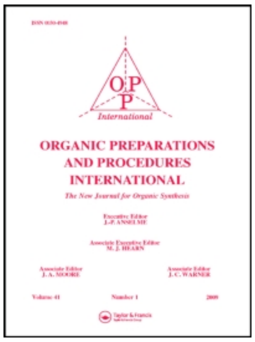


Taylor & Francis
Taylor & Francis Group

Organic Preparations and Procedures International

The New Journal for Organic Synthesis

ISSN: 0030-4948 (Print) 1945-5453 (Online) Journal homepage: http://www.tandfonline.com/loi/uopp20

# Short Synthesis of 2-oxo-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

**Laurence W. Reilly Jr.,, Randall B. Nelson, & Gordon W. Gribble**

**To cite this article:** Laurence W. Reilly Jr.,, Randall B. Nelson, & Gordon W. Gribble (2018) Short Synthesis of 2-oxo-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine, Organic Preparations and Procedures International, 50:5, 509-511, DOI: 10.1080/00304948.2018.1525985

**To link to this article:** https://doi.org/10.1080/00304948.2018.1525985

*Organic Preparations and Procedures International*, 50:509–511, 2018

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2018.1525985

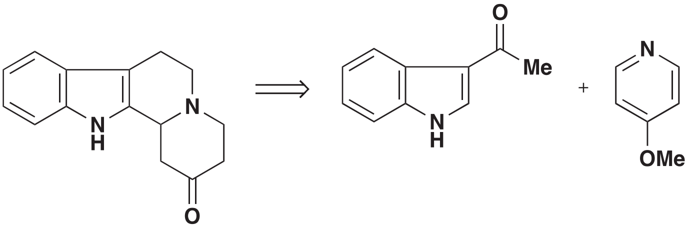
# OPPI BRIEF

# Short Synthesis of 2-oxo-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

Laurence W. Reilly Jr., Randall B. Nelson, and
Gordon W. Gribble

Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA

The title compound, 2-oxo-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine (**1**), was first synthesized in 1952 by Groves and Swan[1] as an entry point to the yohimbine-reserpine-corynantheine family of alkaloids. Subsequently, this indole ketone was prepared by several groups,[2–14] and Kametani parlayed **1** into a synthesis of yohimbine.[5] In connection with a project in our laboratory we required a short, efficient, and atom-economical preparation of **1**. Of the several known syntheses of **1** only the method of Potts and Nasri[4] seemed suitable for us. We now describe a modification of this synthesis that involves the coupling of 3-acetylindole (**2**) and 4-methoxypyridine (**3**) (*Scheme 1*).



**1** **2** **3**

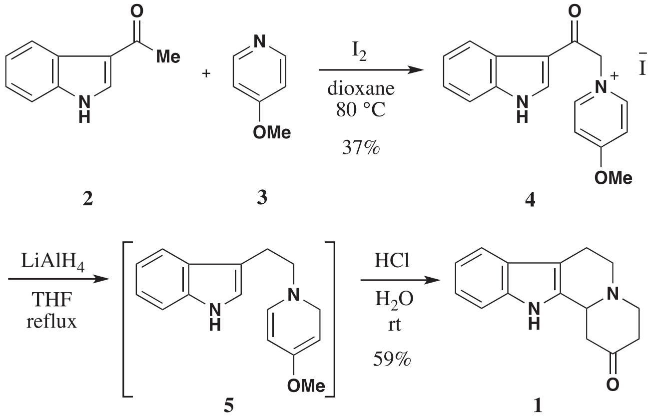
**Scheme 1.** Retrosynthesis of 1.

Our synthesis of **1** is shown in *Scheme 2*. Whereas Potts and Nasri employed bromine in their process,[4] we found that iodine is superior in the reaction between 3-acetylindole (**2**) and 4-methoxypyridine (**3**) to give pyridinium salt **4**, in modest yield after crystallization. Reduction of pyridinium salt **4** with $LiAlH_4$ in THF and acid treatment of the intermediate dihydropyridine **5** resulted in Pictet-Spengler cyclization and hydrolysis of the enol ether to give **1** in 59% yield after chromatography. Although the overall yield is only 20–25%, this process satisfies our aforementioned criteria.

Received December 4, 2017; in final form February 21, 2018.

Address correspondence to Gordon W. Gribble, Department of Chemistry, Dartmouth College, Hanover, NH 03755, USA. E-mail: gordon.w.gribble@dartmouth.edu

Moreover, both 3-acetylindole (**2**)[15] and 4-methoxypyridine (**3**)[16] are commercially available or easily synthesized.



**Scheme 2.** Synthesis of 1.

## Experimental Section

*4-Methoxypyridine (**3**).*[16] To a solution of 45.0 g (0.360 mol) of 4-methoxypyridine-*N*-oxide (Olin) in 1.5 L of 2M $H_2SO_4$ was added over 135 min 90.0 g (1.38 mol) of zinc dust. The solution was heated at 98 °C for 16 h before it was cooled and basified with concentrated $NH_4OH$. Decanting and filtering the aqueous solution from unreacted zinc and extraction with ether gave, after drying over anhydrous $K_2CO_3$ and concentration *in vacuo*, a cloudy yellow oil. Distillation at $H_2O$ aspirator pressure gave 17.6 g (45%) of **3** as a colorless oil: bp 150–160 °C with external heating from a heat gun (lit.[17] bp 185 °C (712 Torr)).

*4-Methoxy-1-(2-(3-indolyl)-2-oxoethyl)pyridinium iodide (**4**).* A mixture of 5.00 g (0.031 mol) of **2** (Sigma) and 7.02 g (0.064 mol) of **3** in 50 mL of dry dioxane was heated on a steam bath until solution was complete. Iodine (4.82 g) was added and heating was continued for 10 min. More iodine (3.15 g) was added (a total of 7.97 g; 0.031 mol) and the solution was heated for 1 h with occasional swirling. The reaction mixture was cooled to room temperature and 50 mL of absolute ethanol was added. Upon cooling to 0 °C there was deposited in several crops 4.51 g (37%) of crystalline **4**. Recrystallization from ethanol yielded **4** as golden needles: mp >250 °C; TLC (40% $CH_3OH$ in $CHCl_3$) $R_f = 0.10$, stains purple.

*Anal.* Calcd. for $C_{16}H_{15}N_2O_2I$: C, 48.75; H, 3.84; N, 7.11. Found: C, 48.24; H, 3.36; N, 7.11.

*2-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine (**1**).* To a suspension of 2.43 g (0.064 mol) of $LiAlH_4$ in 250 mL of THF under dry nitrogen at 0–5 °C was added 4.48 g (0.011 mol) of **4**. The reaction mixture was refluxed for 4 h before it was cooled to 0–5 °C and treated with 25 mL of $H_2O$. The gelatinous mixture was filtered through Celite and the filter cake was washed with THF. This solution was made strongly acidic with 25 mL of 9M HCl and allowed to stand at room temperature for 15 h. Ice was added and the aqueous solution was basified with concentrated $NH_4OH$ and extracted with $CH_2Cl_2$. The organic phase was washed with $H_2O$ and brine, dried over anhydrous

$K_2CO_3$, and concentrated *in vacuo*. Column chromatography of the resultant red gum (activity III neutral alumina, elution with benzene-ether (1:1) and then $CHCl_3$) yielded 1.57 g (59%) of **1** as tan crystals. Recrystallization from 15% hexane in toluene yielded **1** as yellow needles: mp 185–185.5 °C (lit.[4] mp 181–182 °C).

## Acknowledgment

We gratefully acknowledge support from Dartmouth College.

## ORCID

Gordon W. Gribble http://orcid.org/0000-0002-7573-0927

## References

1. L. H. Groves and G. A. Swan, *J. Chem. Soc.*, 650 (1952).
2. G. B. Kline, *J. Am. Chem. Soc.*, **81**, 2251 (1959).
3. E. Winterfeldt, *Chem. Ber.*, **97**, 2463 (1964).
4. K. T. Potts and I. D. Nasri, *J. Org. Chem.*, **29**, 3407 (1964).
5. T. Kametani, Y. Hirai, M. Kajiwara, T. Takahashi, and K. Fukumoto, *Chem. Pharm. Bull.*, **23**, 2634 (1975).
6. J. P. Vacca, *Tetrahedron Lett.*, **26**, 1277 (1985).
7. G. Blaskó, K. Honty, L. Novák, and C. Szantáy, *Acta Chim. Acad. Sci. Hung.*, **99**, 35 (1979).
8. A. Brandi, S. Garro, A. Guarna, A. Goti, F. Cordero, and F. De Sarlo, *J. Org. Chem.*, **53**, 2430 (1988).
9. M. Rubiralta, A. Diez, and C. Vila, *Tetrahedron*, **46**, 4443 (1990).
10. M. Rubiralta, A. Diez, and C. Villa, *Tetrahedron Lett.*, **31**, 3347 (1990).
11. M. E. Kuehne and R. S. Muth, *J. Org. Chem.*, **56**, 2701 (1991).
12. H. Waldmann, M. Braun, M. Weymann, and M. Gewehr, *Synlett*, 881 (1991).
13. V. S. Giri and P. J. Sankar, *Synth. Commun.*, **22**, 3095 (1992).
14. L. Liu and L. Zhang, *Angew. Chem. Int. Ed.*, **51**, 7301 (2012).
15. M. A. Metwally, S. Shaaban, B. F. Abdel-Wahab, and G. A. El-Hiti, *Curr. Org. Chem.*, **13**, 1475 (2009).
16. E. Profft and G. Schulz, *Arch. Pharm.*, **294**, 292 (1961).
17. E. Spinner and J. C. B. White, *Chem. Ind.*, **1784** (1967).