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A CONVENIENT SYNTHESIS OF 7,8-DIHYDROISOQUINOLIN-5(*6H*)-ONE

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Abstract : A new high-yield two step synthesis of 7,8-dihydroisoquinolin-5(*6H*)-one (3) from 5,6,7,8-tetrahydroisoquinoline (1) is described.

7,8-Dihydroisoquinolin-5(*6H*)-one (3) is a useful intermediate for the synthesis of novel pharmaceutical agents. [1,2,3,4]

A number of synthetic routes to this molecule from commercially available 5,6,7,8-tetrahydroisoquinoline (1) are described in the literature however all these methods have serious draw-backs in terms of yield, practicality and safety.

Various authors have reported direct oxidation of (1) with either CrO_3[5,6] or $KMnO_4$[3], however, these reagents are not regioselective and yields are poor (4-25 %).

Epsztajn and Bieniek[1] have described the synthesis of (3) via the oxidation (CrO_3) of 5-hydroxy-5,6,7,8-tetrahydroisoquinoline which was obtained from (1) in a three-step procedure involving N-oxide formation (H_2O_2), regiospecific introduction of acetate (Ac_2O) and hydrolysis (HCl). The overall yield was 27 % and four separate distillation steps were required to isolate the desired product in pure form.

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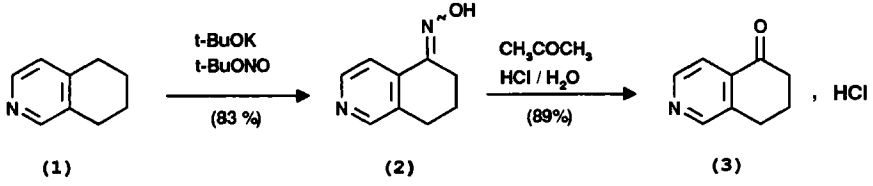
Finally, Wu and Kover[2] prepared (3) by applying Thummel's[7] methodology. In this procedure (1) is converted to its 5-benzylidene derivative ($PhCHO/Ac_2O$) and the latter is ozonolised to afford (3). Unfortunately, no experimental details or yields were given.

In this communication we report a practical, high yield, two-step route to (3) that does not require the use of potentially dangerous oxidising agents such as ozone, hydrogen peroxide, chromium trioxide or potassium permanganate.

Our method is based upon the regioselective nitrosation of (1) employing similar conditions to those described by Goto[8] for the nitrosation of 1-alkylisoquinolines. Thus, the reaction of (1) with potassium tert. butoxide in dry THF followed by tert. butylnitrite affords 7,8-dihydroisoquinolin-5(*6H*)-one oxime (2) as a light beige solid in 83 % isolated yield. Hydrolysis of this oxime with a mixture of acetone and 6N hydrochloric acid over a 15 hours period affords ketone (3) which is readily isolated by filtration (yield of crude product 89 %, overall yield crude (3) from (1) 74 %). HPLC analysis revealed this product to be 97.2 % ketone (3) and 2.8 % unreacted oxime (2) and it is thus sufficiently pure for use as starting material for most reactions. However, if need be, the crude ketone can be easily purified by column chromatography.



EXPERIMENTAL

7,8-Dihydroisoquinolin-5(*6H*)-one, oxime (2).

A 1L round bottom flask was equipped with a magnetic stirrer and a pressure equalized addition funnel which was protected by means of a calcium

chloride drying tube. The flask was charged with 22.4 g (0.2 mole) of potassium tert. butoxide and dry THF (200 mL) and stirred until a clear solution was obtained (15 min). A solution 13.3 g (0.1 mole) of 5,6,7,8-tetrahydroisoquinoline (1) in dry THF (250 mL) was added rapidly and the solution was stirred at room temperature for 15 hours. The reaction mixture was cooled in an ice bath and 30.9 g (35 mL ; 0.3 mole) of tert. butyl nitrite (tech ; 90 %) was added dropwise during 30 mins. At the end of the addition the ice bath was removed and the reaction mixture was stirred for 20 hours at room temperature during which time a light-brown precipitate formed. Brine (100 mL) was added and the reaction was extracted with ethyl acetate (250 mL x 1 and 100 mL x 2). The combined extracts were concentrated and the crystalline residue was triturated with toluene. Filtration gave 14.7 g of crude product which was recrystallized from 50 % aqueous ethanol to give 13.5 g (83 %) of 7,8-dihydroisoquinolin-5(*6H*)-one oxime (2) as beige crystals m.p. 173-174°C ; IR (KBr) 1592 cm^{-1} ; ^1H NMR* (DMSO-d6) : 1.7-1.9 (m, 2H), 2.6-2.8 (m, 4H), 7.7(d, 1H), 8.35 (d, 1H), 8.45 (s, 1H), 11.65 (s, 1H) ; Anal. Calc. for $C_9H_{10}N_2O$: C : 66.66 ; H : 6.21 ; N : 17.27 ; Found : C : 66.51 ; H : 6.22 ; N : 17.01.

MS DCI.NH_3 ; $M+H^+$ = 163 a.m.u.

* attempts to determine the stereochemistry of the oxime by NOE experiments were unsuccessful due to rapid interconversion of the *syn* and *anti* forms in DMSO-d6.

7,8-Dihydroisoquinolin-5(*6H*)-one hydrochloride (3)

In a 2L round bottom flask equipped with a magnetic stirrer and a water cooled Liebig condenser were placed 13.4 g (0.083 mole) of 7,8-dihydroisoquinolin-5(*6H*)-one, oxime (2), acetone (600 mL) and 6N hydrochloric acid (240 mL). The resulting clear solution was heated at reflux for 15 hours, cooled and concentrated under reduced pressure. The residue was triturated with ethanol (50 mL) and the ethanolic mixture was again concentrated under reduced pressure in order to eliminate traces of water. Trituration with fresh ethanol (50

mL) produced a cristalline solid which was collected by filtration and washed with ethanol to afford 13.5 g (89 %) of 7,8-dihydroisoquinolin-5(*6H*)-one hydrochloride as very light beige crystals m.p. 233-4°C, purity HPLC 97.2 %.

An aliquot (4 g) of this material was basified with 1N NH_4OH and extracted into ethyl acetate. The organic extracts were concentrated to afford the crude base (3 g) which was purified by column chromatography (SiO_2, CH_2Cl_2/CH_3OH 9:1). Salification (HCl/ethanol) produced 2.10 g of 7,8-dihydroisoquinolin-5(*6H*)-one hydrochloride m.p. 235.3-235.8°C (Lit.[5] 235-236°C) ; IR (KBr) 1705 cm^{-1}. ^1H NMR (DMSO-d6) Keto form : 2.05-0.2 (m, 2H), 2.7-2.8 (m, 2H), 3.0-3.1 (m, 2H), 8.05 (d, 1H), 8.8 (d, 1H), 9.02 (s, 1H). Enol form 2.4(m, 2H), 2.9(t, 2H), 5.75(t, 1H), 7.80(d, 1H), 8.7(d, 1H ; s,1H).
Anal. Calc. for $C_9H_9NO.HCl$ C : 58.87 ; H : 5.49 ; N : 7.63 ;
Found : C : 58.88 ; H : 5.50 ; N : 7.64

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References

1) J. Epsztajn and A. Bieniek - *J. Chem. Soc., Perkin Trans*, 1 **1985**, 213.
2) E.S.C. Wu and A. Kover *Synth. Commun.* **1994**, 24(2), 273.
3) W. Glassco, J. Suchocki, C. George, B.R. Martin and E.L. May, *J. Med. Chem.*, **1993**,36, 3381.
4) EP 0293777 (Merrell Dow Pharmaceuticals Inc.)
5) N. Sugimoto, H. Kugita and T. Tanaka, *J. Pharm. Soc. Jpn.*, **1956**, 76, 1308.
6) D.G. Jones and G. Jones, *J. Chem. Soc.* (C), **1969**, 707.
7) R.P. Thummel, F. Lefoulon, D. Cantu and R. Mahadevan, *J. Org. Chem.*, **1984**, 49, 2208.
8) Y. Tagawa, H. Arakawa and Y. Goto, *Heterocycles*, **1989**, 29(9), 1741.

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