Efficient and Scalable Methods for Synthesis of Midazolam Drug with an Annulation Process

Taghizadeh, Mohammad Javad*[+], Chahardoli, Esmaeil; Malakpouri, Gholam Reza
Department of Chemistry, Faculty of Science, University of Imam Hossein, Tehran, I.R. IRAN

ABSTRACT: *The reported methods for the synthesis of midazolam include a number of disadvantages, such as high production costs and low yields. The purpose of this investigation was to develop a more economical and technically feasible route to the synthesis of midazolam. In this research, two easy and scalable synthetic methods for the production of midazolam drugs are presented. One-pot condensation of imidoyl chloride or 1,4-benzodiazepinic N-nitrosoamidines with carbanion of two isocyanide reagents is described and two important and key tricyclic ring intermediates are synthesized. These imidazole-type structures can be derivatives by the alkylation of the imidazole ring with tert-butyl magnesium chloride at 0 °C in excellent yield, which has not been described for these intermediates in the literature.*

KEYWORDS: *Midazolam; Imidoyl chlorides; 1,4-Benzodiazepinic N-nitrosoamidines; Imidazobenzodiazepine; Tosylmethyl isocyanide; Ethyl isocyanoacetate; Cyclization.*

INTRODUCTION

Benzodiazepines have extensive drug effects and it is the most commonly used in psychiatry [1]. Among them, some of the imidazobenzodiazepines or 1,4-benzodiazepines are welded together with three rings to exhibit biological activity. These series of therapeutic agents have shown their role in blocking a prominent place on GABA receptors in CNS [2-3]. Midazolam is a fast and short-acting imidazobenzodiazepine derivative [4-5]. The reported methods for the synthesis of midazolam include a number of disadvantages, such as high production costs and low yields. These syntheses would be costly on a technical scale since they would require expensive safety precautions for the handling of primary substances and removing impurities. The purpose of this investigation was to develop a more economical and technically feasible route to the synthesis of midazolam.

Many methods have been reported for synthesizing imidazobenzodiazepine [6–11]. Among all these methods, those passing through the intermediate 1,4-benzodiazepin-2-ones **1** seem more logical [12–15]. The chemical activation of cyclic secondary amide in benzodiazepines is necessary for the insertion of the imidazole ring. As part of a program directed toward the construction of the imidazole ring instead of the carbonyl group at a portion at C-2 of the diazepine ring **1**, a leaving group must be created, then replacement of the leaving group moiety through treatment with the nucleophiles isocyanide [16–23] or nitromethane [24], and the imidazole ring is formed in multi-steps on a diazepine ring **1** (Scheme 1). Leaving groups used for this synthetic route such as imidoyl chlorides, imidoyl phosphates, and 1,4-benzodiazepine *N*-nitrosamines [25]. Imidoyl chlorides and imidoyl phosphates are very prone

***** *To whom correspondence should be addressed.*
+ *E-mail*: *mohammadjavadtaghizadeh31@yahoo.com*
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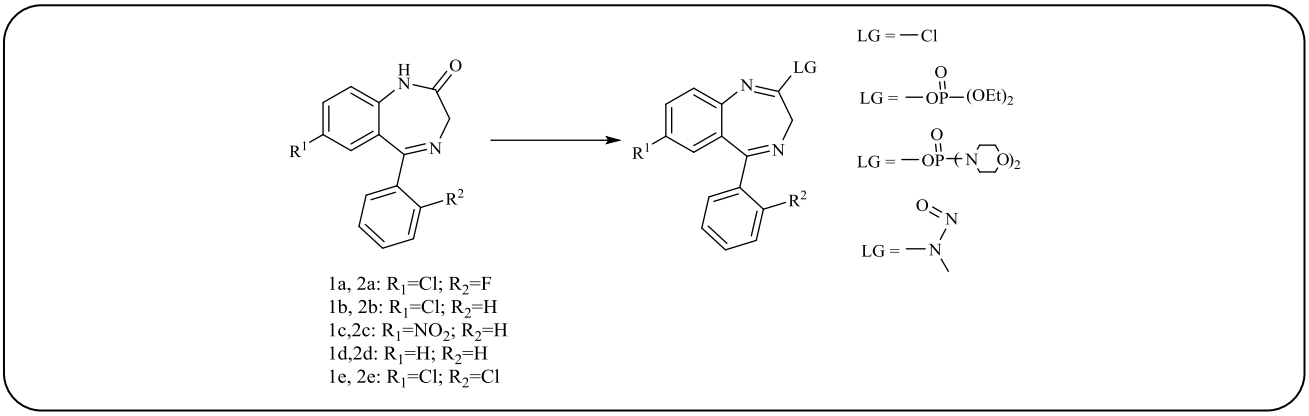


Scheme 1: Synthesis of Imidoyl intermediates.

to hydrolysis in solution and proved difficult for analyses. For example, ^{1}H NMR analysis showed only the primary substance.

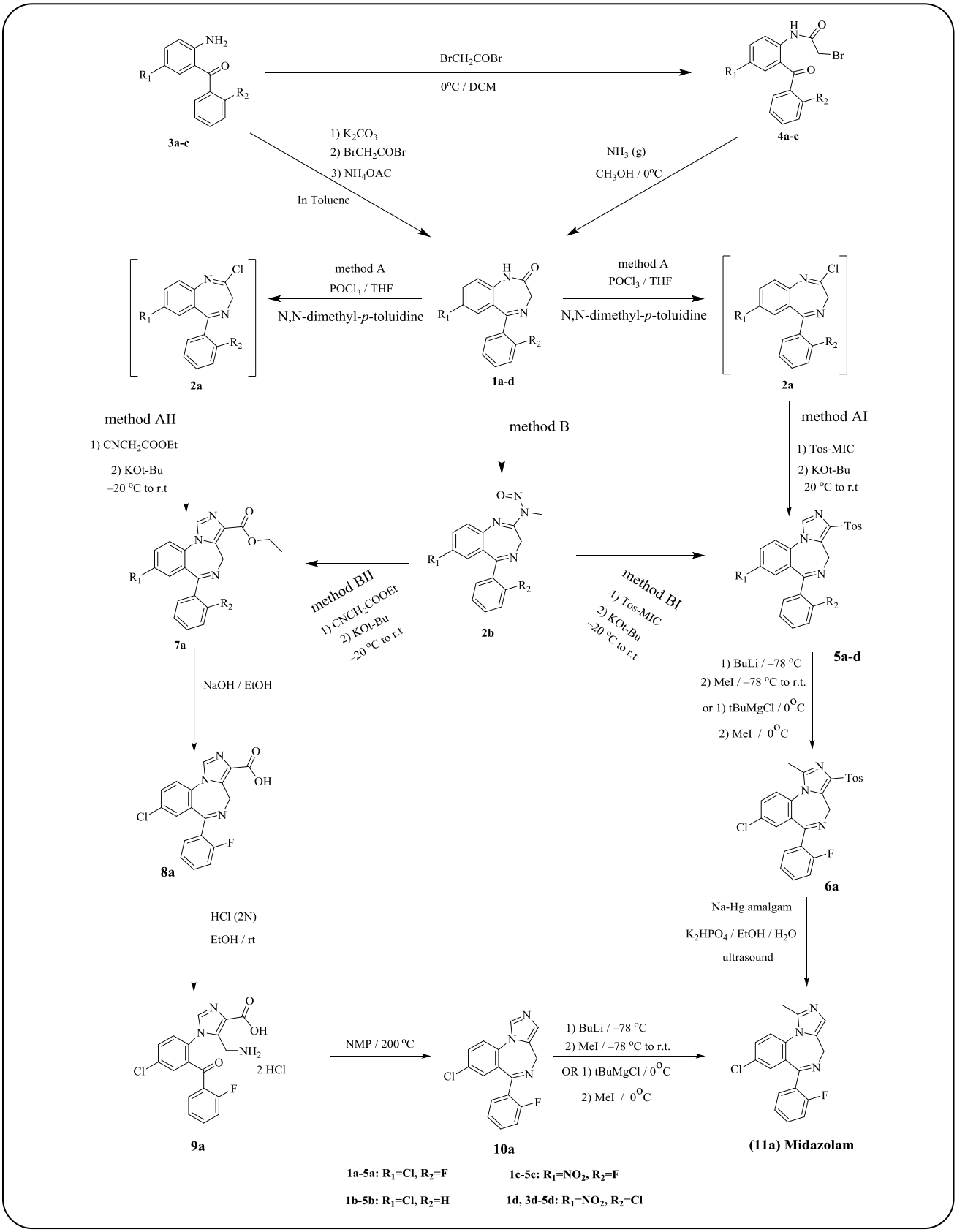
1,4-Benzodiazepinic *N*-nitrosoamidines and imidoyl chlorides are useful intermediates for the synthesis of tricyclic benzodiazepines [26]. Certainly, a one-pot condensation of Tos-MIC with 1,4-benzodiazepinic *N*-nitrosoamidines have been used for synthesis of midazolam drug and 3-(4-tosyl)imidazo[1,5-*a*][1,4]benzodiazepines [27]. The possibility of synthesizing imidazobenzodiazepines by using the carbanion of isocyanides with the activated form of benzodiazepines such as imitates, imidoyl halide, monophosphate, and *N*-nitrosoamidines have been reported [28-31]. But the overall yield of these reactions was moderate. Herein, we describe several methods for the synthesis of 6-phenyl-4*H*-benzo[*f*]imidazo [1,5-*a*][1,4]diazepine (5a-d, 7-11a, 6a; Scheme 2) from the reaction of imidoyl chlorides and 1,4-benzodiazepine *N*-nitrosoamidines with isocyanide reagents, which some of these methods are new and not yet described in the literature. In addition, these methodologies have been used for the synthesis of midazolam and tricyclic benzodiazepines and their ambiguities. Purification was resolved and the most economical and technically most feasible synthesis is pointed out.

RESULT AND DISCUSSION

The purpose of this investigation was to develop a more economical and technically feasible method for the synthesis of the midazolam drug. In this regard, all methods for the synthesis of tricyclic benzodiazepines were investigated. We have developed several alternative pathways for midazolam synthesis, in which the multi-step synthesis via 1,4-benzodiazepin-2-ones **1** demonstrated the best yield for production on a technical scale. All methods accomplished for the synthesis of midazolam are shown below (Scheme 2).

There are several methods for the synthesis of 1,4-benzodiazepines that have been reported in the literature. With the use of (**3**) as starting material by the conventional ways 2-(2-bromoacetamido)-5-chloro-2′-flourobenzophenone (**4**) was synthesized [32–36], which was cyclized with methanolic ammonia. From a chemical point of view, cyclocondensation of amido benzophenone (**4**) with ammonia generated *in-situ* is the most reported method for this goal. Notably, one-pot synthesis is an efficient strategy to improve the yield of the synthesis of 1,4-benzodiazepin. In addition, the use of an alkali such as potassium carbonate can greatly increase the yield of the primary amide synthesis. The use of ammonium acetate in an aprotic solvent can be a method feasible for the amination and cyclization step [37].

In the next step construction of the imidazole ring fused to the 1,2 position of the benzodiazepine nucleus must be performed. Preparation of imidazole ring on benzodiazepine nucleus involves a multistep process and has a complex chemistry. The synthesis of this imidazole ring was facilitated via the transformation of secondary amides of benzodiazepine to a leaving group then a carbon-carbon bond forming reaction on position 2 with carbanion must be performed. Several benzodiazepine intermediates such as amidines, *N*-nitrosoamidines [38], imidoyl halides [39-41], thioamides [42, 43], monophosphates [44], have been reported for the preparation of tricyclic benzodiazepines.

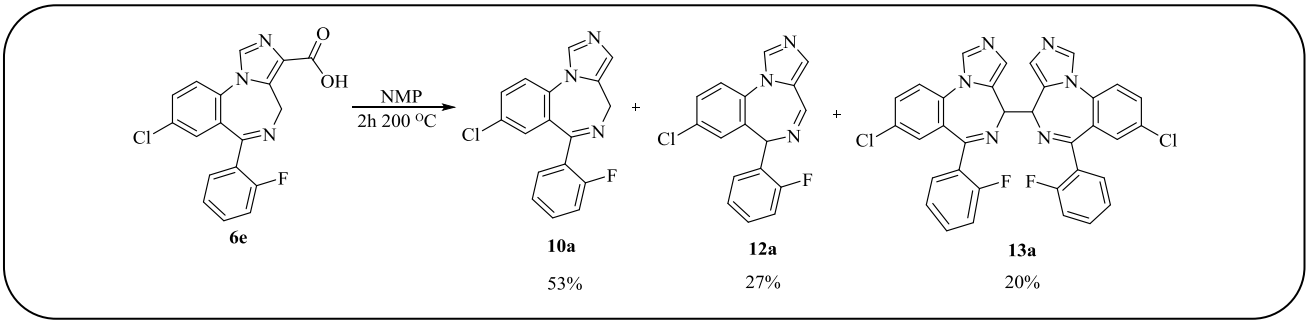


Scheme 2: Synthesis of midazolam.

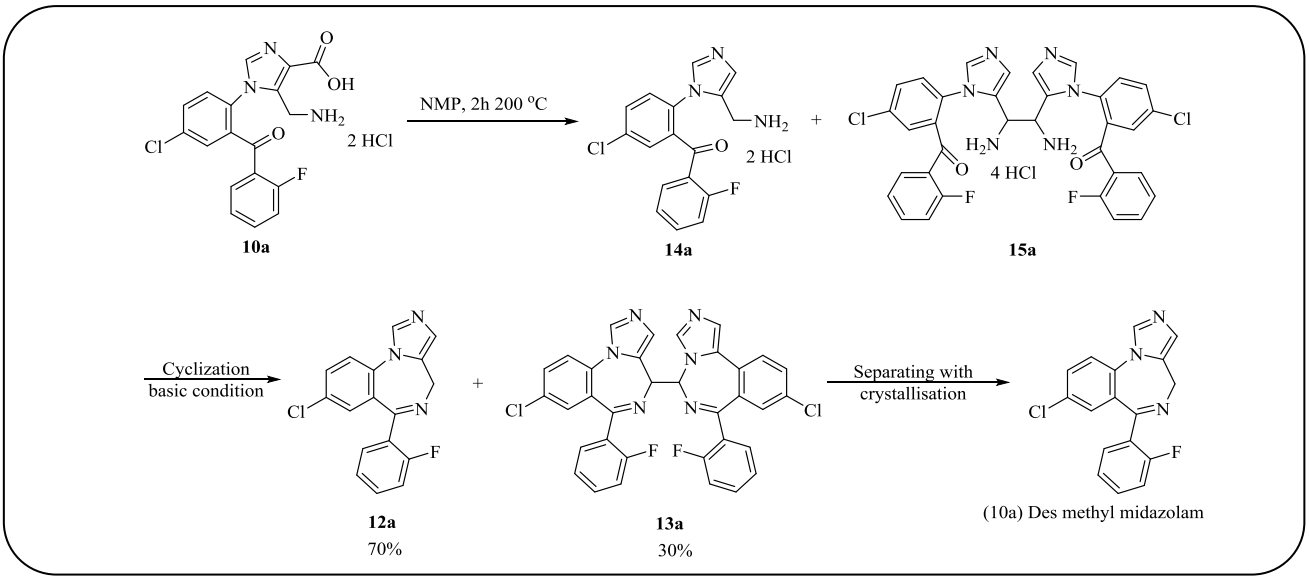
In this paper, we described the reaction of some imidoyl chlorides (**a**) or *N*-nitrosoamidines (**b**) which with carbanion for synthesizing imidazobenzodiazepines by a one-pot annulation process. Chlorination of the amide anions with phosphoryl chloride afforded the novel imidoyl chloride **(2a)** which was very prone to hydrolysis in the solution that cannot be separated. These intermediates should be reacted directly to the next step. Iminochloride **(2a)** was prepared by the dropwise addition of an excess of $POCl_3$ to a hot solution (at 100 °C) of the amide **(1)** in the presence of excess *N*,*N*-dimethyl-*p*-toluidine. The resulting dark red solution was evaporated. The residue was dissolved in dry THF and used directly in the subsequent step.

Moreover, *N*-nitrosoamidines were successfully employed for the construction of imidazobenzodiazepines. *N*-nitrosoamidines **(2b)** could be synthesized by the sequence of steps described in the literature [45]. Amides **(1)** were converted into the corresponding thioamides by reaction with phosphorus pentasulfide. The reaction of these thioamides with methylamine obtained the amidine counterparts, which were converted into the desired starting materials by nitrosation with sodium nitrite in acetic acid [46]. As part of a program directed toward the development of relevant midazolam, the construction of the imidazo ring was considered a crucial step for the synthesis of gram quantities of imidazobenzodiazepine analogs. We have found that imidazo ring can be prepared in a simple procedure by reacting N-nitrosoamidines or iminochloride with potassium *tert*-butoxide and isocyanide reagents, in that order, in the same reaction vessel. Compound **(5)** and **(7)** was readily isolable in 60-70% yield. Isocyanide reactions include tosylmethyl isocyanide (Tos-MIC) and ethyl isocyanoacetate. The one-pot imidazo-annulation of benzodiazepine with isocyanide had been reported in the literature [47-50]. Certainly, we proposed for the first time the use of imidoyl chloride as a user interface for the synthesis of midazolam. In this research, we presented a relatively new method for the synthesis of imidazole ring through the reaction of *N*-nitrosoamidine with ethyl isocyanoacetate in the presence of potassium *tert*-butoxide. Also, we provide a series of simple methods for removing impurities and by-product, which results in the scalable production of this compound. In this research, two improved and scalable methods for the synthesis of midazolam have been described. In method **A**, *in situ* condensation with carbanion of Tos-MIC or ethyl isocyanoacetate gives entry to imidazobenzodiazepines. After the formation of the intermediate of imidoyl chloride, isocyanides were added portion-wise to a solution of iminochloride at -20°C and under argon. Then, potassium *tert*-butoxide (1.1 eq) was added portion-wise to the solution. The synthesized intermediates were purified by washing them with diethyl ether. In method **B**, in an optimized procedure, isocyanides were added portion-wise to a solution of the *N*-nitrosoamidine in THF at –20 ºC. Then, potassium *tert*-butoxide (1.1 eq) was added portion-wise to the solution. This process helps in the formation of the carbanion of ethyl isocyanoacetate or Tos-MIC and the reaction of better with nitrosoamidine and iminochloride to prepare imidazole derivatives. This is the first time that a reaction of N-nitrosoamidines and ethyl isocyanoacetate has been described. In addition, the process enables the construction of tricyclic benzodiazepine derivatives, compounds with potential biological properties. In the methods **AI** and **BI** for the synthesis of midazolam, the reaction of **(5)** with butyllithium at –78 °C followed by the addition of methyl iodide led to the formation of tri-substituted imidazobenzodiazepines **(6)** in good yields. Moreover, butyllithium is very sensitive and difficult-to-handle compared to other bases, its application involved the low temperature for preventing side reactions. An alternative to butyl lithium is, *tert*-butyl magnesium chloride, and it does not have the limitations of working with butyl lithium. It can be freshly prepared and, used at higher temperatures of -20 ° C to 0 ° C. The last step in this method is the elimination of tosyl groups. The most yield of tosyl groups elimination is reported using Na–Hg amalgam and K_2HPO_4 (four equivalents) in a mixture of ethanol-THF (1:1) [28, 29].

In the methods **AII** and **BII** for synthesizing midazolam, hydrolysis of **(7a)** (a basic condition in ethanol, room temperature) led to the synthesis of carboxylic acid **(8a)** in good yields [29, 30]. For the ethyl ester moiety on the imidazole ring hydrolysis, the use of an excessive amount of alkali is essential. After completing the reaction, ethanol was removed under reduced pressure and the solution was allowed to cool then the pH value was adjusted to 4 by adding 1 N HCl dropwise. Finally, the product was purified using diethyl ether. The next step in the synthesis of midazolam is thermal decarboxylation of 8-chloro-6-(2- fluorophenyl)-4*H*-benzo[f]imidazo



Scheme 3: Synthesis of desmethyl midazolam.



Scheme 4: Synthesis and purification of desmethyl midazolam.

[1,5-*a*][1,4]diazepine-3-carboxylic acid (tricyclic acid) **(8a)** [31]. The thermal decarboxylation reaction in high boiling point solvent such as *N*-methyl pyrrolidone (NMP), at 200 ° C for 2 hr results in a mixture of products of desmethyl midazolam **(10a)** and of isomer impurity **(12a)** and dimer product **(13a**) at a 53:27:20 ratio (Scheme 3). The three products are separated by column chromatography [51]. This method is impractical for large-scale preparation of midazolam, because of the costly chromatography equipment required. The reaction mixture obtained from the thermal decarboxylation under alkaline ambiances such as potassium hydroxide or potassium tert-butoxide in methanol followed by an acidic ambiance provides a mixture of desmethyl midazolam and *iso*-desmethyl midazolam at a ratio 75:5. The final removal of the impurities from the product occurs through crystallization of the product in ethyl acetate and hexane solvents.

A suitable method to avoid the formation of isomer impurity is the conversion of intermediate (**8a**) to its salt. In fact, the decarboxylation reaction of the compound (**9a**) allows for avoiding the formation of the isomer impurity (**12a**). The cyclization reaction of the compound (**14a**) can be accomplished by decarboxylation with an alkaline solution or directly with a base. The final removal of the dimer impurities (**13a**) from the product occurs through crystallization of the product in ethyl acetate/heptane. Acid hydrolysis of the derivative (**8a**) can be performed by dissolving an inorganic acid in the presence of alcohol at ambient temperature. The last step for the synthesis of midazolam **(11a)** is methylation at position 2 of the imidazole ring which can be completed with n-butyl lithium at –78 °C or *tert*-butyl magnesium chloride at 0 °C followed by the addition of methyl iodide in excellent yield (Scheme 4).

EXPERIMENTAL SECTOIN

General

All the chemical material was used as purchased (Merck) for the reactions without further purification. All the organic solvents were purchased from commercial suppliers and were purified according to standard procedures. Infrared spectra were obtained using a Perkin–Elmer Spectrom-100 FT-IR spectrometer. IR spectra of liquids were recorded as thin films on NaCl plates. The ^{1}H NMR and ^{13}C NMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 250 and 62.5 MHz, respectively. Mass spectra were recorded on Agilent Technologies, Model: 5975C VL MSD by EI mass spectrometry on a Q-TOF instrument. Thin-layer chromatography was carried out on silica gel 60 F-254 TLC plates of 20 cm × 20 cm. Column chromatography was accomplished using Merck Silica gel 60 (0.063–0.200 mm). Elemental analysis on C, H, and N was accomplished using a Perkin-Elmer 2400 Elemental Analyzer.

2-Bromo-N-(4-chloro-2-(2-fluorobenzoyl)phenyl) acetamide (4a)

To a solution of (2-amino-5-chlorophenyl)(2-fluorophenyl)methanone **3a** (0.15 g, 0.6 mmol) in dry CH_2Cl_2 (10 mL) at 0 °C was added dropwise bromoacetyl bromide (0.12 mL, 2.3 mmol). After stirring the mixture at 0 °C for 4 h, the reaction solution was quenched with ammonia solution 5% (30 mL) and extracted with CH_2Cl_2 (2 ×25 mL). The combined organic layers were dried over $MgSO_4$, concentrated in a vacuum, and the white product was washed with diethyl ether and cold methanol for further purification. Yield: 0.2 g (0.54 mmol, 90%); pale white solid. Mp 131–133 °C, IR (ν_{max}, KBr): 1648, 1690 cm^{-1} 2(C=O), 3014 cm^{-1} (-CH_2), 3387 cm^{-1} (N-H). ^{1}H NMR (250 MHz, $CDCl_3$, δppm): 4.24 (s, 2H), 7.17-7.35 (m, 2H), 7.49-7.64 (m, 4H), 8.72 (d, *J*=7.5 Hz, 1H), 11.96 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm): 43.2, 116.5, 116.8, 122.5, 124.6, 124.7, 124.9, 126.5, 126.7, 128.6, 130.5, 130.6, 133.1, 133.1, 133.9, 134.1, 135.0, 138.2, 157.6, 161.6, 165.7, 195.5.

7-Chloro-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepin- 2-one (4b)

This product was prepared from **3b** according to the general procedure described above. Yield: 0.324 g (0.92 mmol, 92%); pale yellow solid. Mp 100–102 °C, IR: (ν_{max}, KBr): 1629, 1680 cm^{-1} 2(C=O), 3018 cm^{-1} (-CH_2), 3221 cm^{-1} (N-H). ^{1}H NMR (250 MHz, $CDCl_3$, δppm): 4.03 (s, 2H), 7.50-7.56 (m, 4H), 7.63-7.69 (m, 1H), 7.73-7.76 (m, 2H), 8.56-8.60 (d, *J*=10.0 Hz, 1H), 11.33 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm): 29.5, 123.1, 125.5, 128.4, 128.7, 130.1, 132.7, 133.2, 133.9, 137.6, 137.9, 165.1, 197.9.

2-Bromo-N-(2-(2-fluorobenzoyl)-4-nitrophenyl) acetamide (4c)

To a solution of (2-amino-5-nitrophenyl)(2-fluorophenyl)methanone **3c** (0.52 g, 2 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise chloroacetyl chloride (0.63 mL, 8mmol). After stirring the mixture at 0 °C for 2 h, the reaction mixture was warmed to room temperature and stirred for 10 h. After this time, the reaction solution was quenched with ammonia solution 5% (30 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried over $MgSO_4$, concentrated in a vacuum, and the white product was washed with cold methanol for further purification. Yield: 0.639 g (1.9 mmol, 95%); white solid. Mp 160–162 °C, IR (ν_{max}, KBr): 768 cm^{-1} (C-Cl), 1345, 1510 cm^{-1} (-NO_2), 1642, 1692 cm^{-1} 2(C=O), 3215 cm^{-1} (N-H). ^{1}H NMR (250 MHz, $CDCl_3$, δppm): 4.08 (s, 2H), 7.19-7.38 (m, 2H), 7.55-7.66 (m, 2H), 8.43-8.46 (m, 2H), 8.93-8.97 (d, 1H), 12.16 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δppm): 43.2, 116.6, 116.9, 121.2, 123.1, 125.0, 125.1, 125.8, 126.0, 127.5, 129.0, 129.1, 129.8, 130.6, 130.7, 134.2, 134.6, 134.8, 142.4, 144.6, 157.6, 161.6, 166.2, 195.2.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-benzo[e][1,4] diazepin-2-one (1a)

A solution of 2-bromo-*N*-(4-chloro-2-(2-fluorobenzoyl) phenyl) acetamide **4a** (0.370 g, 1 mmol) in methanol (20 mL) was cooled to 0 °C with stirring. A moderate current of *in situ* formed ammonia gas is bubbled through the solution (500–600 mL. per minute), for 2 h longer (over a 2 h period), then the reaction mixture was stirred for 2h at room temperature. The solvent was evaporated under a vacuum to produce a combined organic layer as a yellow-white solid. This combined organic layer was washed with cool toluene for further purification. Yield: 0.202 g (0.7 mmol, 70%); white solid. Mp 204–206 °C, IR (ν_{max}, KBr): 1614 cm^{-1} (C=N), 1688 cm^{-1}

(C=O), 2967 cm^{-1} (-CH_2), 3184 cm^{-1} (N-H). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 4.40 (s, 2H), 7.06-7.30 (m, 4H), 7.44-750 (m, 2H), 7.57-7.63 (m, 1H), 9.68 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 56.7, 116.2, 116.5, 122.9, 124.4, 124.5, 127.1, 127.3, 129.2, 129.3, 129.4, 131.5, 131.5, 132.1, 132.3, 132.4, 136.5, 158.4, 162.5, 166.8, 171.6. Anal. Calcd for $C_{15}H_{10}ClFN_2O$: C, 62.40; H, 3.49; N, 9.70. Found: C, 61.52; H, 3.28; N, 9.90.

7-Chloro-5-phenyl-1,3-dihydro-2H-benzo[e][1,4]diazepin- 2-one (1b)

This product was prepared from **4b** according to the general procedure described above to afford after washing cool toluene for further purification. Yield: 0.332 g (1.23 mmol, 82 %); pale yellow solid. Mp 195–197 °C, IR (ν_{max}, KBr): 702 cm^{-1} (C-Cl), 1680 cm^{-1} (C=O), 2958 cm^{-1} (CH_2), 3105 cm^{-1} (N-H). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 4.25 (s, 2H), 7.14-7.22 (m, 3H), 7.33-7.47 (m, 5H), 10.14 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 56.6, 122.9, 128.5, 128.8, 129.7, 130.7, 130.8, 131.9, 137.5, 138.7, 170.1, 172.1.

7-Chloro-5-(2-fluorophenyl)-1,3-dihydro-2H- benzo[e][1,4] diazepin-2-one (1a); one pot reaction

To a vigorously stirred of (2-amino-5-chlorophenyl)(2-fluorophenyl)methanone **1a** (1.00 g, 4 mmol) in dry toluene (20 mL) at 0 °C was added portion wise K_2CO_3 (1.66 g, 12 mmol). After stirring the mixture at 0 °C for 30 min, bromoacetyl bromide (0.7 mL, 8 mmol) was added dropwise at 0 °C and stirred for 4h at room temperature and the progress of the reaction was monitored by TLC. After completion of the reaction, NH_4OAc (0.92 g, 12 mmol) was added to the mixture at room temperature and stirred in reflux condition for 2.5 h. When the reaction was completed, as was shown by TLC, the mixture was washed twice with 30 mL sodium chloride saturation solution and washed with water (30mL) then dried with sodium sulfate and evaporated under vacuum.

Iminochloride (2); General Procedure

Amidobenzodiazepine (1 mmol) and *N*,*N*-dimethyl-*p*-toluidine (2 mmol) were mixed in toluene and heated to 100 °C. Then, $POCl_3$ (1.1 mmol) was added dropwise and heated at 100 °C for 2.5 h. The resulting dark red solution was evaporated to dryness and the residue re-dissolved in dry THF and used directly in the subsequent step. The desired product **2** was obtained in good yields. Iminochlorides are unstable, and as a result, proved difficult to analyze.

Tosyl imidazo [1,5-a][1,4]benzodiazepines (5); General Procedure

The Iminochloride solution obtained from the previous step was cooled to –20 °C and Tos-MIC (1.1 mmol) was added portionwise, followed by the addition of *t*-BuOK (1.21 mmol). The resulting solution was stirred at 25°C for 4 h. Then, the reaction mixture was quenched with sat.aq $NaHCO_3$ (30 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was added with Et_2O (50 mL). The suspension was stirred at 25°C for 10 min and the resultant precipitate was filtered and washed with Et_2O (50 mL). The desired product **5** was obtained in good yields. (Overall yield 70-85%)

8-Chloro-6-(2-fluorophenyl)-3-tosyl-4H-benzo[f]imidazo [1,5-a][1,4]diazepine (5a): Method AI

7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2*H*-benzo[*e*][1,4]diazepin-2-one (2.03 g, 7 mmol) and *N*,*N*-dimethyl-*p*-toluidine (2.02 mL, 14 mmol) were mixed in toluene (20 mL) and heated to 100 °C. Then $POCl_3$ (0.72 mL, 7.7 mmol) was added dropwise and heated at 100 °C for 2.5 h. The resulting dark red solution was evaporated to dryness and the residue re-dissolved in THF (30 mL) and used directly in the subsequent step. The resulting solution was cooled to –20 °C and Tos-MIC (1.5 g, 7.7 mmol) was added portion wise, followed by the addition of *t*-BuOK (0.951 g, 8.47 mmol). The resulting red-brown solution was stirred at room temperature for 4 h. Then, the resultant light yellow reaction solution was quenched with sat.aq $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was treated with Et_2O (30 mL). The suspension was stirred at 25°C for 5 min and the resultant precipitate was filtered and washed with Et_2O (50 mL). The desired light yellow-white product **5a** was obtained with an overall yield of 60%. Mp: 250–253 °C. IR (ν_{max}, KBr): 612 cm^{-1} (C-Cl), 1148, 1305 cm^{-1} (SO_2), 1487, 1614 cm^{-1} (C=C arom) 1633 cm^{-1} (C=N), 2924 cm^{-1} (-CH_2-). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 2.37 (s, 3 H), 4.12 (br s, 1 H), 6.13 (br s, 1 H), 7.02 (t, *J*=7.5 Hz, 1 H), 7.24–7.31 (m, 4 H), 7.48–7.52 (m, 2 H), 7.60–7.70 (m, 2 H),

7.93–8.02 (m, 3 H). ^{13}C NMR (62.5 MHz, $CDCl_3$): 21.6, 44.3, 116.0, 116.4, 124.5, 124.6, 127.2, 127.4, 127.9, 129.8, 130.2, 130.4, 131.4, 132.4, 132.6, 133.9, 135.3, 136.2, 137.2, 138.1, 144.3, 158.1, 162.1, 165.2. Anal. Calcd for $C_{24}H_{17}ClFN_3O_2S$: C, 61.87; H, 3.68; N, 9.02. Found: C, 61.67; H, 3.67; N, 9.20.

8-Chloro-6-phenyl-3-tosyl-4H-benzo[f]imidazo [1,5-a][1,4]diazepine (5b)

This product was prepared from **1b** according to the general procedure described above to afford after washing with diethyl ether (50% hexanes–EtOAc). Yield: 0.632 g (1.41mmol, 80%); yellow-orange solid. Mp: 157–159 °C. IR (ν_{max}, KBr): 609 cm^{-1} (C-Cl), 1145, 1324 cm^{-1} (SO_2), 1489, 1611 cm^{-1} (C=C arom). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 2.31 (s, 3 H), 3.99 (d, *J* = 12.9 Hz, 1 H), 6.07 (d, *J* = 12.9 Hz, 1 H), 7.22 (d, *J* = 7.5 Hz, 2 H), 7.29–7.45 (m, 7 H), 7.55–7.59 (m, 1 H), 7.83 (s, 1 H), 7.93 (d, *J*= 8.0 Hz, 2 H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 21.6, 44.3, 124.4, 128.0, 128.4, 129.4, 129.5, 129.8, 130.8, 131.9, 132.4, 133.6, 135.1, 136.7, 138.0, 138.9, 144.3, 168.2.

8- Nitro -6-(2-fluorophenyl)-3-(4-toluenesulfonyl)-4H-imidazo [1,5-a][1,4]benzodiazepine (5c)

This product was prepared from **1c** according to the general procedure described above to afford after chromatography separation (50% hexanes–EtOAc). Yield: 0.345 g (0.72 mmol, 62%); pale yellow-orange solid. Mp: 225–228 °C. IR (ν_{max}, KBr): 1155, 1321 cm^{-1} (SO_2), 1354, 1532 cm^{-1} (NO_2). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 2.39 (s, 3 H), 4.13 (br s, 1 H), 6.24 (br s, 1 H), 6.98–7.05 (t, *J*=7.5 Hz, 1 H), 7.23–7.34 (m, 3 H), 7.50–7.55 (dd, 1 H), 7.74–7.78 (d , 2 H), 7.98–8.02 (d, 3 H), 8.22 (s, 1 H), 8.47–8.51 (d, 1H), ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 21.7, 44.3, 116.2, 116.5, 124.2, 124.9, 126.1, 126.5, 126.7, 126.9, 128.1, 129.9, 130.1, 131.5, 133.1, 133.2, 135.3, 136.1, 137.6, 138.2, 144.6, 146.3, 158.1, 162.1, 164.7.

8- Nitro -6-(2-chlorophenyl)-3-(4-toluenesulfonyl)-4H-imidazo [1,5-a][1,4]benzodiazepine (5d)

t-BuOK (0.246 g, 2.2 mmol) was added portion wise to a stirred solution of clonazepam **1d** (0.631 g, 2 mmol) in dry THF (40 mL) at 0 °C. After 20 min, the mixture was cooled to –20 °C with stirring, then diethyl chlorophosphate (0.404 mL, 2.8 mmol) was added dropwise over 5 min. After stirring this mixture at 0 °C for 30 min, the resulting yellow solution was cooled to –20 °C, and Tos-MIC (0.429 g, 2.2 mmol) was added portion wise, followed by the addition of *t*-BuOK (0.271 g, 2.42 mmol). The resulting red-brown solution was stirred at room temperature for 4 h. Then, the resultant light yellow reaction solution was quenched with sat.aq $NaHCO_3$ (150 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was concentrated in a vacuum and the resulting dark brown solid residue was dissolved in Et_2O (30 mL) and the resultant solution was filtered from viscose residue. The organic phases were dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was chromatographed to afford the desired orange product **5d** with an overall yield of 85%. Mp: 145–147 °C. IR (ν_{max}, KBr): 609 cm^{-1} (C-Cl), 1145, 1330 cm^{-1} (SO_2), 1348, 1486 cm^{-1} (NO_2), 2922 cm^{-1} (CH_3). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 2.41 (s, 3 H), 4.17 (br s, 1 H), 6.24 (br s, 1 H), 7.27–7.35 (m, 3 H), 7.45–7.49 (m, 2 H), 7.67–7.70 (m, 1 H), 7.73–7.77 (d , 1 H), 7.99–8.07 (m, 4 H), 8.46–8.51 (dd, 1 H), ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 21.7, 44.3, 124.0, 125.8, 126.9, 127.6, 128.1, 129.9, 130.0, 130.3, 131.3, 131.8, 132.3, 135.2, 136.1, 137.7, 138.9, 144.6, 146.3, 167.4.

1,4-Benzodiazepinic N-Nitrosoamidine

N-(7-Chloro-5-(2-fluorophenyl)-3H-benzo[e][1,4] diazepin-2-yl)-N-methylformamide (2b)

To a solution of amide **1a** (5.00 g, 17.32 mmol) in anhydrous acetonitrile (50 mL), phosphorus pentasulfide (7.7 g, 17.32 mmol), and $NaHCO_3$ (8.73 g, 103.91 mmol) were added, and the mixture was heated under reflux for 18 h and cooled to room temperature. Then, distilled H_2O was added (50 mL) and the resultant solution was stirred for 3 h. The solid was filtered, washed with distilled H_2O (2 × 30 mL), and dried under vacuum. The solid was dissolved in acetonitrile (100 mL) and methylamine (25 mL, 40% aq solution) was added dropwise at room temperature. The solution was stirred for 3 h, then, distilled H_2O (150 mL) was added to the reaction mixture. The solid was filtered, washed with more H_2O, and dried under a vacuum. To a solution of the aforementioned solid in acetic acid (25 mL), sodium nitrite (2.39 g, 34.64 mmol) was added in portions over 30 min and the reaction mixture was stirred for 3 h at room temperature. The product precipitated in crystalline form by gradually adding H_2O (200 mL). The precipitate was washed with H_2O and dissolved in dichloromethane.

The solution was washed with sat. aq $NaHCO_3$ (50 mL), dried (Na_2SO_4) and concentrated to afford the desired *N*-nitroso amidine **2b**. The resultant solid can be recrystallized in Et_2O–hexane. Yield: 3.05 g (9.25 mmol, 53%); yellow solid. IR (V_{max}, KBr): 1411 cm^{-1} (N=O), 1583 cm^{-1} (C=N). ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 3.35-3.42 (m, 3H), 3.77-3.82 (m, 2H), 6.62-6.65 (m, 3H), 6.70-6.76 (m, 2H), 7.15-7.23 (m, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 28.2, 53.8, 116.2, 116.6, 124.2, 124.3, 125.1, 128.6, 128.7, 129.2, 131.3, 131.8, 131.9, 149.7, 157.3, 162.6, 167.5.

8-Chloro-6-(2-fluorophenyl)-3-tosyl-4H-benzo[f]imidazo [1,5-a][1,4]diazepine (5a): Method BI

To a stirred solution of 1,4-benzodiazepinic *N*-nitrosoamidine (1.00 g, 3 mmol) in dry THF (25 mL) at –20 °C under argon, Tos-MIC (0.65 g, 3.32 mmol) was added portionwise. After a further 5 min, *t*-BuOK (0.41 g, 3.6 mmol) was added portionwise to a solution. After stirring this mixture at –20 °C for 3h, the resulting red-brown solution was stirred at 0 °C for 4 h. Then, the resultant solution was quenched with sat.aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined organic layer was dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was treated with diethyl ether (25 mL). The suspension was stirred at 25°C for 20 min and the resultant precipitate was filtered and washed with Et_2O (25 mL). The desired light yellow-white product **5a** was obtained with an overall yield of 70%.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3-(4-toluenesulfonyl) -4H-imidazo[1,5-a][1,4] benzodiazepine (6a)

To a solution of **5a** (2.00 g, 4.29 mmol) in dry THF (20 mL) at 0 °C, 10 mL *tert*-butyl magnesium chloride solution 4.71 mmol (0.11g Mg and 0.51 mL *tert*-butyl chloride) was added dropwise under argon gas. After stirring the mixture at 0 °C for 30 min, then methyl iodide (0.4 mL, 6.43 mmol) was added dropwise. The resulting black solution was stirred vigorously for 4 h at 0°C. After this time, the resultant green mixture was allowed to warm to room temperature. The solution was stirred at 25 °C overnight. After this time, the resultant light brown reaction solution was quenched with sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum. The resulting solid residue was purified by recrystallized in Et_2O–DCM. The desired white product **6a** obtained with an overall yield of 80% (1.65 g). Mp: 269–271 °C. IR (ν_{max}, Br): 1610 cm^{-1} (SO_2). ^1H NMR (250 MHz, $CDCl_3$, δ ppm): 2.37 (s, 3H), 2.50 (s, 3H), 3.97 (d, *J*=13.0 Hz, 1H), 6.10 (d, *J*=13.0, 1H), 7.01 (m, 1H), 7.27 (m, 4H), 7.37 (d, *J*=7.5 Hz, 1H), 7.46 (m, 1H), 7.58 (d, *J*=7.5 Hz, 1H), 7.72 (m, 1H), 8.01 (d, *J*=7.5 Hz, 2H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 14.1, 21.6, 44.7, 116.0, 116.4, 124.6, 126.0, 128.0, 129.5, 129.7, 131.3, 131.3, 131.3, 132.2, 132.3, 132.5, 132.7, 134.0, 135.2, 137.4, 138.4, 144.0, 145.1, 158.3, 162.3, 165.0.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a][1,4]benzodiazepine; Midazolam (11a)

This product was prepared from **6a** according to the procedure described in the literature [9]. Yield: 0.117 g (0.36 mmol, 72%); yellow solid. Mp 158–160 °C, ^1H NMR (250 MHz, DMSO, δ ppm): 2.85 (s, 3H), 4.22 (d, *J*=13.0 Hz, 1H), 5.27 (d, *J*=13.0 Hz, 1H), 7.29-7.41 (m, 3H), 7.58-7.76 (m, 3H), 7.94 (m, 1H), 8.10 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 13.1, 44.8, 116.1, 116.5, 116.8, 125.0, 127.1, 127.2, 127.8, 129.8, 131.4, 131.9, 132.2, 132.6, 133.1, 133.3, 134.0, 135.4, 145.3, 158.2, 162.2, 164.0. Anal. Calcd for $C_{18}H_{13}ClFN_3$: C, 66.36; H, 4.02; N, 12.90. Found: C, 66.32; H, 4.04; N, 13.01.

Ethyl 8-Chloro-6-(2'-fluorophenyl)-4H-imidazo [1,5-a][1,4]benzodiazepine-3-carboxylate (7a); Method AII

7-chloro-5-(2-fluorophenyl)-1,3-dihydro-2H-benzo[e][1,4]diazepin-2-one (2.03 g, 7 mmol) and *N*,*N*-dimethyl-*p*-toluidine (2.02 mL, 14 mmol) were mixed in toluene (20 mL) and heated to 100 °C. Then $POCl_3$ (0.72 mL, 7.7 mmol) was added dropwise and heated at 100 °C for 2.5 h. The resulting dark red solution was evaporated to dryness and the residue dissolved in THF (30 mL) and cooled to –20 °C and ethyl isocyanoacetate (0.84 mL, 7.73 mmol) was added dropwise, followed by the addition of *t*-BuOK (0.95 g, 8.51 mmol). The reaction mixture was stirred at −20 °C for 1 h. Then, the solution was stirred at room temperature for 4 h. The resultant light yellow reaction solution was quenched with sat.aq $NaHCO_3$ (150 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was treated with Et_2O (30 mL). The suspension was stirred at 25°C for 5 min and the resultant precipitate was filtered,

and washed with Et_2O (50 mL) to give most of the desired tricyclic systems **1a**. The mother liquor was further purified by chromatography on silica gel (40:60 EtOAc: Petroleum ether) to afford the additional product. The desired light yellow-white (pale yellow) product **7a** was obtained with an overall yield of 60% (0.79 g). IR (ν_{max}, KBr): 1563, 1613 cm^{-1} 2(C=N), 2928, 2960 cm^{-1} (-C_2H_5) 1722 cm^{-1} (C=O). ^{1}H NMR (250 MHz, $CDCl_3$, δ ppm): 1.34 (t, *J*=7.5 Hz, 3H), 4.03 (br s, 1H), 4.33 (q, *J*=7.5 Hz, 2H), 6.05 (br s,1H), 6.94 (m, 1H), 7.14-7.25 (m, 2H), 7.34-7.47 (m, 1H), 7.50-7.59 (m, 3H), 7.89 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 14.5, 45.0, 60.8, 116.1, 116.4, 124.0, 124.6, 124.6, 128.8, 129.5, 130.3, 131.3, 132.2, 132.4, 132.5, 132.9, 133.6, 134.4, 138.3, 158.2, 162.2, 162.9, 165.1. Anal. Calcd for $C_{20}H_{15}ClFN_3O_2$: C, 62.59; H, 3.94; N, 10.95. Found: C, 61.40; H, 3.70; N, 10.99.

Ethyl 8-Chloro-6-(2'-fluorophenyl)-4H-imidazo [1,5-a][1,4]benzodiazepine-3-carboxylate (7a); Method BII

To a stirred solution of 1,4-benzodiazepinic *N*-nitrosoamidine **2b** (1.00 g, 3 mmol) in dry THF (25 mL) at –20 °C under argon, ethyl isocyanoacetate (0.36 mL, 3.33 mmol) was added dropwise, followed by the addition of *t*-BuOK (0.41 g, 3.66 mmol). The reaction mixture was stirred at −20 °C for 1 h. Then, the solution was stirred at room temperature for 4 h. The resultant light yellow reaction solution was quenched with sat.aq $NaHCO_3$ (50 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum and the resulting solid residue was treated with diethyl ether (30 mL). The suspension was stirred at 25°C for 5 min and the resultant precipitate was filtered and washed with Et_2O (20 mL) to give most of the desired tricyclic systems **2b**. The mother liquor was further purified by chromatography on silica gel (40:60 EtOAc: Petroleum ether) to afford the additional product. The desired light yellow-white (pale yellow) product **7a** was obtained with an overall yield of 73% (0.85 g).

8-Chloro -6-(2'-fluorophenyl)-4H-imidazo [1,5-a][1,4] benzodiazepine-3-carboxylic acid (8a)

The synthesized ester **7a** (1.00 g, 2.6 mmol) from the previous step was dissolved in EtOH (80 mL) and 2 N aq NaOH (8 mL) was added dropwise to the solution. The reaction mixture was stirred at 25°C for 4 hours. The solvent evaporated and dried under reduced pressure. This solid residue was cooled to 0 °C. The mixture was adjusted at the same temperature to *PH*=4 by the dropwise addition of a solution of 1 N HCl. The resultant precipitate was filtered under vacuum and dried at room temperature. The precipitate was crushed and then suspended in diethyl ether (100 mL). After stirring at 0 °C for 1 h, the mixture was filtered under a vacuum. The solid was dried to afford **6e** as a yellow solid with an overall yield of 98% (0.906 g). IR (ν_{max}, KBr): 1611 cm^{-1} (C=O), 2400-3550 cm^{-1} (O-H). ^{1}H NMR (250 MHz, $CDCl_3$, □ ppm): 4.12 (br s, 1H), 6.09 (br s, 1H), 7.05 (m, 1H), 7.30 (m, 2H), 7.50 (m, 1H), 7.66 (m, 2H), 8.08 (m, 1H), 8.98 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 45.1, 116.4, 125.2, 125.9, 127.9, 129.3, 129.8, 130.2, 131.9, 132.3, 132.6, 133.0, 133.5, 136.1, 138.2, 158.0, 160.1, 162.3, 164.5.

5-(Amino methyl)-1-{4-chloro-2-[(2-fluorophenyl) carbonyl] phenyl}-1H-imidazole-4-carboxylic acid dihydrochloride (9a)

The tricyclic acid **6e** (1.00 g, 2.81 mmol) from the previous step was dissolved in EtOH (80 mL) at room temperature and an aqueous solution of 2 M HCl (8 mL) was added dropwise to the solution. The ring closure dihydrochloride intermediate precipitated from the reaction mixture after the addition of the acid solution. The reaction mixture was stirred for 4 hours. The resultant salt was filtered under a vacuum and washed with cold ethanol (3 × 20 mL). The solid was dried to afford **7e** as a light yellow product with an overall yield of 83% (1.04 g).

8-Chloro -6-(2-fluorophenyl) -4H-imidazo [1,5-a][1,4] benzodiazepine (10a)

The dihydrochloride salt **9a** (3.00 g, 6.72 mmol) from the previous was dissolved in NMP (40 mL) at room temperature. The reaction mixture was reflux at 200 °C for 2 h. Then, the reaction mixture was cooled to 25°C. The resulting solution was adjusted to *PH*=11 by the dropwise addition of 10% Na_2CO_3. The solution was extracted with EtOAc (3 × 25 mL) and washed with water (2×40 mL). The final organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to obtain an orange solid. The solid was crystallization in ethyl acetate/heptane (1:1) 20 mL. The solids were isolated by filtration, and washed with ethyl acetate/heptane (1:1), 62% (1.3 g). IR (ν_{max}, KBr): 758 cm^{-1} (C-Cl), 1487, 1606 cm^{-1} (C=C arom), 3080 cm^{-1} (CH arom), ^{1}H NMR (250 MHz,

$CDCl_3$, δ ppm): 4.21 (br s, 1H), 5.22 (br s,1H), 6.98-7.07 (m, 2H), 7.23-7.34 (m, 2H), 7.43 (m, 1H), 7.55-7.62 (m, 3H), 7.97 (s, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$, δ ppm): 45.5, 116.3, 116.5, 123.8, 124.5, 126.2, 127.8, 127.9, 129.8, 130.3, 131.1, 132.0, 132.1, 132.3, 132.5, 133.2, 133.8, 134.7, 158.2, 162.2, 164.4.

8-Chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a][1,4]benzodiazepine; Midazolam (11a)

To a solution of **10a** (2.00 g, 6.42 mmol) in dry THF (20 mL) at 0 °C, 10 mL *tert*-butyl magnesium chloride solution 7 mmol (0.17g Mg and 0.77 mL *tert*-butyl chloride) was added dropwise under argon gas. After stirring the mixture at 0 °C for 30 min, then methyl iodide (0.6 mL, 9.62 mmol) was added dropwise. The resulting black solution was stirred vigorously for 4 h at 0°C. After this time, the resultant green mixture was allowed to warm to room temperature. The solution was then stirred at 25 °C overnight. After this time, the resultant light brown reaction solution was quenched with sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 50 mL). The combined organic phases were dried over Na_2SO_4 and concentrated in a vacuum. The resulting solid residue was treated with Et_2O (30 mL). The suspension was stirred at 25°C for 5 min and the resultant precipitate was filtered and washed with Et_2O (10 mL). The desired white product **11a** was obtained with an overall yield of 90% (1.876 g).

CONCLUSIONS

In this research, two easy and scalable synthetic methods for the production of midazolam drug is presented. The 1,4-benzodiazepines was synthesized with high yield and one-pot reaction. In the next step, 1,4-benzodiazepines *N*-nitrosamines were synthesized with the described method in the literature and imidoyl chlorides intermediate was synthesized using $POCl_3$ in the presence of a *N,N*-dimethyl-*p*-toluidine as a catalyst. One-pot condensation of imidoyl chlorides with mono-anion of ethyl isocyanoacetate or tosylmethyl isocyanide under mild conditions led to the synthesis of imidazobenzodiazepine. In the first method (AI), tosylmethyl isocyanide (Tos-MIC) is used and the number of synthetic steps is decreased in comparison to previous report. In the last step, methylation by using n-butyllithium at –78 °C or *tert*-butyl magnesium chloride at 0°C followed by the addition of methyl iodide, then elimination of tosyl groups using Na–Hg amalgam and K_2HPO_4 obtained the midazolam. In the second method (AII) ethyl isocyanoacetate which is commonly used for the formation of some imidazobenzodiazepines, is consumed to midazolam synthesis. Finally, decarboxylation with alkali solution and alkylation with butyl lithium and methyl iodide obtained midazolam product.

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