Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

A facile convergent route to indoloquinolines

Hari K. Kadam, Deesha D. Malik, Lalitprabha Salgaonkar, Ketan Mandrekar & Santosh G. Tilve

To cite this article: Hari K. Kadam, Deesha D. Malik, Lalitprabha Salgaonkar, Ketan Mandrekar & Santosh G. Tilve (2017): A facile convergent route to indoloquinolines, Synthetic Communications, DOI: 10.1080/00397911.2017.1359303

To link to this article: http://dx.doi.org/10.1080/00397911.2017.1359303

A facile convergent route to Indoloquinolines

Hari K. Kadam

Department of Chemistry, St. Xavier's College, Mapusa, Goa, India

Deesha D. Malik

Department of Chemistry, Goa University, Taleigao Plateau, Goa, India

Center for Biomimetic Systems, Ewha Womans University, Seoul, Korea

Lalitprabha Salgaonkar

Department of Chemistry, St. Xavier's College, Mapusa, Goa, India

Ketan Mandrekar

Department of Chemistry, Goa University, Taleigao Plateau, Goa, India

Santosh G. Tilve

Department of Chemistry, Goa University, Taleigao Plateau, Goa, India

Address correspondence to Hari K. Kadam, Department of Chemistry, St. Xavier's College, Mapusa, Goa – 403507, India. Fax: + 91-832-2262356. E-mail: harikadam05@gmail.com

Supporting Information

Full Experimental details are available via the Supplementary Content section of this article's webpage.

ABSTRACT

A convergent route to indoloquinolines is developed via Aldol condensation. This two step method utilizes commercially available *2*-oxoindole and *o*-nitrobenzaldehyde as starting materials. Chromatography-free method is accomplished for preparing several derivatives of indoloquinolines with desirable aromatic substitutions.

KEYWORDS: aldol reaction, indoloquinoline, natural product, oxoindole, synthesis

Introduction

Nitrogen containing heterocyclic compounds is a noble class of chemical entities incorporated in medicinal studies. The diverse biological responses of such compounds in antiviral, anticancer, antibacterial, and other studies make them a challenging target of synthetic development for organic chemists.[1] Indoloquinoline alkaloids belong to one such class. *6H*-indolo[*2,3-b*]quinolone **1**, a natural product isolated from isolated from the leaves of *Justicia betonica*, (**Figure 1**) exhibit promising biological properties.[2]*4*-methyl-*6H*-indolo[*2,3-*

b]quinoline **(I)** exhibited excellent antiproliferative activity against human hepatocellular carcinoma HepG2 and human breast carcinoma MCF-7 cells.[3a] Neocryptoepine **(II)** or *5*-methyl-*5H*-indolo[*2*,*3*-*b*]quinoline is a natural product isolated from roots of the West African plant *Cryptolepis sanguinolenta* and exhibits antiplasmodial, antitumor activity and DNA binding properties.[3b] *N*,*N*-Diethyl-*N*-(*5*-methyl-*5H*-indolo[*2*,*3*-*b*]quinolin-*8*-yl)pentane-*1*,*4*-diamine **(III)**, *1*-(*3*-(*2*-Chloro-*5*-methyl-*5H*-indolo[*2*,*3*-*b*]quinolin-*11*-ylamino)-propyl)-*3*-phenylurea **(IV)** and *1*-(*3*-(*2*-Methoxy-*5*-methyl-*5H*-indolo[*2*,*3*-*b*]quinolin-*11*-ylamino)propyl)-*3*-phenylurea **(V)** showed excellent antimalarial activity.[4]

The useful biological properties and potential medicinal use of these indoloquinolines have resulted in several synthetic methods being developed and reviews in literature.[3–7] In this paper, we report a two step method using commercially available *2*-oxoindole and *o*-nitrobenzaldehyde as starting materials for synthesis of indoloquinolines via Aldol condensation.

Results and Discussion

At the onset, we contemplated that *2*-oxoindole **3** and *o*-nitrobenzaldehyde **4** can give us olefinic condensed product as described in scheme 1 via Aldol reaction which can further be converted to indoloquinolines via method involving reduction[6] and cyclisation.

In view of this, *2*-oxoindole **3** and *o*-nitrobenzaldehyde **4** were reacted in Aldol reaction conditions using piperidine as base to give required condensed olefinic Aldol product **2** as geometrical isomeric mixture[8] in moderate yield. This reaction was further optimised to provide maximum yield by precisely tuning the reaction condition and time. We were successful in avoiding the uneconomic, environmentally harmful and time consuming column chromatography to obtain the required product from this step.

The Aldol reaction used here provided us a convenient and efficient alternative to other costly, tedious and laborious processes by avoiding preparation of any unstable precursors, use of toxic reagents and metals and ultimately giving condensed olefinic compounds. Further the Aldol product **2** was subjected to nitroreduction[6] and cyclisation which was further optimised with EtOH-AcOH (1:3) at 120 °C for 48h to give indoloquinoline in good yield. The overall yield in this two step method as described in Scheme 2 was far more comparable with the one step or one pot methods available in literature.[7]

Having established a short two step chromatography free route from easily available starting materials, we further extended it to prepare derivatives of indoloquinolines with desired aromatic substitutions. Dimethoxy-indoloquinoline, Methylenedioxy-indoloquinoline and Chloro-

indoloquinoline derivatives were obtained in around 73-78% overall yields in two steps as described in **Table 1**.

Experimental

General procedure for Aldol product **2a-d**: In a dry 100mL round bottom flask, *2*-oxindole **3a-b** (1 mmol), *o*-nitrobenzaldehydes **4a-c** (1.2 mmol) and EtOH (25mL) were mixed with stirring and Piperidine (0.85mg , 0.01 mmol) in EtOH (2mL) was added dropwise while stirring at r.t. Mixture was then refluxed with stirring for 1h . On completion of reaction (monitored by TLC), solvent was removed under vacuum and Et_2O was added, insoluble solid Aldol product **2a-d** separated out and was isolated by filtration.

3-(*2*-nitrobenzylidene)indolin-*2*-one (*geometrical isomeric mixture*);[6] **2a**; Orange solid; M.P. 224-226 °C. IR (KBr): ν 1201, 1342, 1470, 1624, 1686, 1732, 3254, 3332cm $^{-1}$. ^{1}H NMR (DMSO-d_6): δ 6.14 (d, *J = 6.8Hz* , 1H), 6.59 (s, 1H), 6.64 (t, *J = 8.0Hz* , 1H), 6.77 (m, 2H), 7.00 (t, *J = 7.6Hz* , 1H), 7.11 (t, *J = 8.0Hz* , 1H), 7.26 (t, *J = 8.0Hz* , 1H), 7.47 (m, 1H), 10.35 (s, 1H) ppm. LCMS: m/z [M + H] $^+$: 267.1

General Procedure for indoloquinolines **1a-d**: In a dry 100mL round bottom flask, Aldol product **2a-d** (0.8 mmol), Fe powder (0.280g , 5 mmol), EtOH (5mL), AcOH (15mL) and conc. HCl (1mL) were mixed. Mixture was then stirred at 120 °C for 48h . On completion of reaction

(monitored by TLC), mixture was filtered and washed with $CHCl_3$. Solvent was removed under vacuum. 2N NaOH (100mL) was added and product was extracted in $CHCl_3$ (50mL X 3). Extract was dried with anhy. Sodium sulfate, filtered and solvent was removed under vacuum to give indoloquinoline product **1a-d**.

6H-indolo[*2,3-b*]quinoline;[5],[6] **1a**; Brown solid. M.P. > 300 °C. ^{1}H NMR (DMSO-d_6,): δ 7.27 (t, *J = 6.8Hz* , 1H), 7.52 (m, 3H), 7.72 (t, *J = 8.4Hz* , 1H), 7.97 (d, *J = 8.0Hz* , 1H), 8.10 (d, *J = 8.0Hz* , 1H), 8.26 (d, *J = 8.0Hz* , 1H), 9.06 (s, 1H), 11.71 (s, 1H) ppm. ^{13}C NMR (DMSO-d_6): δ 110.9 (CH), 117.8 (Cq), 119.6 (CH), 120.2 (Cq), 121.8 (CH), 122.7 (CH), 123.6 (Cq), 126.9 (CH), 127.5 (CH), 128.2 (CH), 128.62 (CH), 128.65 (CH), 141.4 (Cq), 146.3 (Cq), 152.8 (Cq) ppm.

Conclusion

In conclusion, a two step efficient method is developed for synthesis of indoloquinolines via Aldol reaction using commercially available starting materials. The method is optimised to achieve affordable overall yields and avoiding chromatography purification. The general utility of this method is demonstrated by preparing several derivatives of indoloquinolines with desirable aromatic substitutions.

Acknowledgments

We thank Science & Engineering Research Board (SERB), New Delhi for funding.

References

[1] a) Majumdar, P.; Pati, A.; Patra, M.; Behera, R. K.; Behera, A. K. *Chem. Rev.* **2014**, *114*, 2942−2977. b) Singh, I. P.; Bodiwala, H. S. *Nat. Prod. Rep.* **2010**, *27*, 1781–1800. c) Dumitrascu, F.; Popa, M. M. *Arkivoc* **2014**, *i*, 428–452. d) Bracca, A. B. J.; Heredia, D. A.; Larghi, E. L.; Kaufman, T. S. *Eur. J. Org. Chem.* **2014**, *36*, 7979–8003. e) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar, N.; Kim, C. H.; Verma, A. K.; Choi, E. H. *Molecules* **2013**, *18*, 6620–6662. f) Volla, C. M. R.; Atodiresei, I.; Rueping, M. *Chem. Rev.* **2014**, *114*, 2390−2431. g) Gawande, M. B.; Bonifacio, V. D. B.; Luque, R.; Branco, P. S.; Varma, R. S. *Chem. Soc. Rev.* **2013**, *42*, 5522–5551.

[2] Subbaraju, G. V.; Kavitha, J.; Rajasekhar, D.; Jimenez, J. I. *J. Nat. Prod.* **2004**, *67*, 461–462.

[3] a) Parvatkar, P. T.; Ajay, A. K.; Bhat, M. K.; Parameswaran, P. S.; Tilve, S. G. *Med. Chem. Res.* **2013**, *22*, 88–93. b) Li, M. Y.; Xu, H. W.; Fan, W.; Ye, Q.; Wang, X.; Jiang, B.; Wang, S. L.; Tu, S. J. *Tetrahedron* **2014**, *70*, 1004–1010.

[4] a) Mei, Z. W.; Wang, L. W. J.; Lu, Pang, C. Q.; Maeda, T.; Peng, W.; Kaiser, M.; Sayed, I. E.; Inokuchi, T. *J. Med. Chem.* **2013**, *56*, 1431−1442. b) Sayed, I. E.; Veken, P. V.; Steert, K.; Dhooghe, L.; Hostyn, S.; Baelen, G. V.; Lemiere, G.; Maes, B. U. W.; Cos, P.; Maes, L.; Joossens, J.; Haemers, A.; Pieters, L.; Augustyns, K. *J. Med. Chem.* **2009**, *52*, 2979–2988.

[5] a) Kadam, H. K.; Parvatkar, P. T.; Tilve, S. G. *Synthesis* **2012**, *44*, 1339–1342. b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Curr. Org. Chem.* **2011**, *15*, 1036–1057. c) Volvoikar, P. S.; Parvatkar, P. T.; Tilve, S. G. *Eur. J. Org. Chem.* **2013**, 2172–2178. d) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *J. Org. Chem.* **2009**, *74*, 8369–8372. e) Pitchai, P.; Sathiyaseelan, M.; Nepolraj, A.; Gengan, R. M. *Indian J. Chem.* **2015**, *54B*, 1290–1292. f) Volvoikar, P. S.; Tilve, S. G. *Org. Lett.* **2016**, *18*, 892–895. g) Tokimizu, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2014**, *16*, 3138–3141. h) Ghosh, P.; Purkayastha, P. *RSC Advances* **2014**, *4*, 22442–22448. i) Parvatkar, P. T.; Majik, M. S.; *RSC Advances* **2014**, *4*, 22481–22486. j) Patteux, C.; Levacher, V.; Dupas, G. *Org. Lett.* **2003**, *5*, 3061–3063.

[6] a) Parvatkar, P. T.; Tilve, S. G. *Tetrahedron Lett.* **2011**, *52*, 6594–6596. b) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Tetrahedron Lett.* **2007**, *48*, 7870–7872.

[7] a) Luque, P. V.; Alajarın, R.; Builla, J. A.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 415–418. b) Engqvist, R.; Bergman, J. *Org. Prep. Proc. Int.* **2004**, *36*, 386–390. c) Vaghei, R. G.; Malaekehpoor, S. M. *Tetrahedron Lett.* **2012**, *53*, 4751–4753. d) Borsche, W.; Wagner-Roemmich, M.; Barthenheier, J. *Justus Liebigs Annalen der Chemie* **1942**, *550*, 160–174.

[8] a) Abramovitch, R. A.; Hey, D. H. *J. Chem. Soc.* **1954**, 1697–1703. b) Parvatkar, P. T.; Majik, M. S. *RSC Advances* **2014**, *4*, 22481–22486. c) Hu, Y.; Kang, H.; Zeng, B. W.; Wei, P.; Huang, H. *J. Chem. Res.* **2008**, *11*, 642–643. d) Suthar, S. K.; Bansal, S.; Alam, M. M.; Jaiswal, V.; Tiwari, A.; Chaudhary, A.; Alex, A. T.; Joseph, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 5281–5285. e) Ankati, H.; Akubathini, S. K.; Kamila, S.; Mukherjee, C.; D'Mello, S. R.; Biehl, E. R. *The Open Organic Chemistry Journal* **2009**, *3*, 1–10. f) Wang, G.; Liu, X.; Huang, T.; Kuang, Y.; Lin, L.; Feng, X. *Org. Lett.* **2013**, *15*, 76–79.

Table 1. Derivatives of indoloquinolines prepared using scheme 2

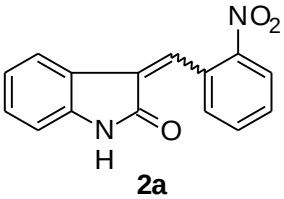
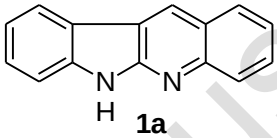
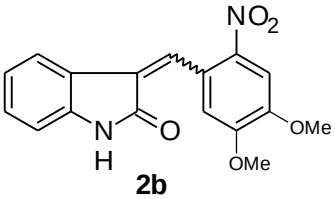
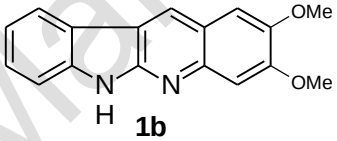
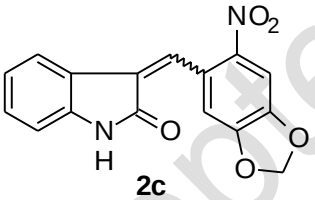
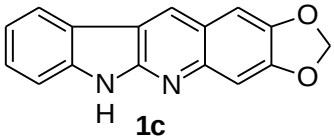
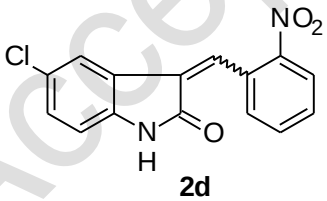
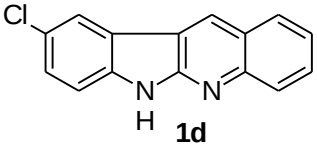
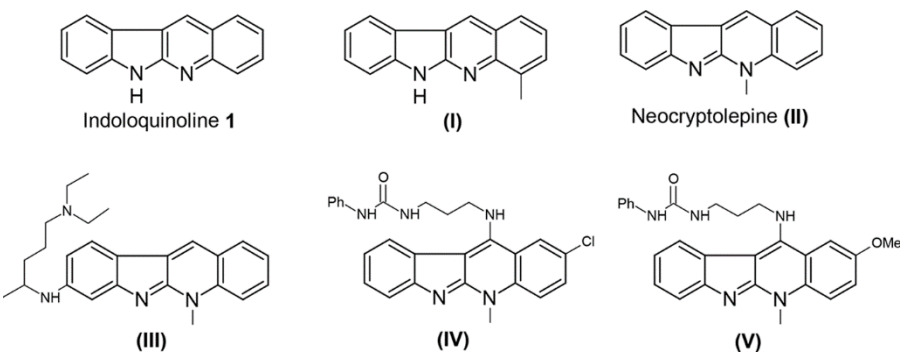
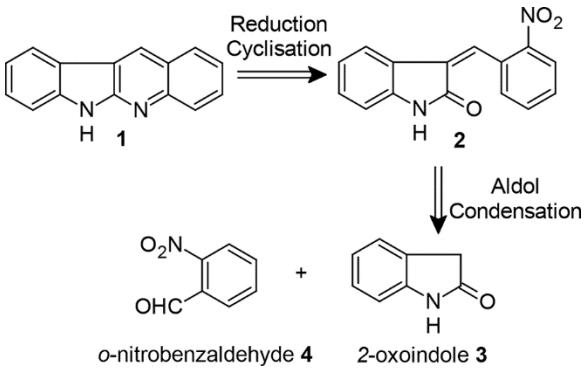
Entry	Aldol products **2** *(geometrical isomeric mixture)*	% Isolated Yield	Indoloquinolines **1**	% Isolated Yield	Overall yield over 2 steps
1	 **2a**	91	 **1a**	86	78.3%
2	 **2b**	89	 **1b**	82	73.0%
3	 **2c**	88	 **1c**	84	73.9%
4	 **2d**	90	 **1d**	84	75.6%

Figure 1. Indoloquinoline 1 and similar medicinally important entities.



Scheme 1. Retrosynthetic analysis of Indoloquinoline 1 via Aldol condensation.



Scheme 2. Two step route to indoloquinolines.