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A CONVENIENT REDUCTION OF PYRIDO[1,2]A PYRIMIDIN-ACETIC ACID USING THE $NABH_4/I_2$SYSTEM

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ABSTRACT

A method for the reduction of pyrido[1,2]a pyrimidin-acetic acid **(I)** system to their corresponding alkanes is reported. The reduction of (Z)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid on reduction with sodium borohydride as the reducing agent in the presence of the iodine in DMF at 0^oC yield (E)-3-ethylidene-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine**(II)** derivatives in good yields. The structures of the synthesized compounds are discussed using IR, ^1H NMR, ^{13}C NMR and Mass Spectrum. The reagent used is safe, simple and economical.

KEYWORDS: Reduction**,** pyrido[1,2]a pyrimidin-acetic acid, Sodium borohydride, Iodine, DMF.

INTRODUCTION

Reagent of choice for the reduction of organic functional group is sodium borohydride for the reduction of carbonyl compounds. Under ambient conditions esters, nitriles, carboxylic acids and amides are resistant towards sodium borohydride [i]**.** Reduction of carboxylic acids viz aliphatic, aromatic, and α,β-unsaturated to their corresponding alcohols and amino acids by sodium borohydride and iodine in THF has been reported recently. Reduction of acids in presence of esters with sodium borohydride in THF has also been reported [ii]. The reagent is simple easy to use and is cost effective. We anticipated that the reduction of **(I)** using sodium borohydride with DMF at 0^oC will lead to the formation of alcohols. Surprisingly, the product was found to be the corresponding alkanes.

The conversion of carboxylic acid to its methyl group is a important step in synthetic chemistry. Various methods are available for the conversion of carbonyl functions into a methylene group in a single-step. But there is no method involving one step for the conversion of carboxylic acids into methyl groups. The available method involves the conversion of carboxylic acids into aldehydes or alcohols first and then subsequent reduction to methyl group. Reduction of aromatic carboxylic acid groups to methyl groups using multi-steps have been reported earlier without purification of the intermediates [iii]. One-pot reduction of aliphatic

monocarboxylic acids to methyl groups have also been reported [iv][v]. The reduction of **(I)** to their corresponding alkanes in one step is described here.

EXPERIMENTAL

General methods

The Infrared (IR) spectra were recorded in KBr pellet technique on an **IR-AFFINITY-I.** Absorption frequencies were quoted in reciprocal centimeter. Nuclear Magnetic Resonance (^{1}H-NMR and ^{13}C NMR) spectra were determined by Bruker modern 400MHz NMR instrument in $CDCl_3$ solvent, with tetra methyl silane as the internal reference. Chemical shift were quoted in parts per million (ppm). The mass spectrum was recorded using Jeol GC-mate –II spectrophotometer. The solvents and reagents used for the synthesis were of reagent grade and were purified by standard methods.

General procedure for synthesis of (E)-3-ethylidene-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine derivatives

(E)-3-ethylidene-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine(IIA): At room temperature solution of (Z)-2-(2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid **(IA)** (10 mmol) in DMF (20 ml) was added slowly to $NaBH_4$ (12 mmol) in DMF (20 ml)with stirring, until the evolution of gas ceases. To this was added iodine (5 mmol) in DMF (20 ml) slowly at 0ºC. Stirring was continued for one hour. After the completion of the reaction 5ml of 3NHCl was added carefully and the mixture was extracted with ether. The combined ether extract was washed with 3 N NaOH (3 X 10 ml) and brine and dried over $MgS0_4$. Evaporation of the organic layer gave the product. Pure compound was obtained after recrystallization from chloroform .Yield 91%, m.p.251°C:IR(KBr,υ,cm^{-1}):1643cm^{-1},1612cm^{-1}(C=N),1512cm^{-1}(C=C)and2360cm^{-1}(–CH_3); ^{1}HNMR(400MHz,$CDCl_3$,δ,ppm):1.25(2H,m,-CH_2),1.8-2.5(3H,d,-CH_3),2.96(2H,s,-CH_2),5.43(1H,s,=CH),6.44-6.60(1H,d,=CH),7.38-7.40(1H,d,=CH),7.87(1H,s,=CH), 7.96 (1H,s,=CH);^{13}C NMR (300 MHz, $CDCl_3$, δ, ppm):17.41, 29.69, 108.81, 111.29, 122, 139,141,144,146 and 153.

(E)-3-ethylidene-7-iodo-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine(IIB): At room temperature solution of the (Z)-2-(7-iodo-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid **(IB)** (10 mmol) in DMF (20 ml) was added slowly to $NaBH_4$ (12 mmol) in DMF (20 ml) with stirring, until the evolution of gas ceases. To this was added Iodine (5 mmol) in DMF (20 ml) slowly at 0ºC. Stirring was continued for one hour. After completion of the reaction 5ml of 3 N HCl was added carefully and the mixture was extracted with ether. The combined ether extract was washed with 3 N NaOH (3 X 10 ml) and brine and dried over $MgS0_4$. Evaporation of the organic layer gave the product. Pure compound was obtained after recrystallization from chloroform. Yield 91%, m.p.251°C;IR(KBr,υ,cm^{-1}):1620cm^{-1},1473cm^{-1}(C=N),1512cm^{-1}(C=C)and2360cm^{-1}(–CH_3);^{1}HNMR(400MHz,$CDCl_3$,δ,ppm):2.6(2H,s,-CH_2),3.008(3H,d,-CH_3),4.78(2H,s,=CH_2),6.37-6.39(1H,d,=CH),7.62(1H,d,=CH),7.68(1H,d,=CH),8.19(1H,s,=CH).^{13}CNMR(300MHz,$CDCl_3$,δ,ppm):19.24,40.05,110.97,113.40,145.11,146.80,150.29,153.56and,157.59.

(E)-7-bromo-3-ethylidene-3,4-dihydro-2H-pyrido[1,2-a]pyrimidine(IIC): At room temperature solution of the (Z)-2-(7-bromo-2-oxo-2H-pyrido[1,2-a]pyrimidin-3(4H)-ylidene)acetic acid **(IC)** (10 mmol) in DMF (20 ml) was added slowly to $NaBH_4$ (12 mmol) in DMF (20 ml) with stirring, until the evolution of gas ceases. To this was added Iodine (5 mmol) in DMF (20 ml) slowly at 0ºC. Stirring was continued for one hour. After completion of the reaction 5ml of 3 N HCl was added carefully and the mixture was extracted with ether. The

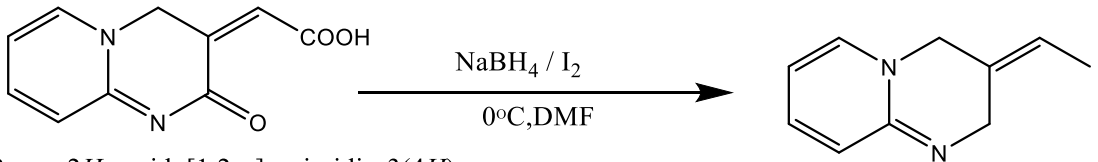
combined ether extract was washed with 3 N NaOH (3 X 10 ml) and brine and dried over $MgS0_4$. Evaporation of the organic layer gave the product. Pure compound was obtained after recrystallization from chloroform .Yield 91%, m.p.251° C: IR (KBr,υ, cm^{-1}): 1620cm^{-1},1473cm^{-1}(C=N),1512cm-1(C=C)and2360cm^{-1}(–CH_3); ^{1}HNMR (400 MHz, $CDCl_3$, δ, ppm) :1.25 (2H,s,-CH_2),1.64(3H,s,-CH_3),4.45(2H,s,-CH_2),6.43(1H,d,=CH),7.48-7.49(1H,d,=CH),7.50-7.51(1H,d,=CH),8.10(1H,s,=CH). ^{13}CNMR (300 MHz, $CDCl_3$, δ, ppm):29.70, 108.23, 110.09, 138.13, 140.66, and, 157.11

RESULTS AND DISCUSSION

Reduction plays a very important role in organic synthesis. Conversion of aromatic carboxylic acids into their methyl esters and reduction to their corresponding alcohols is a key step in the synthesis of many natural products. Hence **(I)** was converted in to ester and reduced in presence of nucleophilic reducing agent sodium borohydride in methanol at 0^{o}C according to the procedure reported[vi][vii]. Since the yield of the reaction was low and formation of the byproducts was high, it was decided to reduce the acid was directly [ii].

Synthesis of IIA

In the present investigation reduction of **(IA)** using $NaBH_4$-I_2 with DMF at 0^{o}C would lead to the formation of **(IIA)** instead of the expected alcohol is reported. The synthesis of target **(II)** derivatives was carried out as outlined in the **Scheme I.** The synthesized compound was characterized by FTIR, ^{1}H NMR, ^{13}C NMR, mass spectral analysis. The IR spectrum of this reaction product showed the expected absorption bands of C=N and C=C at 1643 cm^{-1},1612 $cm^{-1}$and 1512 cm^{-1} corresponding to the aromatic ring and that of the –CH_3 group at 2360 cm^{-1}. The absence of strong absorption band at 1680-1700 cm^{-1} revealed that reduction of –CO group might have occurred. The ^{1}H NMR spectrum of the compound displayed 8 signals and ^{13}C displayed 10 carbon signals. ^{1}H NMR spectrum showed a doublet at δ 1.8-2.5 ppm due to –CH3 group and a singlet at δ 5.43ppm assigned to methylene protons. The remaining aromatic protons appear in the range of δ 6.44-7.96 ppm. Similarly in its ^{13}C NMR spectra display chemical shifts 17.41 and 122 ppm for methyl groups bound to aromatic ring; at 29.69, 108.81, 111.29, 139,141,144,146 and 153 for pyridopyrimidine ring. Additionally, the mass spectrum (m/z) of the compound was founded. Instead of molecular ion peak the compound shows fragmentation peak at 110.3721.



(*Z*)-2-(2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetic acid

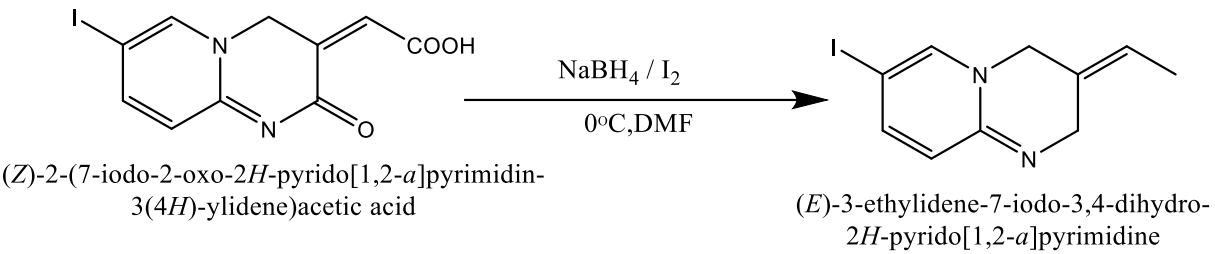
(*E*)-3-ethylidene-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine

Scheme-I

Synthesis of (IIB)

The reduction of **(IB)** using $NaBH_4$-I_2 with DMF at 0^{o}C lead to the formation of **(IIB)** instead of the expected alcohol is reported **Scheme-II**. The IR spectrum of this reaction product showed the expected absorption bands of C=N and C=C at 1620 cm^{-1},1473 $cm^{-1}$and 1512 cm^{-1} corresponding to the aromatic ring and that of the –CH_3 group at 2360 cm^{-1}. The absence of strong absorption band at 1680-1700 cm^{-1} revealed that reduction of –CO group might have occurred. Almost similar patterns were observed in ^{1}H and ^{13}C NMR spectra of the Iodo substituted compound. ^{1}H NMR spectrum showed a doublet at δ 3.008ppm due to –CH3 group and a singlet at δ 6.37ppm assigned to methylene protons. The remaining aromatic protons

appear in the range of δ 7.62 -8.19 ppm. Similarly in its ^{13}C NMR spectra display chemical shifts 19.24and 110.97 ppm for methyl groups bound to aromatic ring; at 40.05, 110.97, 113.40, 145.11, 146.80, 150.29, 153.56and, 157.59 for pyridopyrimidine ring. Additionally, the mass spectrum (m/z) of the compound was found at 285.67.



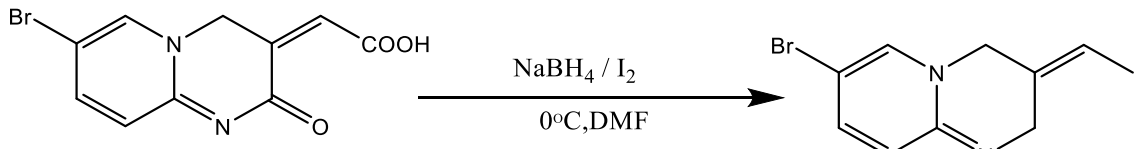
(*Z*)-2-(7-iodo-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetic acid

(*E*)-3-ethylidene-7-iodo-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine

Scheme-II

Synthesis of (IIC)

The reduction of **(IC)** using $NaBH_4$-I_2 with DMF at 0°C lead to the formation **(IIC)** instead of the expected alcohol is reported **Scheme-III**. The IR spectrum of this reaction product showed the expected absorption bands of C=N and C=C at 1620 cm^{-1},1473$cm^{-1}$and 1512 cm^{-1} corresponding to the aromatic ring and that of the $–CH_3$ group at 2360 cm^{-1}. The absence of strong absorption band at 1680-1700 cm^{-1} revealed that reduction of –CO group might have occurred. ^1H NMR spectrum showed a multiplet at 1.64ppm due to $–CH_3$ group and a singlet at δ 6.43ppm assigned to methylene protons. The remaining aromatic protons appear in the range of δ 7.48-8.10 ppm. Similarly in its ^{13}C NMR spectra display chemical shifts 29.70 ppm for methyl groups bound to aromatic ring; at 108.23, 110.09, 138.13, 140.66, and, 157.11 for pyridopyrimidine ring. Additionally, the mass spectrum (m/z) of the compound was found at 238.38. Spectral data studies which were in a good agreement with the proposed structure.



(*Z*)-2-(7-bromo-2-oxo-2*H*-pyrido[1,2-*a*]pyrimidin-3(4*H*)-ylidene)acetic acid

(*E*)-7-bromo-3-ethylidene-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine

Scheme-III

CONCLUSION:

In this investigation is reported a facile synthesis of three **(II)** derivatives. It is important to mention that the reagents used in this method are easy to handle and do not require specific conditions.

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