Tetrahedron Letters 55 (2014) 2876–2878

Contents lists available at ScienceDirect

Tetrahedron Letters

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

Synthesis of oxygenated 2-methylindolines

Meng-Yang Chang *, Yi-Chia Chen, Chieh-Kai Chan

Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan

ARTICLE INFO

Article history:
Received 2 February 2014
Revised 12 March 2014
Accepted 20 March 2014
Available online 28 March 2014

Keywords:
2-Methylindolines
Hydroamination
2-Allylnitrobenzenes

ABSTRACT

A palladium-mediated high-yielding synthesis of oxygenated 2-methylindolines **4** from 2-allylnitrobenzene **1** and hydrazine is developed. The one-pot route combines the reduction of 2-allylnitrobenzene **1** and the sequential intramolecular hydroamination. The protocol provides a novel alternative for the synthesis of substituted 2-methylindoline **4**.

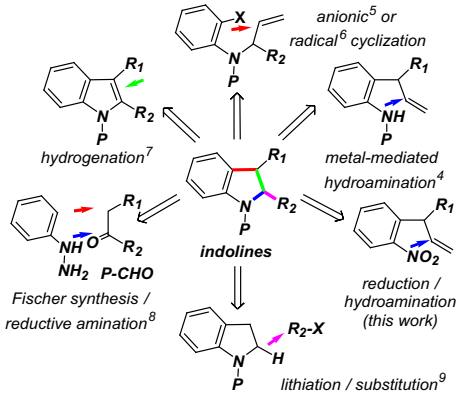
Introduction

Indoline, with a bicyclic benzannulated ring system, is a key pharmacophore for a drug candidate.[1,2] Among those biologically active molecules, 2-methylindoline skeleton is known to be widely used among promising therapeutic agents, such as, indapamide (diuretic).[3] A considerable number of attempts have been made to synthesize the skeleton. The adopted synthetic routes are summarized in Scheme 1.[4–10] The key transformations include intramolecular transition metal-mediated hydroamination of 2-allylanilines (e.g., Ir, Zn, Au, Zr, Cu, Pd),[4] metal–halogen exchange (anionic route)[5] or free radical ring-cyclization of *N*-allyl-2-haloanilines,[6] Lewis acid-mediated hydride reduction or hydrogenation of indoles.[7] Fischer synthesis of ketones with phenylhydrazines is followed by reductive amination of alkyl aldehydes.[8] Lithiation of indolines is followed by substitution route[9] and other approaches.[10]

Results and discussion

In continuation of our investigation on the synthesis of dihydro-1-benzazepines into the synthetic application of 2-allylnitrobenzene **1**,[11] palladium-catalyzed the one-pot route of 2-methylindoline **4** with hydrazine, is investigated herein, including (i) nitro group reduction of 2-allylnitrobenzene **1** and (ii) intramolecular hydroamination of the corresponding 2-allylaniline **3**. 2-Allylnitrobenzene **1** was prepared in modest yields according to the known reported methods from 2-methoxy-5-nitrophenol (**2**), as shown in Scheme 2.[11] The expeditious ring-closure forms a core indoline structure.

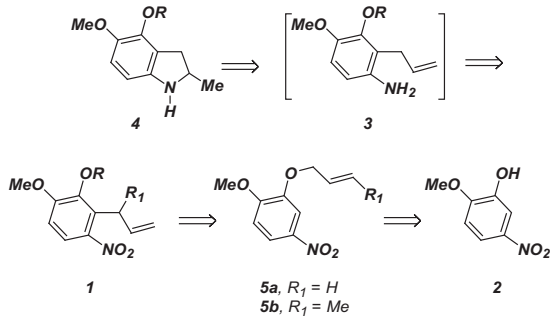
To achieve the best reaction conditions, **1a** (R = Me) was selected as the model substrate. One-pot reaction of **4a** was treated with **1a** and Pd/C (10%, 50 mg) as the catalyst in boiling a co-solvent of toluene and aqueous hydrazine (80%). The reaction process was monitored by TLC until the reactant **1a** was consumed. By exchanging different solvents and adjusting the co-solvent ratio with aqueous N_2H_4 (80%) and the reaction time, different yields of **4a** were observed (Table 1, entries 1–10). To enhance the yield of **4a**, the amounts of 10% Pd/C were further examined (entries 11–12). But, no obvious improvement was found by the addition of Pd/C with less (10 mg) or higher (100 mg) loading amounts. Based on the experiments, we established that the 1:1 volume



Scheme 1. Synthetic routes of indolines.

* Corresponding author. Tel.: +886 7 3121101x2220; fax: +886 7 3125339.
E-mail address: mychang@kmu.edu.tw (M.-Y. Chang).

http://dx.doi.org/10.1016/j.tetlet.2014.03.095
0040-4039/

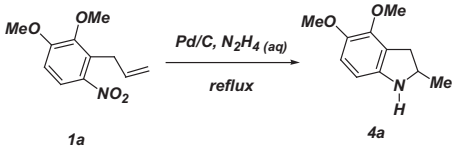


Scheme 2. Retrosynthesis of oxygenated 2-methylindolines **4**.

ratio of toluene and $N_2H_{4(aq)}$ (10 mL) is an optimal combination for elevating the yields of **4a** under boiling conditions for 25 h (entry 4). With the results in hand, one-pot facile preparation of substituted indolines **4** was examined. From our previous reports,[11] a facile three-step route was employed to create skeleton **1**, starting with **2** via (1) O-allylation of **2** with allyl bromide (Table 2, entries 1–5) or *trans*-crotyl bromide (entry 6), (2) Claisen rearrangement of *O*-allyl-1-nitrobenzene and (3) O-alkylation of the resulting 2-allyl-3-nitrophenol **5a** or **5b** with alkyl bromides (R = methyl, isopropyl, *n*-butyl, cyclopentyl, *n*-octyl).

When O-3-substituted 2-allyl-nitrobenzenes **1a–f** (Table 2, entries 1–6) were treated under optimal reaction conditions, we observed that indolines **4a–f** provided 70–84% yields.[12] Changing the R substituent, a dioxygenated indoline was isolated via the one-pot reduction/hydroamination protocol. Following the procedure, synthesis of bis-indoline was examined next. As shown in Scheme 3, four bis-3-*O*-linked 2-allyl-nitrobenzenes **7a–d** with different lengths of carbon linear chain (propyl, butyl, hexyl and octyl) reacted with the one-pot condition to afford a skeleton of bis-indolines **7a–d** at 70–78% yields. Adjusting the reaction temperature to rt, the skeleton of *o*-allylanilines **8a–d** (58–65%) was isolated in major products along with trace amounts of *o*-allylanilino-indolines **9a–d** (8–14%), as shown in Scheme 4. From the phenomenon,

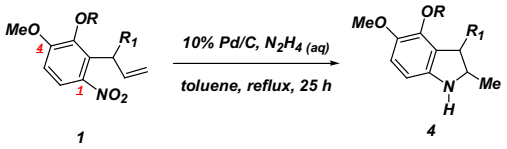
Table 1
Synthesis of compound **4a**[a]



Entry	Solvent (mL), N_2H_4 (mL), time (h)	**4a**, Yield[b] (%)
1	Toluene (10), 1, 10	42
2	Toluene (10), 5, 10	70
3	Toluene (10), 5, 25	74
4	Toluene (5), 5, 25	84
5	Toluene (5), 5, 50	78
6	Toluene (1), 10, 25	70
7	DME (5), 5, 25	66
8	1,4-Dioxane (5), 5, 25	60
9	THF (10), 5, 25	44
10	EtOH (5), 5, 25	56
11	Toluene (5), 5, 25	65[c]
12	Toluene (5), 5, 25	76[d]

[a] The reactions were run on a 1.0 mmol scale with **1a**, N_2H_4 (80% in H_2O), Pd/C (10%, 50 mg) in refluxing temperature.
[b] The isolated **4a** were >95% pure as determined by ^1H NMR analysis.
[c] Pd/C (10%, 10 mg) was added.
[d] Pd/C (10%, 100 mg) was added.

Table 2
Synthesis of skeleton **4**[a]



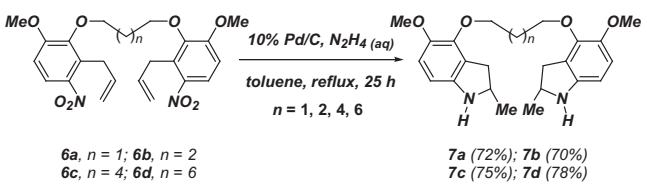
Entry	**1**, R =, R_1 =,	**4**, Yield[b] (%)
1	**1a**, Methyl, H	**4a**, 84
2	**1b**, Isopropyl, H	**4b**, 80
3	**1c**, *n*-Butyl, H	**4c**, 81
4	**1d**, Cyclopropyl, H	**4d**, 76
5	**1e**, *n*-Octyl, H	**4e**, 83
6	**1f**, Methyl, methyl	**4f**, 70

[a] The reactions were run on a 1.0 mmol scale with **1**, N_2H_4 (80% in H_2O), Pd/C (10%, 50 mg) in refluxing temperature.
[b] The isolated **4** were >95% pure as determined by ^1H NMR analysis.

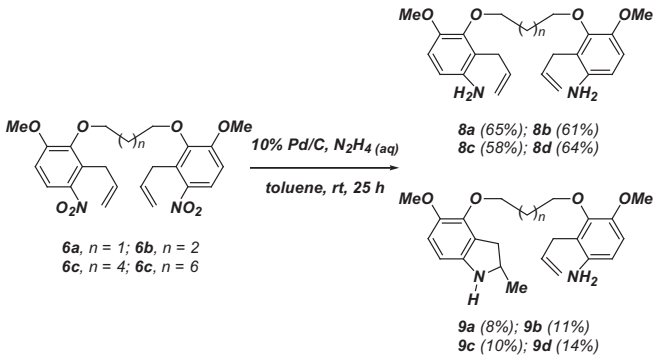
we found that the reaction temperature could control product distribution. To deserve to be mentioned, the color of the isolated skeletons **8** and **9** (pale yellow) was easily converted into a brownish color at room temperature within 1 h under air atmosphere. This color change shows that quinine derivatives should be formed.

Attempts to construct other oxygenated indoline skeletons are examined next. Skeleton **10** was subjected to the one-pot reduction/hydroamination, but 2-allylanilines **11** was isolated as the sole compound with good yields (80–84%) and no cyclized skeleton **12** was observed (Scheme 5). Increasing the time (25 → 100 h) in the reaction of **10a** with a one-pot protocol showed no **12a** was yielded. To explore the feasibility, scope, and limitations of this approach, reaction of **13** or **15** (prepared from ring-closing metathesis of **4a** or cross metathesis of **1a**) provided bis-anilines **14** or **16** at 65% or 58% yields (Scheme 6). A skeleton of indoline was still not found. The structure of **15** was determined by single-crystal X-ray crystallography.[13]

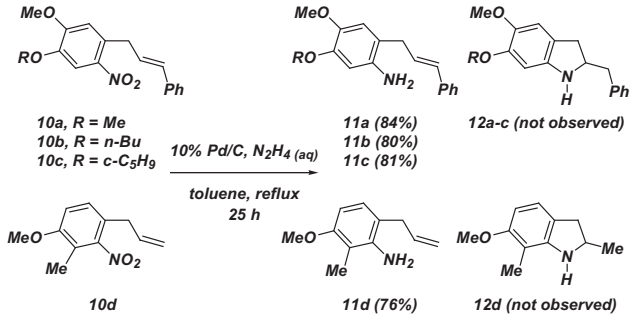
According to the above results, we envision that the position of the methoxy group on a benzene ring is an important substituent controlling the formation of indoline via the hydroamination ring-closing process. As shown in Table 2, the C4 electron-donating methoxy group of skeleton **1** could promote the C1 amino group (from nitro-reduction) to easily cyclize with the *o*-allyl group. When the position of the C4 methoxy group was moved to a C3 position, the indoline ring was not formed (for **10d**). The plausible reason should be C4-substituent forces the *o*-allyl moiety closer to the C1 amino group via the required aminopalladation procedure. The resulting phenomenon with the accelerated cyclization is similar to Thorpe-Ingold effect.[14] On the other hand, the *o*-allyl group was a key arm in the formation of an indoline skeleton, as shown in Scheme 5. For the *o*-cinnamyl side chain (for **10a–c**), the C1 amino group was not cyclized with the olefinic motif of the styryl group since it possessed the steric hindrance which impeded its coordination to palladium center. The similar results have been found for the ineffective cyclization of skeleton **13** and



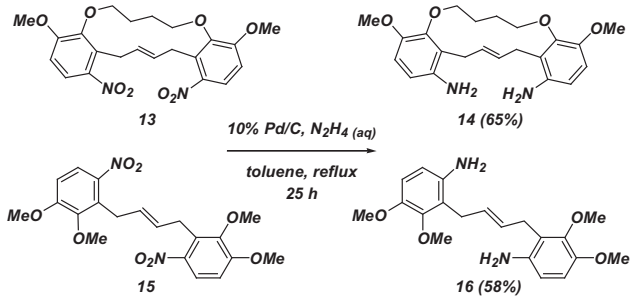
Scheme 3. Synthesis of skeleton **7**.



Scheme 4. Synthesis of skeletons **8** and **9**.



Scheme 5. Synthesis of skeleton **11**.



Scheme 6. Synthesis of compounds **14** and **16**.

15. To affect the hydroamination process, C4-substituent and less hindrance were needed.

Conclusion

In summary, we have successfully presented a one-pot synthetic methodology for oxygenated indolines **4** and **7**, which involves the tandem reduction of nitrobenzenes **1** and **6** with 10% palladium on the activated carbon, 80% aqueous solution of hydrazine and hydroamination of the resulting 2-allyl anilines. Further investigation regarding one-pot cascade synthesis of functionalized heterocycles will be conducted and published in due course.

Acknowledgments

The authors would like to thank the National Science Council of the Republic of China for its financial support (NSC 102-2113-M-037-005-MY2).

Supplementary data

Supplementary data (scanned photocopies of NMR spectral data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.03.095.

References and notes

1. (a) Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787; (b) Liu, K. G.; Robichaud, A. J. *Drug Dev. Res.* **2009**, *70*, 145.
2. (a) Temperini, C.; Cecchi, A.; Scozzafava, A.; Supuran, C. T. *J. Med. Chem.* **2009**, *52*, 322; (b) Khan, P. M.; Correa, R. G.; Divlianska, D. B.; Peddibhotla, S.; Sessions, E. H.; Magnuson, G.; Brown, B.; Suyama, E.; Yuan, H.; Mangravita-Novo, A.; Vicchiarelli, M.; Su, Y.; Vasile, S.; Smith, L. H.; Diaz, P. W.; Reed, J. C.; Roth, G. P. *ACS Med. Chem. Lett.* **2011**, *2*, 780.
3. (a) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1929**, *1990*, 33; (b) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893; (c) Adachi, S.; Koike, K.; Takayanagi, I. *Pharmacology* **1996**, *53*, 250.
4. For Ir, see: (a) Liu, W. B.; He, H.; Dai, L.-X.; You, S.-L. *Synthesis* **2009**, 2076; For Zn, see: (b) Yadav, J. S.; Reddy, B. V. S.; Rasheed, M. A.; Kuman, H. M. S. *Synlett* **2000**, 487; For Au, see (c) Zhang, J.; Yang, C.-G.; He, C. *J. Am. Chem. Soc.* **2006**, *128*, 1798; For Zr, see: (d) Leitch, D. C.; Payne, P. R.; Dunbar, C. R.; Schafer, L. L. *J. Am. Chem. Soc.* **2009**, *131*, 18246; For Cu, see: (e) Turnpenny, B. W.; Hyman, K. L.; Chemler, S. R. *Organometallics* **2012**, *31*, 7819; (f) Liwosz, T. W.; Chemler, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 2020; (g) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250; (h) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573; (i) Lin, J.-S.; Xiong, Y.-P.; Ma, C.-L.; Zhao, L.-J.; Tan, B.; Liu, X.-Y. *Chem. Eur. J.* **2014**, *20*, 1332; For Pd, see: (j) Schultz, D. M.; Wolfe, J. P. *Org. Lett.* **2010**, *12*, 1028; (k) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906; (l) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690; (m) Michael, F. E.; Cochran, B. M. *J. Am. Chem. Soc.* **2006**, *128*, 4246.
5. (a) Ketcha, D. M.; Lieurance, B. A. *Tetrahedron Lett.* **1989**, *30*, 6833; (b) Lanzilotti, A. E.; Littell, R.; Fanshawe, W. J.; McKenzie, T. C.; Lovell, F. M. *J. Org. Chem.* **1979**, *44*, 4809; (c) Coulton, S.; Gilchrist, T. L.; Graham, K. *Tetrahedron* **1997**, *53*, 791; (d) Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* **2004**, *6*, 2213; (e) Chandrasekhar, S.; Basu, D.; Reddy, C. R. *Synthesis* **2007**, 1509.
6. (a) Bailey, W. F.; Carson, M. W. *Tetrahedron Lett.* **1997**, *38*, 1329; (b) Bailey, W. F.; Luderer, M. R.; Mealy, M. J. *Tetrahedron Lett.* **2003**, *44*, 5303; (c) Zhang, D.; Liebeskind, L. S. *J. Org. Chem.* **1996**, *61*, 2594; (d) Nakao, J.; Inoue, R.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* **1910**, *1997*, 62; (e) Uchiyama, M.; Kameda, M.; Mishima, O.; Yokoyama, N.; Koike, M.; Kondo, Y.; Sakamoto, T. *J. Am. Chem. Soc.* **1998**, *120*, 4934.
7. (a) Li, C.; Chen, J.; Fu, G.; Liu, D.; Liu, Y.; Zhang, W. *Tetrahedron* **2013**, *69*, 6839; (b) Kurono, N.; Honda, E.; Komatsu, F.; Orito, K.; Tokuda, M. *Tetrahedron* **2004**, *60*, 1791; (c) Murphy, J. A.; Rasheed, F.; Gastaldi, S.; Ravishanker, T.; Lewis, N. *J. Chem. Soc., Perkin Trans. 1* **1997**, 1549; (d) Leroi, C.; Bertin, D.; Dufils, P.-E.; Gigmes, D.; Marque, S.; Tordo, P.; Couturier, J.-L.; Uerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943; (e) Pitts, M. R.; Harrison, J. R.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 955.
8. Liu, K. G.; Lo, J. R.; Robichaud, A. J. *Tetrahedron* **2010**, *66*, 573.
9. Gross, K. M. B.; Jun, Y. M.; Beak, P. *J. Org. Chem.* **1997**, *62*, 7679.
10. (a) Kang, K. H.; Kim, Y.; Im, C.; Park, Y. S. *Tetrahedron* **2013**, *69*, 2542; (b) Correa, A.; Tellitu, I.; Dominguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 8316; (c) Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470; (d) Gleave, D. M.; Brickner, S. J.; Manninen, P. R.; Allwine, D. A.; Lovasz, K. D.; Rohrer, D. C.; Tucker, J. A.; Zurenko, G. E.; Ford, C. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1231; (e) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966; (f) Yin, Y.; Zhao, G. *Heterocycles* **2006**, *68*, 23; (g) Dion, I.; Vicent-Rocan, J.-F.; Zhang, L.; Cebrowski, P. H.; Lebrun, M.-E.; Pfeiffer, J. Y.; Bedard, A.-C.; Beauchemin, A. M. *J. Org. Chem.* **2013**, *78*, 12735.
11. Chang, M.-Y.; Chan, C.-K.; Lin, S.-Y. *Heterocycles* **2013**, *87*, 1519.
12. *A representative synthetic procedure of skeleton **4** is as follows*: Pd/C (10%, 50 mg) was added to a stirred solution of skeleton **1** (1.0 mmol) in toluene (5 mL) at rt. The reaction mixture was stirred at rt for 10 min. N_2H_4 (80% in H_2O, 5 mL) was added to the reaction mixture at rt. The reaction mixture was refluxed for 25 h, cooled to rt, and the solvent was concentrated. The residue was diluted with water (10 mL) and the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine, dried, filtered and evaporated to afford crude product. Purification on silica gel (hexanes/EtOAc = 4/1 ~ 2/1) afforded skeleton **4**. For **4a**, yield = 84% (162 mg); brown oil; HRMS (ESI, M^++1) calcd for $C_{11}H_{16}NO_2$ 194.1181, found 194.1188; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, J = 8.0 Hz, 1H), 6.30 (d, J = 8.0 Hz, 1H), 4.02–3.95 (m, 1H), 3.86 (s, 3H), 3.78 (s, 3H), 3.33 (br s, 1H), 3.22 (dd, J = 8.4, 15.6 Hz, 1H), 2.67 (dd, J = 7.6, 15.6 Hz, 1H), 1.29 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.47, 145.86, 145.77, 121.65, 112.44, 103.95, 60.00, 56.94, 55.82, 35.63, 22.10.
13. CCDC 979311 (**15**) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; E-mail: deposit@ccdc.cam.ac.uk).
14. (a) Levine, M. N.; Raines, R. T. *Chem. Sci.* **2012**, *3*, 2412; (b) Beesley, R. M.; Ingold, C. K.; Thorpe, J. F. *J. Chem. Soc., Trans.* **1915**, *107*, 1080.