et_3N in DMF at 120 °C under



Scheme 1 Our previous synthesis of densely functionalized indoles.⁴



Scheme 2 Cu-mediated intramolecular cascade reaction of **1** leading to novel 2,2'-spirobi[indolin]-3-one derivatives (**2**).

Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Gachibowli, Hyderabad 500 046, India. E-mail: manojitpal@rediffmail.com;

Tel: +91 40 6657 1500

[†] Electronic supplementary information (ESI) available: Experimental procedures, spectral data for all new compounds, copies of spectra and HPLC. CCDC 993261. For ESI and crystallographic data in CIF or other format see DOI: 10.1039/ c4cc08911a



^{*a*} All the reactions were performed using **1a** (0.1 mmol) and a catalyst in the presence/absence of a base (1 equiv.) in a solvent (2 mL) at 120 $^{\circ}$ C under air. ^{*b*} Isolated yield. ^{*c*} 1 equiv. of benzoquinone was added. ^{*d*} Reaction was performed under nitrogen.

air and the product 2a was obtained in a 25% yield after 3 h (entry 1 in Table 1). Though unexpected, we were delighted to observe the formation and isolation of 2a that was characterized as a novel spirobi[indolin]-3-one derivative. Its 3D architecture attracted our attention and prompted us to explore this new reaction further. The use of a different catalyst $Cu(OTf)_2$ (entry 2 in Table 1) and base Cs_2CO_3 (entry 3 in Table 1) afforded 2a in 30% and 56% yields, respectively. The combination of Cu(OTf)₂/Cs₂CO₃ afforded 2a in 60% yield (entry 4 in Table 1) whereas the product formation was almost suppressed in the presence of benzoquinone (entry 5 in Table 1). An unidentified polar material was obtained as a side product in this case. Until this, we were not aware of the role of the base in the present cascade reaction. However, we observed that the reaction proceeded well in the absence of base when performed in the presence of $Cu(OTf)_2$ (entry 6 in Table 1). Next, to avoid the use of a stoichiometric amount of catalyst we wanted to make this method a truly catalytic one. Accordingly, the reaction was performed using 20 mol% of Cu(OTf)₂. To our satisfaction, the reaction proceeded well to afford the expected product in a 58% yield (entry 7 in Table 1) though the reaction time was a bit longer at 6 h. We then examined the use of aqueous DMF in place of DMF alone. To our surprise the reaction was completed within 1.5 h affording a better yield of 2a (entry 8 in Table 1). Indeed, the use of a lower quantity of $Cu(OAc)_2 \cdot H_2O$ also provided a similar outcome (entry 9, Table 1). These observations clearly indicate that the reaction is not moisture sensitive. To make the process more economic without significantly affecting the product yield, we examined the use of a cheaper catalyst, i.e. CuI in aqueous DMF (entries 10-12, Table 1). We found that 10 mol% CuI in 7:3 DMF: H₂O afforded

2a in 66% yield within 2 h (entry 12 in Table 1). Finally, the role of the catalyst was also established by performing the reaction in its absence, whereby no product was formed (entry 13 in Table 1). Notably, the increase in the reaction time from 2 h to 8 h when performing the reaction in the absence of air under nitrogen (entry 14, Table 1) indicated the key role of aerial oxygen in the present reaction. Nevertheless, we preferred the conditions of entry 12 over entry 8 (Table 1) due to the comparable reaction time and yield in addition to the involvement of an inexpensive catalyst.

With the optimized conditions in hand, we further investigated the substrate scope of this new cascade reaction. Thus, a variety of cyclopenta[b]indoles^{4b} (1) were employed in this Cu-mediated reaction (Table 2). The presence of halogens (F, Cl, Br, entries 3, 4, 6-13, 15 and 16, Table 2), electron donating groups (e.g. Me and OMe, entries 5, 10 and 1-17, Table 2) and an electron withdrawing group $(NO_2, entry 17, Table 2)$ on the indole ring of 1 was tolerated. The reaction proceeded well in all these cases affording the desired product in good to acceptable yields. In general, better yields of 2 were observed when an electron donating group was present. We also examined the effect of the nature of the sulfonamide moiety present in 1. Accordingly, cyclopentaindole 1 containing alkyl (entries 1 and 6, Table 2), aryl (entry 7, Table 2) and heteroaryl (entries 2-5 and 8-17, Table 2) sulfonamide groups was employed and the reaction proceeded as usual to afford the corresponding products. We then examined the reaction of compounds 1r-t individually with different substitution patterns (Scheme 3).5 While 1r and 1s afforded 2r and 2s, respectively, in acceptable yield, 1t afforded 2t in low yield.

Table 2 Synthesis of 2,2'-spirobi[indolin]-3-one derivatives (2) from cyclopentaindoles $\left(1\right) ^{a}$



^{*a*} All the reactions were performed using 1 (0.1 mmol), 10 mol% of CuI in DMF : $H_2O(7:3)$ (1.5 mL) at 120 °C for 1.5–4 h in the presence of air. ^{*b*} Isolated yield.



Scheme 3 Cu-mediated intramolecular cascade reaction of 1r-t.

All the synthesized compounds were well characterized by spectral (NMR, IR and MS) data. For example, the IR (1718 cm^{-1}) and ¹³C NMR [$\delta_{\rm C}$ 197.2 (C_f)] spectra of 2**b** indicated the presence of a -C=O group. Its ¹H NMR signals in the aliphatic region at δ 3.90 (d, 1H_a), 3.55 (dd, 1H_b¹), 2.88 (td, 1H_b), 2.08–2.00 (m, 1H_c¹) and 1.93 (dd, 1H_c) clearly identified the respective protons whereas the 13 C NMR signals at δ_c 50.2 (C_c), 49.7 (C_a), 32.6 (C_b) and 95.9 (C_{α}) identified three aliphatic and one sp³ guaternary carbon, respectively. The ¹H-¹H COSY spectra of 2b indicated that (i) H_a coupled with H_b and H_b^{-1} , (ii) H_b coupled with H_b^{-1} , H_c , H_c^1 and H_a , (iii) H_b^1 coupled with H_b , H_c , H_c^1 and H_a , (iv) H_c coupled with H_b^{1} , H_b and Hc^{1} , and (v) H_c^{1} coupled with H_b^{1} , H_b and H_c. The ¹H-¹³C HMQC spectra revealed that (i) C_a coupled with H_a, (ii) C_b coupled with H_b and H_b¹ and (iii) C_c coupled with H_c and H_c¹. The DEPT spectrum of **2b** showed the presence of 7 quaternary, 2 CH₂ and 12 CH carbons. Moreover, the proposed arrangement was confirmed by HMBC correlations (Fig. 1). Finally, the molecular structure of a representative compound 2j was confirmed unambiguously by single crystal X-ray diffraction study (Fig. 2). 6

A proposed reaction mechanism involving the reaction of **1** with aerial oxygen in the presence of CuI in the first step leading to the intermediate **E-1** is shown in Scheme 4.⁷ An intramolecular ring closure aided by HI involving the -C—N-moiety and the proximate amidic nitrogen of **E-1** affords **E-2**. The subsequent ring opening of the fused cyclopentane ring of **E-2** followed by the cleavage of the peroxide bond furnishes the spiro intermediate **E-3**. This step is facilitated by the participation of the fused indoline moiety of **E-2**, which after being a charged species in **E-3** undergoes subsequent aromatization to give **E-4**. The regeneration of CuI^{8a} from **E-4** completes the



Fig. 1 Compound 2b and its HMBC correlations.



Fig. 2 ORTEP representation of 2j. Thermal ellipsoids are drawn at 50% probability level.



Scheme 4 The proposed reaction mechanism.

catalytic cycle and affords E-5. A further intramolecular ring closure^{8b,c} of E-5 aided by HI furnished the desired product 2.^{8d} This ring closure and thereby the product yield can be influenced by the nature of R³ *i.e.* electron donating or withdrawing group (see Table 2). A similar pathway can be presented with $Cu(\pi)X_2$ (X = OAc, OTf *etc.*) catalysts by replacing the -OCu moiety with -OCuX. It is evident that the presence of a base added externally is not necessary in this pathway. However, the catalyst is required to facilitate the initial step and thereby the entire process. It appears that benzoquinone can perhaps compete with oxygen in the first step affording an adduct similar to E-1 thereby decreasing the yield of the desired product (entry 5, Table 1). While the precise reason for the faster reaction observed in aqueous DMF in comparison to DMF alone (entry 7 vs. 8 and 12, Table 1) was not clearly understood, the ability to absorb and retain a higher volume of oxygen by aqueous DMF was perhaps enhanced to a great extent due to the presence of water. However, the presence of a larger volume of water did not improve the reaction time or yield (entry 10 vs. 11, Table 1) due to the lesser solubility of 1 in 1:1 aqueous DMF.

Because each cyclopentaindole (1, Table 2) is a $\sim 1:1$ mixture of enantiomers (confirmed by chiral HPLC of 1c), it



Scheme 5 One-step synthesis of paullone like compound 3.

afforded **2** also as a 1:1 mixture of enantiomers⁹ (not 2 pairs, confirmed by chiral HPLC of **2c**); the present reaction appears to be a facial selective one, *i.e.* separate re and si face attack occurred during the intramolecular ring closure of the individual enantiomers of **E-1** (Scheme 4).

To demonstrate the potential of this method, compound **2a** was converted to **3** possessing a paullone¹⁰ like structural framework in a single step (Scheme 5). Thus, **2a** when treated with methanolic KOH participated in a sequential demesylation followed by ring opening and subsequent aromatization to afford **3**. The presence of two NH groups and a –CH₂CH₂– moiety in **3** was confirmed by the appearance of two D₂O exchangeable signals at δ 9.42 (bs, 1H) and 3.85 (bs, 1H) along with two triplets at δ 3.36 (t, *J* = 6.0 Hz, 2H) and 2.86 (t, *J* = 6.0 Hz, 2H) in the ¹H NMR spectra. Moreover, the ¹³C NMR including DEPT experiments showed the presence of 7 quaternary carbons along with 8 CH and 2 aliphatic CH₂ groups that confirmed the structure of **3**.

In conclusion, we have described a Cu-mediated unprecedented cascade reaction of cyclopenta[*b*]indoles in the presence of air to furnish an array of 2,2'-spirobi[indolin]-3-one based novel and complex molecules useful for academic and industrial R & D. This operationally simple, straightforward and inexpensive yet innovative method involves the rearrangement of several bonds including a facial selective intramolecular ring closure in which Cu plays a key role. One-step and direct synthesis of a paullone like compound highlighted the potential of this method. The present research results could be a new and useful addition to indole chemistry as well as cascade reactions.

BP and RA thank CSIR, New Delhi, India for research fellowships. Authors thank the management of DRILS for support.

Notes and references

1 For excellent books, see: (a) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH,

Weinheim, Germany, 2006; (b) T. J. J. Muller, *Metal Catalyzed Cascade Reactions*, Springer, New York, 2006. For an in depth account, see: (c) L. Q. Lu, J. R. Chen and W. J. Xiao, *Acc. Chem. Res.*, 2012, **45**, 1278.

- 2 (a) For a recent book, see: P.-F. Xu and W. Wang, Catalytic Cascade Reactions, John Wiley & Sons, Inc., Hoboken, New Jersey, 2014; (b) R. A. Bunce, Tetrahedron, 1995, 48, 13103; (c) L. F. Tietze and U. Belifuss, Angew. Chem., Int. Ed., 1993, 32, 131; (d) M. Ihara and K. Fukumoto, Angew. Chem., Int. Ed., 1993, 32, 1010; (e) C. P. Jasperse, D. P. Curran and T. L. Fevig, Chem. Rev., 1991, 91, 1237.
- 3 (*a*) B. Tan, G. Hernández-Torres and C. F. Barbas, III, *J. Am. Chem. Soc.*, 2011, **133**, 12354; (*b*) A. Bazgir, Z. Noroozi Tisseh and P. Mirzaei, *Tetrahedron Lett.*, 2008, **49**, 5165; (*c*) for a recent synthesis of similar class of compounds, see: W. Ding, Q.-Q. Zhou, J. Xuan, T.-R. Li, L.-Q. Lu and W.-J. Xiao, *Tetrahedron Lett.*, 2014, 55, 4648.
- 4 (a) B. Prasad, B. Y. Sreenivas, D. Rambabu, G. R. Krishna, C. M. Reddy,
 K. L. Kumar and M. Pal, *Chem. Commun.*, 2013, 49, 3970; (b) B. Prasad,
 B. Y. Sreenivas, G. R. Krishna, R. Kapavarapu and M. Pal, *Chem. Commun.*, 2013, 49, 6716.
- 5 We thank reviewers for suggesting these experiments.
- 6 Crystal data of **2j**: molecular formula = $C_{22}H_{17}FN_2O_4S_2$, formula weight = 456.50, crystal system = monoclinic, space group = P2(1)/c, a = 9.0012 (2) Å, b = 11.6897 (3) Å, c = 19.0204 (5) Å, V = 1999.06 (9) Å³, T = 296 K, Z = 4, $D_x = 1.517$ Mg m⁻³, μ (Mo-K α) = 0.31 mm⁻¹, 14591 reflections measured, 3409 independent reflections, 2957 observed reflections [$I > 2.0\sigma(I)$], $R_{int} = 0.027$, Goodness of fit = 1.05. CCDC 993261.
- 7 For the generation of a E-1 type intermediate from the fused indole derivatives, see: (a) R. W. Clawson Jr., R. E. Deavers III, N. G. Akhmedov and B. C. G. Soderberg, *Tetrahedron*, 2006, 62, 10829; (b) the possibility of a Wagner-Meerwein type rearrangement of E-1 leading to the corresponding spiro derivative (cf. B. Witkop and B. Patrick, J. Am. Chem. Soc., 1951, 73, 2188) was unlikely as that would generate an unfavourable and strained 4-membered ring.
- 8 (a) For similar reactions of Cu(1)alkoxides with alkyliodides, see: G. M. Whitesides, J. S. Sadowski and J. Lilburn, J. Am. Chem. Soc., 1974, 96, 2829; (b) for a similar type of intramolecular cyclization under Rh-catalyzed dehydrogenative conditions, see: P. Patel, B. N. Reddy and C. V. Ramana, Tetrahedron, 2014, 70, 510; (c) to understand and visualize physically the three-dimensional position of atoms in E-5 during its intramolecular ring closure a ball-andstick model was used. The model clearly shows (see ESI⁺ for images) that the orientation of ethanol side chain of E-5 is flexible and can bring the -CH2OH group in a close proximity to the -NH- moiety thereby facilitating the ring closure; (d) though our attempt to isolate any of these intermediates in pure form was not successful, however, systematic MS analysis of reaction sample after 1, 2 and 3 h indicated the presence of unprotonated E-5. For example, the peak at 441 (in addition to 423 of product 2s) in the MS spectra of the reaction sample of **1s** after 1 h accounted for M + 1 signal of the corresponding E-5 which was decreased as the reaction progressed further.
- 9 HPLC of the crude product indicated the presence of a single diasteromer along with some minor impurities. For example, HPLC of crude **2a** showed a major peak at 14 min [>60%; diluent, MeCN:H₂O (80:20)] with no other significant peak within ± 2 min.
- 10 Paullones belong to a family of benzazepinones and are known to possess promising antitumoral along with cyclin-dependent kinases (CDKs) inhibitory properties, see: C. Schultz, A. Link, M. Leost, D. W. Zaharevitz, R. Gussio, E. A. Sausville, L. Meijer and C. Kunick, J. Med. Chem., 1999, 42, 2909.