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Research Article

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New approach for the preparation of key intermediates of nadifloxacin

Anil Kumar*, Bhuwan Bhashkar and Jigar Bhavsar

Department of Chemical Research, Mankind Research Centre, IMT, Manesar, Gurgaon, Haryana(India)

ABSTRACT

*Present research is focused on preparation of 2-bromo-4,5-difluoroacetanilide, compound **4**, one of the key intermediate mostly used in the preparation of Nadifloxacin, by the bromination of 3,4-difluoroacetanilide compound **3** using novel brominating agent. Current research also identifies specific impurities of Nadifloxacin and origin of its responsible precursors. The present research further provides a new approach to control the amount of these specific impurities in Nadifloxacin by controlling the amount of formation of compounds **2b** and **2c** during the manufacturing process. All prepared compounds are characterized by FT-IR, ^{1}HNMR and LC-MS.*

Key words: Preparation of Nadifloxacin, Bromination, Intermediate, Impurities, Precursors

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INTRODUCTION

Nadifloxacin,9-Fluoro-8-(4-hydroxy-piperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-i,j]quinoline-2-carboxylic acid (Figure 1) is a topical fluoroquinolone antibiotic generally used for the treatment of acne vulgaris[1-2].It is also used to treat bacterial skin infections[3], gonorrhoea[4], respiratory tract infection[5] and other different infections[6-7].

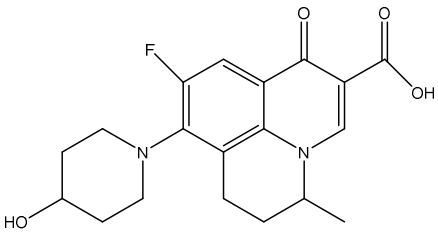


Figure 1: Nadifloxacin

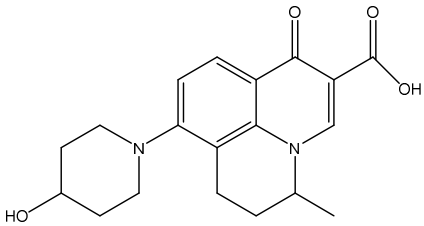


Figure 2: Impurity of Nadifloxacin

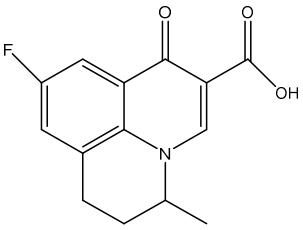
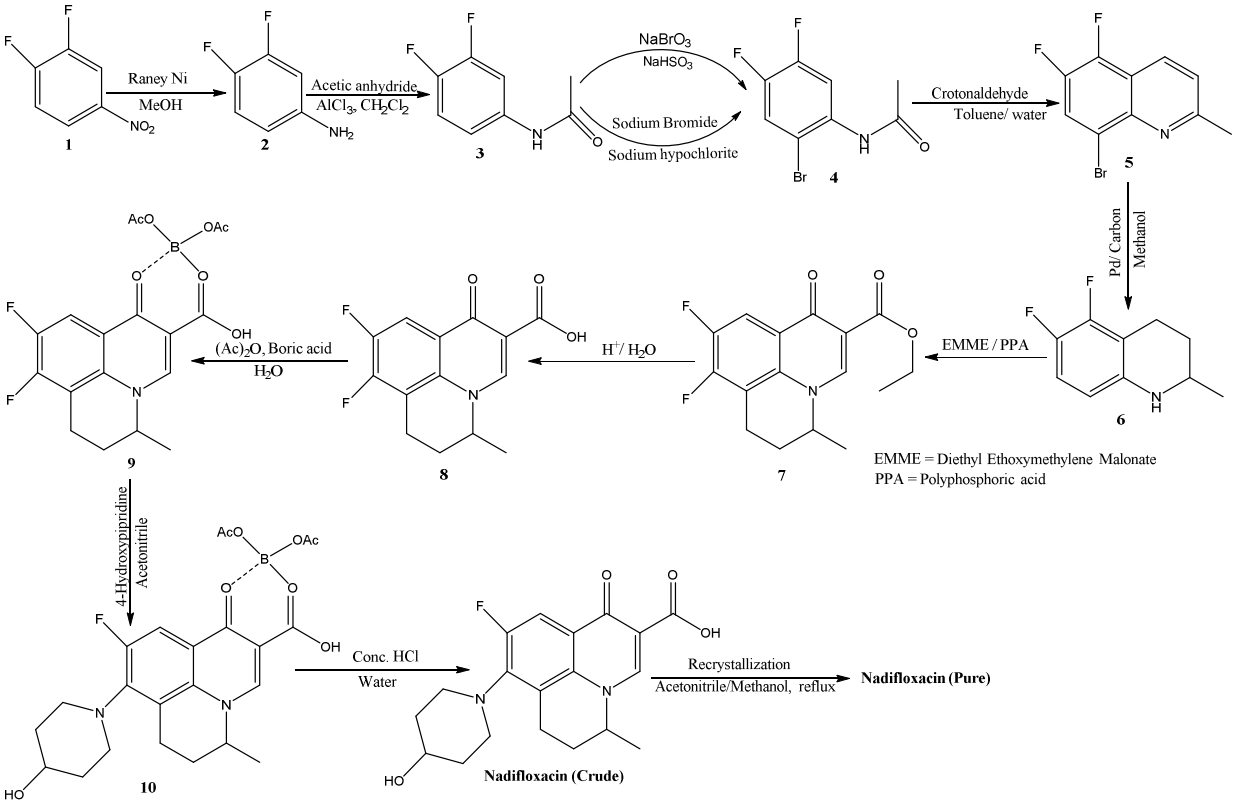


Figure 3: Impurity of Nadifloxacin

Nadifloxacin is tricyclic fluoroquinolone which was first time reported by Otsuka Pharmaceutical Co. Ltd, Japan[8]. Innovator disclosed a method of preparation of Nadifloxacin, started from compound **2**. There are numbers of method reported for the preparation of Nadifloxacin using different starting material through bromination of compound **3**. Although, several methods are in prior art but none of them reported use of sodium bromate/ sodium bisulphite or sodium bromide/ sodium hypochlorite as brominating agent for bromination of compound **3**.In most of the reported methods, bromine is used for bromination purpose. Hence, bromination method of the present research, particularly for the preparation of compound **4**which is used for the preparation of Nadifloxacin is quite novel. Nadifloxacin is prepared by conventional methods reported in prior art using intermediate compound**4**or prepared as shown in Scheme 1[9-17].During analysis of the final product (Figure 1), two specific impurities as represented in Figure 2 and Figure 3 are also identified. Further research on finding the cause behind the formation of these impurities(Figure 2 and Figure 3), it is observed that compounds**2b**and **2c**are precursors for the said impurities respectively. Current research also provides the solution for minimizing the amount of said impurities in Nadifloxacin.



Scheme 1: Preparation of Nadifloxacin.

EXPERIMENTAL SECTION

The reagent grade chemicals were purchased from the commercial sources viz. Sigma-Aldrich. ^{1}HNMR spectra were measured on a Bruker Asend400 spectrometer in $CDCl_3$ at 400MHz using TMS as an internal standard. All chemical shifts were reported on δ scales. IR spectra were recorded on Nujols or KBr disc on a Perkin Elmer Spectrum ES Version and the LC-MS spectra were recorded on a XevoTQD Waters LC-MS spectrometer. Progress of reaction monitored by High Performance Liquid Chromatography (HPLC) using Waters e2695 HPLC.The analytical data was highly satisfactory.

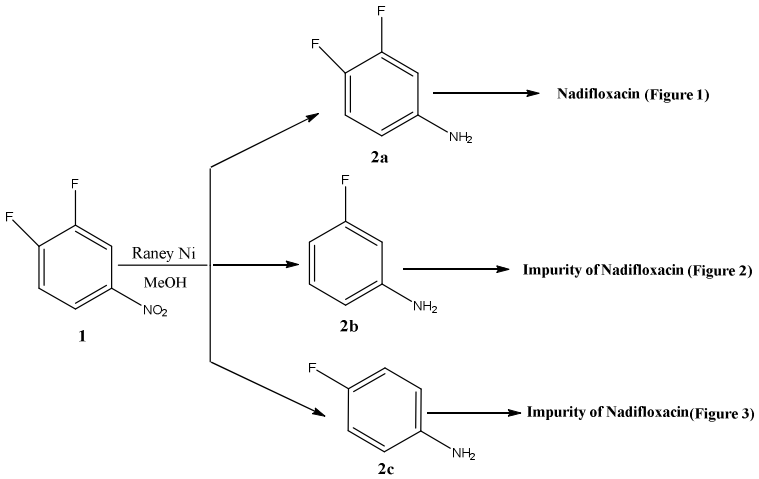
Process for the Preparation of Compound 2

3,4-Difluoronitrobenzene compound **1**(200g, 1.25mol) and Raney nickel (20g, 10%w/w) were charged in autoclave hydrogenator with 1250ml methanol. Reaction is stirred vigorously under pressure (70PSI) of hydrogen gas at room temperature and monitored by HPLC. After the completion of reaction, reaction mass was filtered through celite bed and mother liquir is concentrated under reduced pressure to give oily compound **2** with yield 98% (mixture of**2a**, **2b** and **2c**with HPLC Peak Area 92%, 5% and 2% respectively)as shown in Scheme **2**. Compounds**2a**, **2b** and **2c** were separated over preparative chromatography.

2a: FT-IR (Nujol): 3378, 1614, 1519, 1457, 1266, 1213, 776 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ): 6.95-6.855 (m, 1H), 6-49-6.41 (m, 1H), 6.35-6.28 (m, 1H), 3.58 (s, 2H); LC-MS (M+1) m/z: 130.

2b: FT-IR (Nujol): 3362, 1634, 1622, 1495, 1168, 767 cm^{-1}; ^{1}HNMR ($CDCl_3$, δ): 7.08-7.03 (m, 1H), 6.48-6.40 (m, 2H), 6.38-6.34 (m, 1H), 3.79 (s, 2H); LC-MS (M+1) m/z: 112.1.

2c: FT-IR (Nujol): 3362, 1625, 1509, 1222, 826cm^{-1}; ^{1}HNMR ($CDCl_3$, δ): 6.88-6.81 (m, 2H), 6.60-6.57 (m, 2H), 3.52 (s, 2H); LC-MS (M+1) m/z: 112.1.



Scheme 2: Preparation of Compound **2a**, **2b** and **2c**

Process for the Preparation of Compound 3

Compound**2** (150g, 1.16mol) charged in 500ml methylene dichloride (MDC) and anhydrous aluminium chloride (7.73g, 0.058mol) was added. To this solution, acetic anhydride (220ml, 2.32 mol) added slowly and allow the reaction mass to heat. After completion of the reaction, methylene dichloride distilledout and excess of acetic anhydride quenched with 2500ml water. Reaction mass was filltered, thus obtained solid was dried at 55-60°C to give 3,4-difluoroacetanilidecompound **3** (190g, 1.11mol), Yield: 95.7%; Purity(HPLC) 98.5%; FT-IR (KBr): 3312, 1668, 1633, 1514, 863cm^{-1}; ^{1}HNMR ($CDCl_3$, δ): 7.59-7.55 (m, 1H), 7.41 (s, 1H), 7.09-7.0 (m, 2H), 2.18 (s, 3H); LC-MS (M+1) m/z: 172.1.

Process for the Preparation of Compound 4

3,4-Difluoroacetanilidecompound **3**(190g, 1.11mol) was charged in 2500ml DM water along with sodium bromate (404g, 4.66mol). Resulting suspension is cooled and aqueous solution of sodium bisulphite (485g, 4.66mol) was added (highly exothermic). Reaction mixture was stirred at ambient temperature till the conversion of starting material completed. After completion of reaction, excess bromine is quenched with aqueous solution of sodium metabisulfiteand suspension is filtered to give white solid. The wet material is dried at reduced pressure at 60-65°C to give dry solid of 2-bromo-5,6-difluoroacetanilidecompound **4**(272g, 1.08mol). Yield: 98%; Purity (HPLC): 98%; FT-IR (KBr): 3271, 1667, 1539, 1406, 869cm^{-1}; ^{1}HNMR ($CDCl_3$, δ): 8.35-8.30 (m, 1H), 7.49 (s, 1H), 7.37-7.28 (m, 1H), 2.22 (s, 3H); LC-MS (M+1) m/z: 250.

Alternate Process for the Preparation of Compound 4

3,4-Difluoro acetanilidecompound **3**(174g, 1.01mol) was charged in 700ml methanol and 500ml acetic acid along with sodium bromide (314g, 3.05mol). Resulting suspension is cooled to 10°C and 3850ml solution (3-4% in water) of sodium hypochlorite is added slowly (highly exothermic). Reaction mixture stirred at ambient temperature till the conversion of starting material complete. After completion of reaction, excess bromine is quenched with aqueous solution of sodium metabisulfite and suspension is filtered to give white solid. The wet material is dried at reduced pressure at 60-65°C to give dried solid of 2-bromo-5,6-difluoroacetanilide compound **4**(250g, 1.0mol). Yield: 98%; Purity (HPLC): 97%.

Process for the Preparation of Nadifloxacin

Nadifloxacin was prepared according to Scheme 1 or other available methods reported in litreture[9-17].

RESULTS AND DISCUSSION

Bromination method using sodium bromate/ sodium bisulphite or sodium bromide/ sodium hypochlorite particularly for the preparation of Nadifloxacin is quite novel. In most of the reported methods, bromine is used for bromination purpose. In present disclosure, it is observed that the yield and purity of obtained brominated compound**4** is better than prior art methods. As shown in experiments, both yield and purity of compound **4**which is obtained by using either sodium bromate/ sodium bisulphite or sodium bromide/ sodium hypochlorite is about 98%. Obtained compound **4**, is not only better in yield and purity but also its manufacturing process is eco-friendly and superior in terms of handling and safety than all previously reported literature.

In analysis of the final product (Nadifloxacin shown in Figure 1) impurities of structure given in Figure 2 and Figure 3 were also identified. During further research on finding the cause behind the formation of these impurities (Figure 2 and Figure 3), it was observed that compound **2b**and **2c**areprecursors for the said impurities respectively. Said precursors may carry forward in each and every step along with desired intermediates in usual treatments for the preparation of Nadifloxacin as per Scheme 1 and finally appeared as impurities (Figure 2 and Figure 3) along with Nadifloxacin. It is also observed that the amount of said impurities can be controlled by controlling the amount of compounds**2b** and **2c** formation in the manufacturing process.

Nadifloxacin prepared as per Scheme 1 using Compound **2** (mixture of **2a**, **2b** and **2c**) without minimizing the formation of compounds **2b** and **2c,**having amount of said impurities more than 0.5% and these impurities were never removed or minimized from this limit while performing repeated recrystallization / purifications. Purification not only needed for crude Nadifloxacin but also required for some intermediate steps. These repeated recrystallization and presence of said impurities more than 0.5% makes this process very tedious, uneconomical and obtained product is also not fit for drug regulatory guidelines. From current research it was found that by minimizing the formation of compounds **2b** and **2c** in compound **2**(as exemplified in process for the preparation of compound **2**), it is possible to reduce the amount of said impurities less than 0.1% or tends to be negligible in final product having purity more than 99%. It is clear from the current research that production of compound **2** is a critical step in the preparation of Nadifloxacin which controls the formation of said impurities in final product.

CONCLUSION

Bromination method using sodium bromate/ sodium bisulphite or sodium bromide/ sodium hypochlorite particularly for the preparation of Nadifloxacin is not only better in yield and purity prospective but also is eco-friendly and superior in view of handling and safety than all previously reported literature. Identification and analysis of impurities of Nadifloxacin and responsible precursor are very helpful to control the amount of impurities in final drug product.

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