Organic & Biomolecular Chemistry

COMMUNICATION

View Article Online
View Journal

Cite this: DOI: 10.1039/c5ob00085h

Received 15th January 2015,
Accepted 23rd March 2015

DOI: 10.1039/c5ob00085h

www.rsc.org/obc

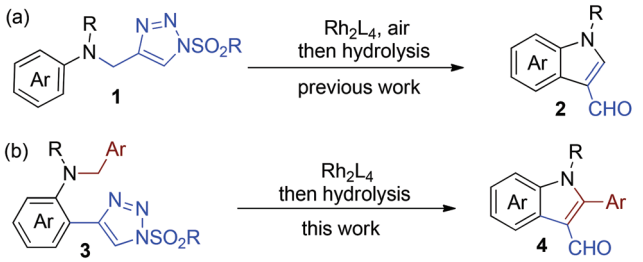
An efficient approach to 1,2,3-trisubstituted indole *via* rhodium catalyzed carbene C_{sp^3}–H bond insertion†

Mei-Hua Shen,* Ying-Peng Pan, Zhi-Hong Jia, Xin-Tao Ren, Ping Zhang and Hua-Dong Xu*

A method for convenient synthesis of *N*-alkyl-2-aryl-indole-3-carbaldehyde has been described. A variety of highly valuable indolyl aldehydes have been prepared through this method. Electron donating groups on both aromatic rings (anilinyl and benzyl) facilitate the formation of the desired products. A benzylic C–H insertion by rhodium carbene is the key step for this transformation.

A 1,2,3-trisubstituted indole moiety constitutes a large number of natural and synthetic biologically active molecules and functional materials. 3-Formyl indole is a versatile intermediate for the synthesis of indole derivatives due to the diverse transformations in which the aldehyde functional group could participate.[1] Conventionally, direct formylation of the corresponding parent indole is the choice for the preparation of this class of molecule, such as Vilsmeier–Haack formylation,[2] Reimer–Tiemann–Gattermann reaction,[3] and recently reported protocols for direct indole formylation.[4] On the other hand, several *de novo* methods for the construction of 3-formyl indole from non-indole precursors have also appeared in the literature which possess some merits devoid in the direct approach.[5]

Since they were discovered as convenient 2-azavinyl carbene progenitors in 2008,[6] 1-sulfonyl 1,2,3-triazoles have been applied with great success in a variety of efficient transformations[7] leading to the construction of unique frameworks otherwise hardly accessible.[8] Our interest in this research area has led to the discovery of several practical reactions,[9] and particularly relevant to the current report is rhodium catalyzed 3-formyl indole synthesis from triazole **1** (Scheme 1, eqn (a)).[9a] A key event in this process is the (formal) insertion of the *in situ* generated metal carbene into the *ortho* anilinyl C_{sp^2}–H bond.[8h,l,m] Here we wish to report a complementary strategy which employed *N*-benzyl anilinyl triazole **3** as the starting material for a facile entry into 1-alkyl-2-aromatic-3-formyl indole **4** (Scheme 1, eqn (b)).

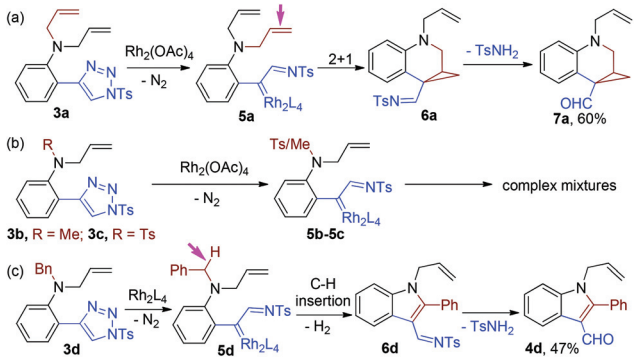


Scheme 1 Complementary *de novo* 3-formyl indole synthesis using sulfonyl triazoles.

Initially, *N*,*N*-bisallyl-anilinyl triazole **3a** was treated with a catalytic amount of $Rh_2(OAc)_4$ in hot toluene under nitrogen and tricyclic aldehyde **7a** was isolated in 60% yield after hydrolysis in an open flask. Efforts to expand this reaction to other close analogues have encountered unexpected difficulties as triazoles **3b** and **3c**, with one allyl group replaced by the methyl or tosyl group respectively, delivered complex reaction mixtures. However, when substrate **3d**, carrying an *N*-benzyl group instead, was subjected to the identical reaction conditions, 1-allyl-2-phenyl-3-formyl indole **4d** was, interestingly, isolated in 47% yield. The divergence in reaction behaviours of **3a–3d** was really intriguing giving the subtle structural discrepancies among these molecules. Even though the exact reason for the substituent sensitive selectivity is not clear at the present stage, it can be deduced that the azavinyl carbenoid **5a** derived from **3a** reacted with one pendent allyl double bond to give cyclopropane **6a** (Scheme 2a); while in intermediate **5d**, the allyl group was out-competed by the neighbouring benzylic C_{sp^3}–H for the rhodium carbene,[10] the resulting indoline intermediate underwent *in situ* dehydrogenative aromatization to give **6d** (Scheme 2c). On the other hand, reactive carbenoids **5b** and **5c** may undergo multiple pathways leading to various products each in small quantities (Scheme 2b).

School of Pharmaceutical Engineering and Life Science, Changzhou University, Changzhou, Jiangsu Province 213164, China. E-mail: meihuashen@gmail.com, huadongxu@gmail.com

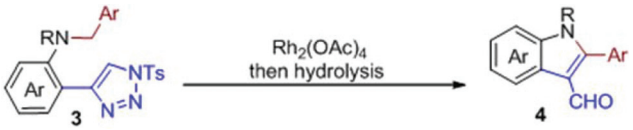
†Electronic supplementary information (ESI) available: The details of experiments, compound characterization and spectroscopic data. See DOI: 10.1039/c5ob00085h

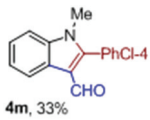
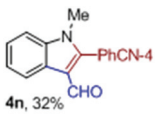
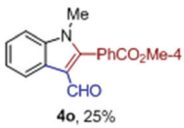
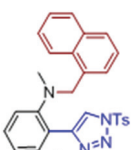
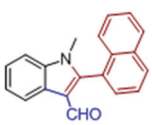
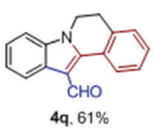


Scheme 2 The divergent outcomes affected by subtle *N*-substituent variations.

We were interested in the C–H insertion pathway as it could serve as a complementary method for our prior *de novo* 3-formyl indole synthesis (Scheme 1a). A range of *N*-benzyl-anilinyl sulfonyl triazoles have been prepared and subjected to the rhodium catalyzed reactions. The data are shown in Table 1. For the *N*,*N*-bisbenzyl series (**3e–3i**), the electronic impact on the reaction is prominent, as evidenced by the 74% and 72% yields of **4g** and **4f** bearing methoxyl and methyl groups at the 6-position respectively, and the decreased yields of chlorinated **4h** (54%) and fluorinated **4i** (52%). The trend that the electron donating group facilitates the indole formation also holds for the substituent effect on the *N*-benzyl moiety. In *N*-benzyl-*N*-methyl series (**3j–3o**), the yield increased from 25% for 4-CO_2Me-benzyl anilinyl triazole **3o** to 55% for

Table 1 Preparation of 3-formyl indoles from sulfonyl triazoles[a]



Substrate	Product, yield[b]	Substrate	Product, yield[b]
 3e	 4e, 65%	 3l	 4l, 55%
 3f	 4f, 72%	 3m	 4m, 33%
 3g	 4g, 74%	 3n	 4n, 32%
 3h	 4h, 55%	 3o	 4o, 25%
 3i	 4i, 52%	 3p	 4p, 63%
 3j	 4j, 38%	 3q	 4q, 61%
 3k	 4k, 47%		

[a] Reaction conditions: step (1) **3** (0.4 mmol), $Rh_2(OAc)_4$ (2.0 mol %), tol (4 mL), 85 °C, under N_2 for 2 h, then volatiles removed under vacuum; step (2) K_2CO_3 (1.6 mmol), MeOH (4 mL), rt, in air overnight. [b] Isolated yield.

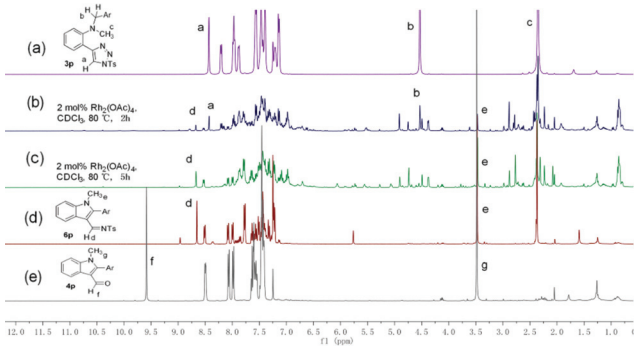


Fig. 1 Monitoring rhodium catalysed triazole decomposition *via* proton NMR.

4-MeO-benzyl anilinyl triazole **3l**. Aromaticity extended 2-naphthalenyl indole **4p** was obtained from **3p** in a much higher yield than the corresponding 2-phenyl indole **4j** from **3j** (63% *vs*. 38%). Moreover, the higher yields in general for the former series than for the latter ones might reflect both steric and statistical effects. Tetracyclic aldehyde **4q** was easily prepared in 61% yield by using triazole **3q** as the substrate.

The reaction of triazole **3p** in $CDCl_3$ was monitored by ^1H NMR for more information (Fig. 1). Peaks a and b almost disappeared when the mixture was heated at 80 °C under N_2 for 5 hours, indicating that triazole **3p** decomposed completely at this point. Along the reaction course, distinct new peaks d and e emerged and grew (Fig. 1a–c). Flash column chromatography of this reaction mixture delivered a semi-purified product which was assigned as indolyl tosylimine **6p** based on ^1H NMR analysis (Fig. 1d). The direct observation of indole **6p** in the reaction mixture rather than its non-aromatic precursor, the corresponding indoline intermediate, suggests an instant *in situ* dehydrogenative aromatization after a carbene C–H insertion event.

In conclusion, 2-(*N*-Alkyl-*N*-benzyl)-anilinyl triazoles have been used as facile starting materials for the synthesis of *N*-alkyl-2-aryl-indole-3-carbaldehydes. Triazoles with an electron donating group on both aromatic rings usually gave higher yields than triazoles with an electron withdrawing group. This method features a rhodium catalyzed C–H functionalization of benzyl aromatic amine and a dehydrogenative aromatization.

The authors wish to thank the Natural Science Foundation of China (21402014 and 21272077), the Natural Science Foundation of Jiangsu Province (BK20131143), the Priority Academic Program Development of Jiangsu Higher Education Institutions (PADA), and Jiangsu Key Laboratory of Advanced Catalytic Materials and Technology (BM2012110).

Notes and references

1 (*a*) D. Kumar, N. M. Kumar, K. Akamatsu, E. Kusaka, H. Harada and T. Ito, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 3916; (*b*) M. G. Bursavich, N. Brooijmans, L. Feldberg, I. Hollander, S. Kim, S. Lombardi, K. Park, R. Mallon and A. M. Gilbert, *Bioorg. Med. Chem. Lett.*, 2010, **20**, 2586; (*c*) M. Sisa, D. Pla, M. Altuna, A. Francesch, C. Cuevas, F. Albericio and M. Alvarez, *J. Med. Chem.*, 2009, **52**, 6217; (*d*) M. A. Colucci, P. Reigan, D. Siegel, A. Chilloux, D. Ross and C. J. Moody, *J. Med. Chem.*, 2007, **50**, 5780; (*e*) N. Fujii, J. J. Haresco, K. A. P. Novak, D. Stokoe, I. D. Kuntz and R. K. Guy, *J. Am. Chem. Soc.*, 2003, **125**, 12074; (*f*) J. F. Sanz-Cervera and R. M. Williams, *J. Am. Chem. Soc.*, 2002, **124**, 2556; (*g*) L. Canoira, J. Gonzalo Rodriguez, J. B. Subirats, J. A. Escario, I. Jimenez and A. R. Martinez-Fernandez, *Eur. J. Med. Chem.*, 1989, **24**, 39.

2 (*a*) P. N. James and H. R. Snyder, *Org. Synth.*, 1959, **39**, 30; (*b*) G. F. Smith, *J. Chem. Soc.*, 1954, 3842; (*c*) F. T. Tyson and J. T. Shaw, *J. Am. Chem. Soc.*, 1952, **74**, 2273; (*d*) A. C. Shabica, E. E. Howe, J. B. Ziegler and M. Tishler, *J. Am. Chem. Soc.*, 1946, **68**, 1156.

3 (*a*) W. J. Boyd and W. Robson, *Biochem. J.*, 1935, **29**, 555; (*b*) A. Ellinger and C. Flamand, *Z. Phys. Chem.*, 1908, **55**, 8; (*c*) A. Ellinger, *Ber.*, 1906, **39**, 2515.

4 (*a*) X. Li, X. Gu, Y. Li and P. Li, *ACS Catal.*, 2014, **4**, 1897; (*b*) H. Fei, J. Yu, Y. Jiang, H. Guo and J. Cheng, *Org. Biomol. Chem.*, 2013, **11**, 7092; (*c*) J. Chen, B. Liu, D. Liu, S. Liu and J. Cheng, *Adv. Synth. Catal.*, 2012, **354**, 2438.

5 (*a*) S. Zhu, A. Das, L. Bui, H. Zhou, D. P. Curran and M. Rueping, *J. Am. Chem. Soc.*, 2013, **135**, 1823; (*b*) C.-Y. Wu, M. Hu, Y. Liu, R.-J. Song, Y. Lei, B.-X. Tang, R.-J. Li and J.-H. Li, *Chem. Commun.*, 2012, **48**, 3197.

6 T. Horneff, S. Chuprakov, N. Chernyak, V. Gevorgyan and V. V. Fokin, *J. Am. Chem. Soc.*, 2008, **130**, 14972.

7 (*a*) H. M. L. Davies and J. S. Alford, *Chem. Soc. Rev.*, 2014, **43**, 5151; (*b*) P. Anbarasan, D. Yadagiri and S. Rajasekar, *Synthesis*, 2014, 3004; (*c*) B. Chattopadhyay and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2012, **51**, 862; (*d*) A. V. Gulevich and V. Gevorgyan, *Angew. Chem., Int. Ed.*, 2013, **52**, 1371.

8 (*a*) Y.-S. Zhang, X.-Y. Tang and M. Shi, *Chem. Commun.*, 2014, **50**, 15971; (*b*) H. Shen, J. Fu, J. Gong and Z. Yang, *Org. Lett.*, 2014, **16**, 5588; (*c*) S. Kim, J. Mo, J. Kim, T. Ryu and P. H. Lee, *Asian J. Org. Chem.*, 2014, **3**, 926; (*d*) A. Boyer, *Org. Lett.*, 2014, **16**, 5878; (*e*) J. Fu, H. Shen, Y. Chang, C. Li, J. Gong and Z. Yang, *Chem. – Eur. J.*, 2014, **20**, 12881; (*f*) T. Miura, T. Nakamuro, C.-J. Liang and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 15905; (*g*) X. Ma, S. Pan, H. Wang and W. Chen, *Org. Lett.*, 2014, **16**, 4554; (*h*) S. Park, W.-S. Yong, S. Kim and P. H. Lee, *Org. Lett.*, 2014, **16**, 4468; (*i*) D. J. Lee, H. S. Han, J. Shin and E. J. Yoo, *J. Am. Chem. Soc.*, 2014, **136**, 11606; (*j*) E. E. Schultz, V. N. G. Lindsay and R. Sarpong, *Angew. Chem., Int. Ed.*, 2014, **53**, 9904; (*k*) R.-Q. Ran, J. He, S.-D. Xiu, K.-B. Wang and C.-Y. Li, *Org. Lett.*, 2014, **16**, 3704; (*l*) J. S. Alford and H. M. L. Davies, *J. Am. Chem. Soc.*, 2014, **136**, 10266; (*m*) B. Rajagopal, C.-H. Chou, C.-C. Chung and P.-C. Lin, *Org. Lett.*, 2014, **16**, 3752; (*n*) F. Medina, C. Besnard and J. Lacour, *Org. Lett.*, 2014, **16**, 3232; (*o*) K. Chen, Z.-Z. Zhu, Y.-S. Zhang, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*,

2014, **53**, 6645; (*p*) T. Miura, Y. Funakoshi, T. Tanaka and M. Murakami, *Org. Lett.*, 2014, **16**, 2760; (*q*) J.-M. Yang, C.-Z. Zhu, X.-Y. Tang and M. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 5142; (*r*) S. W. Kwok, L. Zhang, N. P. Grimster and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2014, **53**, 3452; (*s*) T. Miura, Y. Funakoshi and M. Murakami, *J. Am. Chem. Soc.*, 2014, **136**, 2272; (*t*) S. Chuprakov, B. T. Worrell, N. Selander, R. K. Sit and V. V. Fokin, *J. Am. Chem. Soc.*, 2014, **136**, 195; (*u*) Y. Shi and V. Gevorgyan, *Org. Lett.*, 2013, **15**, 5394; (*v*) T. Miura, T. Tanaka, K. Hiraga, S. G. Stewart and M. Murakami, *J. Am. Chem. Soc.*, 2013, **135**, 13652; (*w*) J. S. Alford, J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 11712; (*x*) J. E. Spangler and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 6802; (*y*) R. Liu, M. Zhang, G. Winston-McPherson and W. Tang, *Chem. Commun.*, 2013, **49**, 4376; (*z*) S. Chuprakov, S. W. Kwok and V. V. Fokin, *J. Am. Chem. Soc.*, 2013, **135**, 4652; (*aa*) B. T. Parr, S. A. Green and H. M. L. Davies, *J. Am. Chem. Soc.*, 2013, **135**, 4716; (*ab*) E. E. Schultz and R. Sarpong, *J. Am. Chem. Soc.*, 2013, **135**, 4696; (*ac*) T. Miura, T. Tanaka, T. Biyajima, A. Yada and M. Murakami, *Angew. Chem., Int. Ed.*, 2013, **52**, 3883; (*ad*) M. Zibinsky and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2013, **52**, 1507.

9 (*a*) H.-D. Xu, K. Xu, Z.-H. Jia, H. Zhou, P. Jiang, X.-L. Lu, Y.-P. Pan, H. Wu, Y. Ding, M.-H. Shen and X.-H. Pan, *Asian J. Org. Chem.*, 2014, **3**, 1154; (*b*) H.-D. Xu, K. Xu, H. Zhou, Z.-H. Jia, H. Wu, X.-L. Lu and M.-H. Shen, *Synthesis*, 2015, **47**, 641; (*c*) H.-D. Xu, Z.-H. Jia, K. Xu, H. Zhou and M.-H. Shen, *Org. Lett.*, 2015, **17**, 66.

10 S. Chuprakov, J. A. Malik, M. Zibinsky and V. V. Fokin, *J. Am. Chem. Soc.*, 2011, **133**, 10352.

