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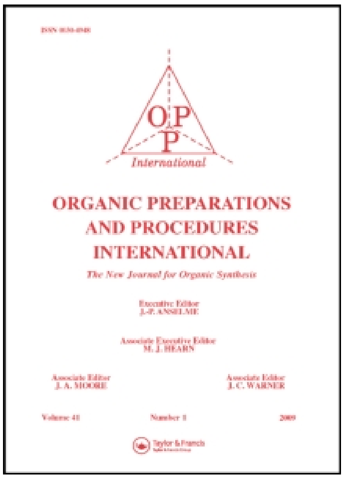

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

AN IMPROVED SYNTHESIS OF 1-BENZOYL-4-KETO-1,2,2A,3,4,5-HEXAHYDROBENZ [cd]INDOLE

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To cite this Article Nichols, David E. , Robinson, J. Michael , Li, George S. , Cassady, John M. and Floss, Heinz G.(1977) 'AN IMPROVED SYNTHESIS OF 1-BENZOYL-4-KETO-1,2,2A,3,4,5-HEXAHYDROBENZ [cd]INDOLE', Organic Preparations and Procedures International, 9: 6, 277 — 280

To link to this Article: DOI: 10.1080/00304947709356088

URL: http://dx.doi.org/10.1080/00304947709356088

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ORGANIC PREPARATIONS AND PROCEDURES INT. 9(6), 277-280 (1977)

AN IMPROVED SYNTHESIS OF 1-BENZOYL-4-KETO-1,2,2a,3,4,5-HEXAHYDROBENZ[cd]INDOLE

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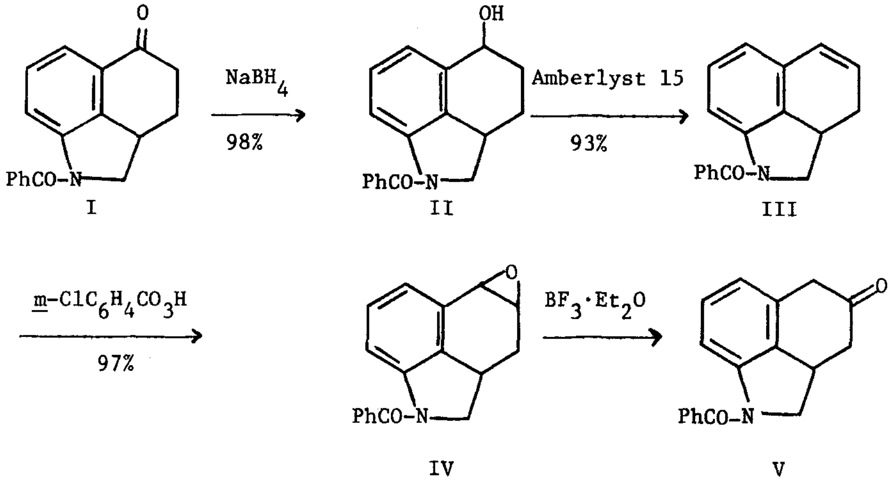
During the course of studies directed toward the synthesis of several ergoline congeners,[1] it became necessary to develop an efficient synthesis of the title compound (V). The overall yield of the four-step synthesis of V from I originally reported by Kornfeld and his group,[2] has been improved from 19% to 70% by our modified procedure.



I II III IV V

Major modifications of the original method involve formation of the tricyclic olefin by acid-catalyzed dehydration of II. The use of p-toluenesulfonic acid on a large scale (>5 g) proved unsatisfactory due to extensive formation of dimeric by-products. This problem was overcome through the use of Amberlyst 15 (Mallinckrodt), a sulfonic acid cation

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exchange resin. Although other cation exchange resins were tried, only Amberlyst 15 gave acceptable results. Indeed, we call attention to the superior properties of this resin as a potential substitute for p-toluenesulfonic acid. It works quite well in organic solvents.

The final conversion of the 4,5-epoxy compound (IV) to the desired ketone V gave the poorest yield of the sequence. Kornfeld et al.[2] employed anhydrous $MgBr_2$ for this transformation, although this reagent does not result in clean formation of V.[3] We examined a variety of Lewis acid catalysts in an effort to find a convenient substitute for $MgBr_2$. Acids tried included aqueous mineral acid, $SnCl_4$, $TiCl_4$, and CF_3COOH. In many instances formation of the desired ketone was detected by TLC analysis, but none of these reagents gave acceptable results. It was finally decided to use $BF_3 \cdot Et_2O$, although yields with this reagent do not appear superior to those reported for $MgBr_2$. However, the reagent is much more convenient to use.

EXPERIMENTAL[4]

1-Benzoyl-5-hydroxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (II). - To a slurry of 25 g (90.3 mmol) of I in 200 ml of EtOH was added a solution of 2.5 g (66 mmol) of $NaBH_4$ in 100 ml EtOH over 10 min. The mixture was stirred at room temperature for 4 hrs. During the first 20 min., the starting material went completely into solution and the product later began to crystallize from solution. The resulting mixture was concentrated nearly to dryness in vacuo at 40° and the residue was suspended in 100 ml H_2O. Then, with stirring, 3 N HCl was added dropwise until the pH was about 7. The product was collected by suction filtration, washed several times with H_2O, and air dried to yield 24.6 g (98%); a sample recrystallized from EtOH melted at 193-194°, lit.[2] mp. 182-183°.

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1-Benzoyl-1,2,2a,3-tetrahydrobenz[cd]indole (III). - A mixture of 10 g (35.8 mmol) of the tricyclic alcohol (II), 2 g of Amberlyst 15 ion exchange resin, and 300 ml of toluene was heated to reflux under N_2, with continuous water removal (Dean-Stark trap). After 2 hrs., TLC analysis (silica gel, C_6H_6-Me_2CO, 9:1) showed that the reaction was complete. The reaction mixture was cooled, filtered and the toluene was removed under reduced pressure. The residual yellow oil solidified and was recrystallized from EtOAc-hexane, yield 8.7 g (93%), mp. 99-100°, lit.[2] mp. 95.5-96.5°.

1-Benzoyl-4,5-epoxy-1,2,2a,3,4,5-hexahydrobenz[cd]indole (IV). - To a solution of 5 g (19.15 mmol) of the olefin (III) in 150 ml of $CHCl_3$ was added all at once, 4.67 g of 85% *m*-chloroperoxybenzoic acid. The solution was swirled until all the peracid was dissolved and placed at 5° for 3 hrs. At this time, TLC analysis indicated that the reaction was complete. Yields were lowered by longer reaction time. The $CHCl_3$ solution was washed with 6 x 75 ml of cold 5% NaOH, followed by 3 x 50 ml of saturated NaCl soln. The combined aqueous solution (including the NaCl washes) was extracted with 2 x 20 ml of $CHCl_3$. The combined organic layer was dried (Na_2SO_4) and concentrated *in vacuo*. Recrystallization from EtOAc and EtOAc-hexane gave a total of 5.15 g (97%) of material, pure by TLC. An analytical sample was obtained by recrystallization from C_6H_6-hexane, mp. 108-109°, lit.[2] mp. 104-105°.

1-Benzoyl-4-keto-1,2,2a,3,4,5-hexahydrobenz[cd]indole (V). - The tricyclic epoxide (IV) (10 g, 36.1 mmol) was dissolved in 300 ml of dry C_6H_6. The solution was heated to 40° with stirring under N_2. Dropwise addition (15 min.) of $BF_3 \cdot Et_2O$ (5.9 ml, 36.1 mmol) resulted in the formation of a heavy white prepipitate. The reaction was stirred at 40° for 1 hr., and was transferred to a separatory funnel and successively washed with two, 100 ml portions of H_2O, 5% $NaHCO_3$, and H_2O. The benzene layer was separated, decanted from the insoluble gum and dried (Na_2SO_4). Filtration and removal of the C_6H_6 under reduced pressure yielded 7.9 g (79%) of a glassy solid which by TLC analysis contained about 90% of V. The insoluble gum which formed was dissolved in $CHCl_3$, washed with H_2O, dried, and concentrated to give 2.5 g of amorphous solid which contained, by TLC analysis, an estimated 20-30% of V. The ketone could be crystallized with difficulty from C_6H_6-ether, mp. 144-148°, lit.[2] mp. 149.5-151.5°.

Acknowledgment. - The authors wish to thank Dr. E.C. Kornfeld, Eli Lilly and Co., Indianapolis, Ind., for generous gifts of the 5-keto starting material used in this work, and the U.S. Public Health Service for financial support (grants CA 13278 and CA 17482 and postdoctoral fellowship CA 02437).

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4. Melting points were determined using a Mel-Temp apparatus and are uncorrected.

(Received August 8, 1977; in revised form October 11, 1977)

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