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Synthesis of an amino moiety in trovafloxacin by using an in-expensive amidine base, *N,N*-diethylacetamidine

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The simple and in-expensive amidine base, *N,N*-diethylacetamidine, has been prepared and utilized in the construction of bicyclic hetero compound, **4** and employed for further reduction of amidic carbonyl groups of **4** by using $NaBH_4/I_2$-THF condition which is an efficient and commercially viable method to prepare **5** towards the synthesis of amino moiety **1**, in Trovafloxacin **2** an antibacterial agent.

Keywords: *N,N*-Diethylacetamidine, bicyclic hetero compounds, $NaBH_4/I_2$-THF, trovafloxacin, antibacterial agent

Trovafloxacin (TRFLX) {(1α,5α,6α)-7-(6-amino-3-azabicyclo[3.1.0]hex-3-yl)-1-(2,4-difluoro phenyl)-6-fluoro-1,4-dihydroxy-4-oxo-1,8-naphtyridine-3-carb-oxylic acid}, **2** is a new synthetic anti-bacterial fluoroquinolone agent which exhibits high activity against a broad spectrum of gram-negative and gram-positive bacteria (aerobic and anaerobic) through inhibition of their DNA gyrase[1].

The *in vitro* activity of trovafloxacin **2** was compared with ten other agents against 100 clinical isolates in the *Bacteroides fragilis* group. Trovafloxacin was the most active quinolone (MIC_{90}, 1 μg/mL) followed by Sparfloxacin (MIC_{90}, 8 μg/mL), Levofloxacin (MIC_{90}, 16 μg/mL) and Ofloxacin (MIC_{90}, 32 μg/mL). Ciprofloxacin was the least active quinolone (MIC_{90}, 64 μg/mL)[2]. Effective *in vivo* activity of fluoroquinolones generally requires use of a diamine at the C-7 position[3].

Results and Discussions

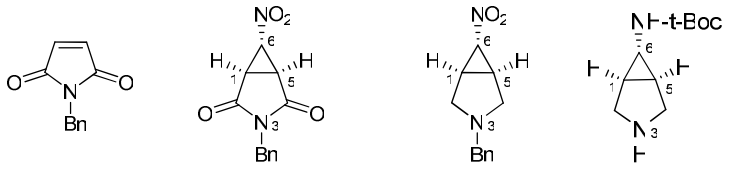
A search of literature revealed very few methods for the construction of bicyclic hetero compounds **(Figure 1)**.

One of those methods was reported by Vilsmaier[4] where 3-azabicyclo[3.1.0] hexane ring system was synthesized with a morpholino moiety in the 6-position *via* the reductive cyclization of a chloro-enamines. Unfortunately, this reaction required several days, and the reaction worked only with the morpholino moiety, which could not be removed after the cyclization. The stereochemistry also depends on the nature of the protecting group on the nitrogen.

Dailey[5] reported a nitro cyclopropanation reaction using ethylnitrodiazoacetate, but this reagent did not work with highly substituted or electron poor double bonds.

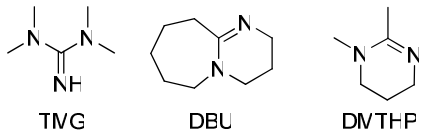
It became apparent that the simultaneous introduce-tion of the 6-amino (or 6-nitro) functionality along with cyclopropane formation would be desirable. The 6-amino group on the 3-azabicyclo[3.1.0]hexane ring system was envisioned to arise *via* Curtius rearrange-ment of the corresponding carboxylic acid. The most direct approach to bicyclic carboxylic acids of this type involves rhodium(II) acetate-mediated cyclo-propanation of an *N*-protected pyrroline with ethyl diazoacetate[6]. In the event, this reaction produced a mixture of *exo*- and *endo*- substituted cyclopropanes. To prepare a single (*exo*-substituted) cyclopropane isomer Brighty[7] reported a longer route by the reaction of *N*-benzylmaleimide with ethyl diazo-acetate followed by pyrolysis of the resulting pyrazoline; amine introduction is then effected using a modified Curtius rearrangement.

To avoid the use of ethyl diazoacetate and diphenylphosphoryl azide, Braish T F reported the use of the tandem Michael-S_N2 reaction to construct the 6-carboxylate-3-azabicyclo[3.1.0] hexane ring system[8]. At this stage the reaction of bromo nitro methane with *N*-benzyl maleimide was attempted in the presence of a base followed by the reduction of carbonyl group using $LiAlH_4$ and BH_3-THF[9].



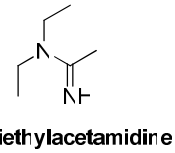
3 **4** **5** **1**

Figure 1



TMG DBU DMTHP

Figure 2



N,N-diethylacetamidine

Figure 3

The need for large quantities of material led to the pursuit of this route and it was observed during the synthesis of (1α,5α,6α)-3-benzyl-6-nitro-3-azabicyclo[3.1.0] hexane-2,4-dione **4**, the major cost is due to the usage of highly expensive amidine bases like TMG, DBU and DMTHP and in the synthesis of (1α,5α,6α)-3-benzyl-6-nitro-3-azabicyclo[3.1.0]hexane-2,4-dione **5**, literature[9] reveals the usage of highly pyrophoric reagents like $LiAlH_4$ and BH_3-THF. Bases like TMG, DBU and DMTHP only gave a variable 15-36% yield[9]. As part of the interest in developing a process for the preparation of the key intermediate, (1α,5α,6α)-3-benzyl-6-nitro-3-aza bicycle[3.1.0]hexane-2,4-dione **4**, several bases have been screened in place of DBU, TMG and DMTHP **(Figure 2)**.

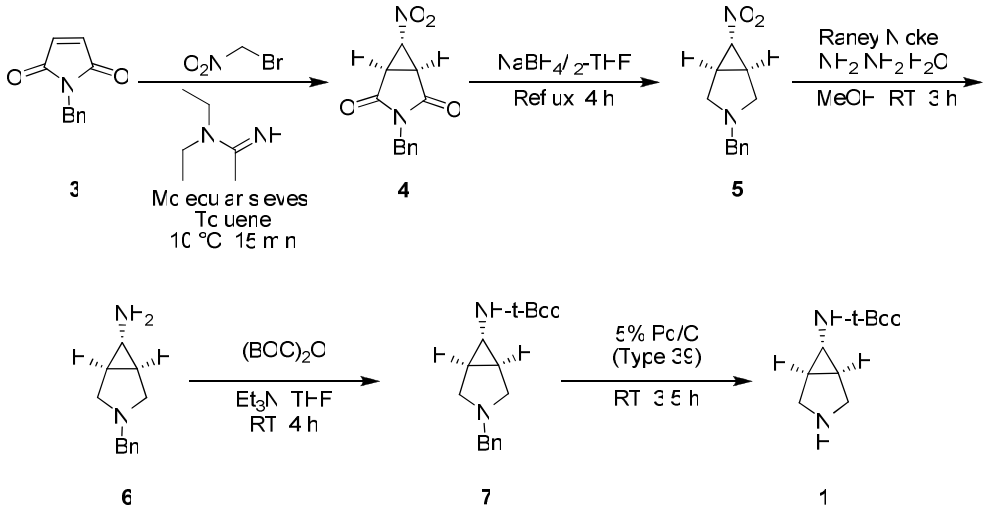
Most of the common bases did not yield the required product. However, owing to the cost of DBU, TMG and DMTHP use of these bases is discouraged in large scale preparation of this intermediate. Having observed that the amidine bases yield alone required intermediate **4**, attention was directed toward finding a relatively inexpensive amidine base which can be easily prepared and scaled up for a large scale preparation of the intermediate **4**. After exploring the use of several amidine bases, it was observed that *N,N*-diethylacetamidine was working as efficiently as DBU, DMTHP and TMG for the preparation of intermediate **4**. It also provided the right *exo* stereochemistry at the 6-position. The undesired *endo* isomer was not detected under these conditions. Based on ^{1}H NMR spectroscopy[10] (δ 4.47, 1H, alpha to nitro), **4** was confirmed as the *exo* product. *N,N*-Diethylacetamidine is not readily available among the lab grade chemicals as well as commercially. Hence, this compound was prepared in the lab using one step method[11] by copper-(I) induced addition of diethylamine with acetonitrile in about 60-65% yield. Similarly, synthesis of *N*-benzylmaleimide[12] has been performed by reacting benzyl amine with maleic anhydride followed by cyclization driven by azeotropic removal of water in the presence of phosphoric acid **(Figure 3)**.

For the reduction of amidic carbonyl groups of **4,** a more convenient and industrially feasible method was developed by using $NaBH_4/I_2$-THF[13] which gave **5** in 95% yield. The reduction of nitro functionality in the 6-position was performed as earlier[9] with Raney Ni and hydrazine as the hydrogen source which provided **6** in 80% yield due to high purity of **5**. **6** upon *N*-protection with di-*t*-butyldicarbonate gave **7** in 90% yield. For debenzylation, several reaction conditions were tried using various types of palladium on carbon. Finally, palladium on carbon (type 39) has worked out very well to get **1** in 95% yield. Based on ^{1}H NMR spectroscopy[9] (δ 2.32, 1H, alpha to amide), the final compound **1** was confirmed as the *exo* product **(Scheme I)**.

In conclusion, this manuscript describes an inexpensive and industrially feasible method for the synthesis of the desired (1α, 5α, 6α)-6-amino-3-azabicyclo [3.1.0] hexane, **1**.

Experimental Section

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), ^{1}H and ^{13}C NMR (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-d_6 and $CDCl_3$ as solvent,



Scheme I

and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column-chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

Preparation of *N*-benzylmaleimide, 3. Maleic anhydride (100 g, 1.02 mole) and ethylene dichloride (600 mL) were taken into a round bottom flask and cooled to 5°C while stirring. Benzylamine (110 g, 1.02 mole) was added in 30 min at below 10°C and the reaction mixture was stirred at the same temperature for an additional 30 min. The solid thus obtained was filtered, washed with ethylene dichloride (100 mL) and air dried at RT for 30 min to give 205 g of *N*-benzylmaleamic acid; 98% yield. The obtained *N*-benzylmaleamic acid (205 g) was taken into a round bottom flask, fitted with a Dean-Stark condenser. *o*-Xylene (1000 mL) and phosphoric acid (50 mL) were then added and the entire mass refluxed for 2 hr with azeotropic removal of water. The reaction mixture was allowed to attain RT and filtered to remove the unwanted solids. The filtrate was washed with water (200 mL), aqueous sodium bicarbonate (200 mL) and water (200 mL). The solvent was distilled off under reduced pressure to give 159 g of colorless solid; 85% yield; m.p. 95-96°C (lit.[14] 94-95°C); ^{1}H NMR (DMSO-d_6): 7.41-7.22 (5H, m), 6.7 (2H, s), 4.61 (2H, s); MS: *m/z* (M^++1) 188.

Preparation of Bromonitromethane. Water (800 mL) was taken into a round bottom flask and cooled to 5°C. To this, a cold solution of sodium hydroxide (65.5 g, 1.64 mole of NaOH in 200 mL of water) and pre cooled nitromethane (100 g, 1.64 mole) were added simultaneously with the aid of two pressure equalizing funnels at -5 to 0°C over a period of 15 min. The reaction mixture was stirred at the same temperature for an additional period of 10 min to produce the nitromethane sodium salt. Meanwhile, water (200 mL) was taken into another round bottom flask and cooled to 0-5°C and to this was added bromine (262 g, 1.62 mole) in 15-30 min at -5 to 0°C. To this cold bromine solution was added the nitro methane sodium salt solution prepared above, in 5 min at below 10°C. The reaction mixture was stirred at the same temperature for further 15 min and distilled azeotropically. The lower layer was collected and redistilled to give 149 g of pure bromonitromethane; 65% yield; (b.p. 149-50°C / 749 mmHg); ^{1}H NMR ($CDCl_3$): 5.6 (s, 2H); MS: *m/z* (M^++1) 141.

Preparation of (1α,5α,6α)-3-*N*-benzyl-6-nitro-2,4-dioxo-3-azabicyclo[3.1.0]hexane, 4. *N*-Benzyl maleimide (100 g, 0.534 mole), toluene (700 mL) and bromonitromethane (112 g, 0.800 mole) were taken into a round bottom flask and cooled to 0°C. To this was added *N,N*-diethylacetamidine (123 g in 500 mL toluene) over a period of 2 hr below 10°C. The reaction mixture was maintained at the same temperature for 15 min followed by the addition of

powdered molecular sieves (25 g). The reaction mixture was allowed to attain RT and the unwanted solid material was filtered and the cake washed with toluene (3×200 mL). The filtrate was washed with water (4×500 mL) and the solvent was removed under reduced pressure to obtain the crude material, which was triturated with isopropanol and filtered to give the pure title compound as a pale yellow solid; yield 19.8%; m.p. 114-15°C; IR (KBr): 1713, 1562 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.31 (m, 5H aromatics), 4.54 (s, 2H, benzylic), 4.47 (t, 1H, alpha to nitro), 3.35 (d, 2H, 3-ring); ^{13}C NMR ($CDCl_3$): δ 27.5, 42.6, 62.3, 128.4, 128.6, 128.8, 134.8, 168.7; MS: *m/z* (M^++1) 247.

Preparation of (1α,5α,6α)-3-*N*-benzyl-6-nitro-3-azabi-cyclo[3.1.0]hexane, 5. $NaBH_4$ (115 g, 3.0642 mole) and THF (1000 mL) were taken into a round bottom flask under N_2 atmosphere and cooled to -10°C under stirring. I_2 (340 g, 1.336 mole) in THF (1000 mL) was added at -10 to 0°C in 1.5 hr. followed by **4** (300 g, 1.218 mole) in THF (1000 mL) in 15 min. The reaction mass was allowed to attain RT, followed by reflux for 4 hr. After the completion of starting material, the reaction mixture was cooled to -10°C and quenched with MeOH (120 mL) over 15 min 10% aqueous NaOH (2000 mL) was added slowly at below 0°C. The reaction mixture was stirred at RT. The organic layer was separated and distilled under reduced pressure. The aqueous layer was extracted with DCM (1000 mL) and this extract was mixed with crude distilled compound and diluted to 3000 mL with DCM, washed with water (3×75 mL) followed by brine (75 mL). Solvent was distilled under reduced pressure to give a syrupy liquid, which is usually carried to the next step without further purification; 95% yield; ^1H NMR ($CDCl_3$): δ 7.35-7.19 (m, 5H, aromatics), 4.63 (t, 1H, alpha to nitro), 3.59 (s, 2H, benzylic), 3.14 (m, 2H, 5-ring), 2.49 (m, 2H, 5-ring), 2.51 (m, 2H, 3-ring); MS: *m/z* (M^++1) 219.

Preparation of (1α,5α,6α)-3-*N*-benzyl-6-amino-3-azabicyclo[3.1.0]hexane, 6. To **5** (25 g, 0.11 mole) in methanol (100 mL) was added Raney nickel (37.5 g) and the mixture was cooled to 5-10°C followed by the addition of hydrazine hydrate (26 mL) in methanol (30 mL) over 1.5 hr at 5-10°C. The reaction mass was stirred at RT for further 3 hr. Reaction was monitored by TLC. After the consumption of starting material, the reaction mass was filtered through a celite pad and the celite pad washed with methanol (20 mL). The combined filtrate was concentrated under reduced pressure. The crude compound was taken into DCM (175 mL), washed with water (3×75 mL) and brine (75 mL). Solvent was removed under reduced pressure, to give an oily compound; yield 80%. ^1H NMR ($CDCl_3$): δ 7.35-7.20 (m, 5H, aromatics), 3.55 (s, 2H, benzylic), 2.92 (d, 2H, 5-ring), 2.65 (m, 1H, alpha to amino), 2.38 (d, 2H, 5-ring), 1.55 (m, 2H, cyclopropyl); MS: *m/z* (M^++1) 189.

Preparation of (1α,5α,6α)-3-*N*-benzyl-6-[t-butoxycarbonylamino]-3-azabicyclo[3.1.0] hexane, 7. The compound **6** (16 g, 0.085 mole), triethylamine (1.2 mL, 0.0085 mole) and THF (160 mL) were taken into a round bottom flask and cooled to 10°C under stirring. Di-*t*-butyldicarbonate (20.4 g, 0.093 mole) was added over 10 min at 10-20°C and the reaction mass was stirred at RT for 4 hr. Reaction mass monitored by TLC. After the consumption of starting material, the solvent was distilled off from reaction mass and the crude solid was taken into DCM (210 mL) and washed with water (3×80 mL) followed by brine (80 mL). Organic layer was treated with decolorizing charcoal (5 g), stirred for 15 min at 40°C and filtered. The solvent was removed under reduced pressure and the solid thus obtained was stirred in petroleum ether (300 mL) and filtered to give white needles; yield 90%; m.p. 131-32°C; ^1H NMR ($CDCl_3$): δ 7.24 (m, 5H aromatics) 3.54 (s, 2H, benzylic), 3.06 (m, 2H, 5-ring), 2.91 (broad, 1H, alpha to amide), 2.43 (m, 2H, 5-ring), 1.52 (m, 2H, 3-ring); MS: *m/z* (M^++1) 289.

Preparation of (1α,5α,6α)-6-t-butoxycarbonyl-amino-3-azabicyclo[3.1.0]hexane, 1. To **7** (18.5 g, 0.064 mole) in of methanol (185 mL) was added 1.8 g of 5% Pd/C (type 39, 50% wet) and hydrogenated at atmospheric pressure and temperature for a period of 3.5 hr. After the reaction was complete, the catalyst was filtered and the filtrate was concentrated to give the crude compound which was triturated with a mixture of ether and pet-ether (1:3) to give the pure compound; yield 95%; m.p. 109-13°C; IR (KBr): 1696, 3359 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.6 (broad, 1H, amide NH), 3.22 - 2.95 (m, 4H, 5-ring), 2.3 (s, 1H, alpha to amide), 1.63 (m, 3H, 3-ring and NH), 1.45 (s, 9H, *t*-butyl); ^{13}C NMR ($CDCl_3$): δ 25.8, 28.1, 29.9, 48.3, 79.1, 156.2; MS: *m/z* (M^++1) 199.

Preparation of *N,N*-Diethylacetamidine. Diethylamine (20 g, 0.273 mole), CuCl (27 g, 0.27 mole) and CH_3CN (100 mL) were taken into RBF and refluxed for 25 hr. Reaction mass was allowed to cool to RT and 30% aq. NaOH solution (200 mL) was added and then stirred for 30 min. The reaction mass was extracted with ether solvent (3×100 mL). The

combined ether layer was washed with 30% NaOH solution (100 mL) and brine (100 mL). The organic layer was concentrated and traces of solvent were removed by application of high vacuum. This crude liquid was distilled under high vacuum to give 20.28 g of colorless liquid; 65% yield (lit.[15] b.p. 72°C (25 mmHg)); ^{1}H NMR (100 MHz, CD_3CN): δ 6 6.35 (s, 1 H), 3.34 (4, 4 H), 2.16 (s, 3H), 1.14 (t, 6 H); MS: *m/z* (M^++1) 115.

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