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ORIGINAL PAPER

Improved and scalable methods for the synthesis of midazolam drug and its analogues using isocyanide reagents

Mohammad Javad Taghizadeh[1] · Gholam reza malakpouri[1] · Abdollah Javidan[1,2]

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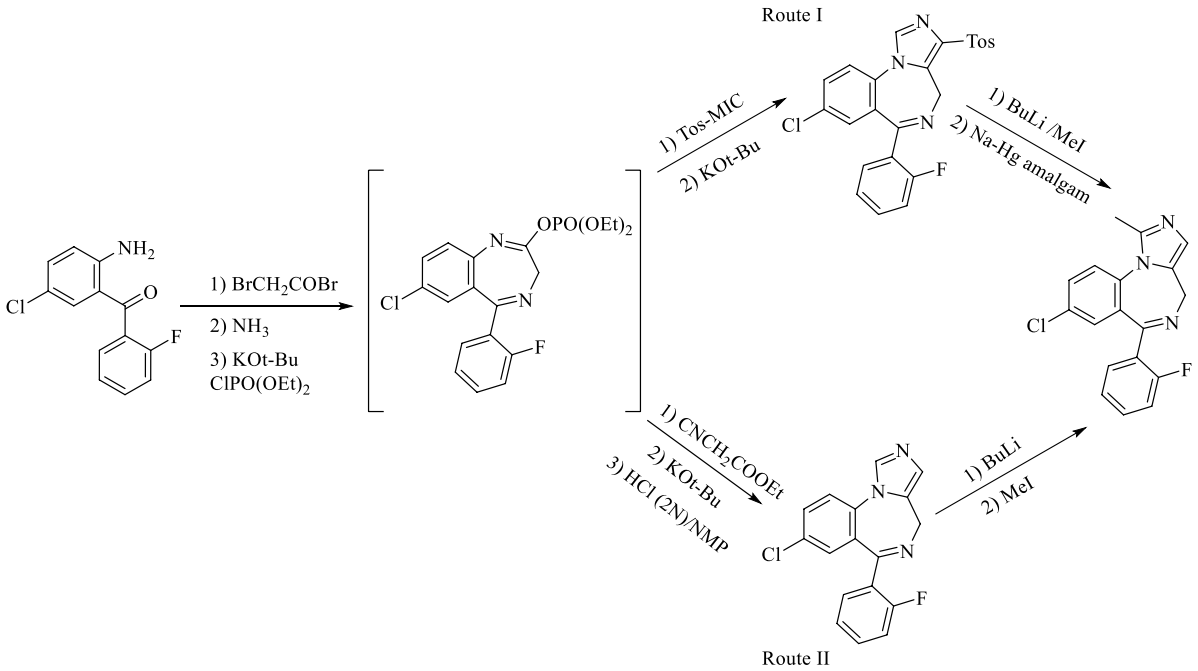
Abstract

In this research, two improved and scalable methods for the synthesis of midazolam and its analogues have been described. Midazolam has been synthesized using isocyanide reagents in satisfactory yield. In this methodology, imidazobenzodiazepine intermediates can be easily prepared via an improved process. One-pot condensation of benzodiazepines with mono-anion of tosylmethyl isocyanide or ethyl isocyanoacetate under mild condition led to formation of imidazobenzodiazepine. In the first method, tosylmethyl isocyanide (Tos-MIC) is used and the number of synthetic steps are decreased in comparison to previous report. In the second method, ethyl isocyanoacetate which is commonly used for the synthesis of some imidazobenzodiazepines, is consumed to generate midazolam. The latter, a relatively different method for the synthesis of midazolam analogues has been reported.

Graphical abstract



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Introduction

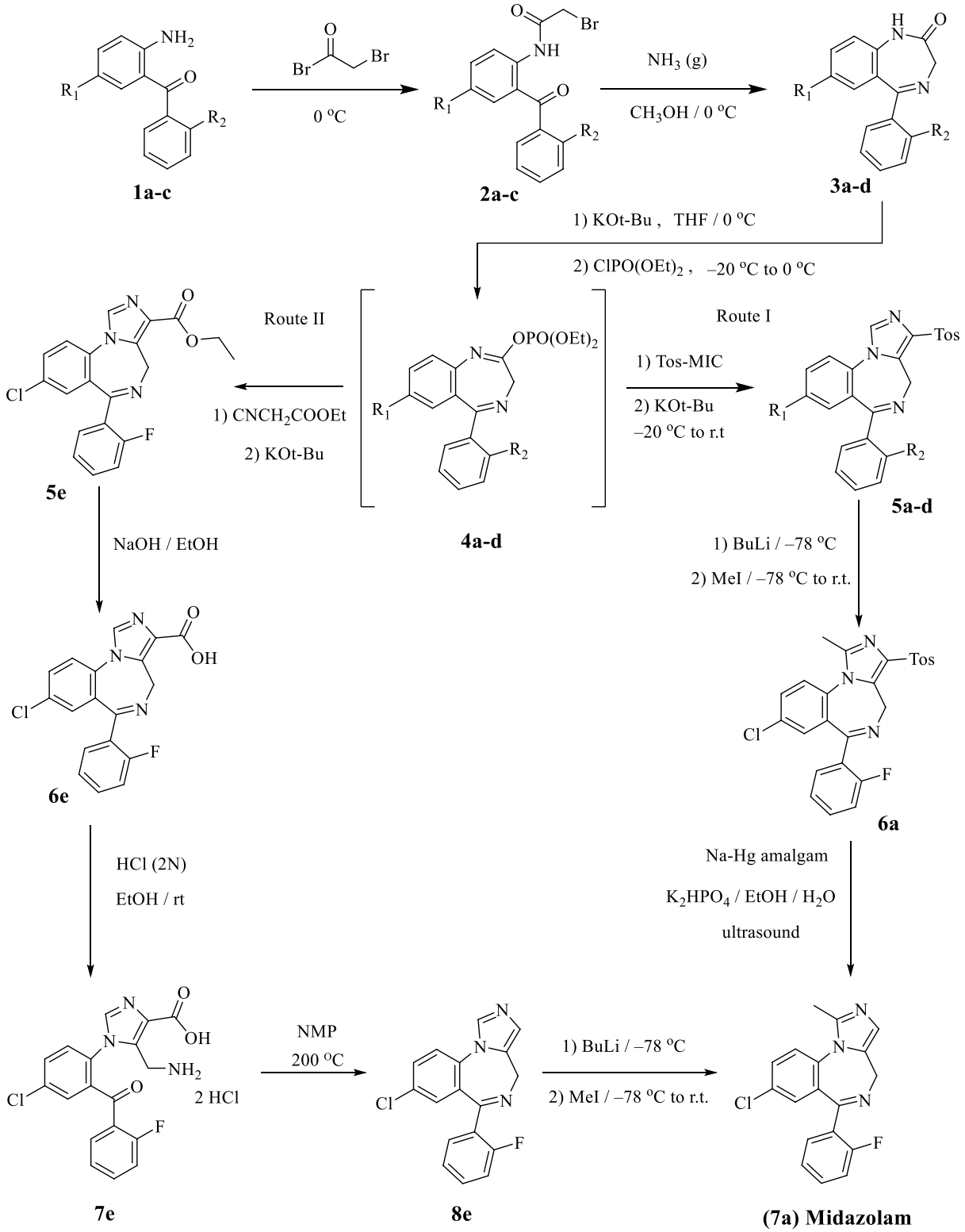
Benzodiazepines (BZDs) and their derivatives belong to a versatile class of biologically active compounds and their synthesis has been receiving much attention in the field of medicinal chemistry [1–6]. Among them the members of 1,4-benzodiazepine family have shown sufficient biological [7, 8] and pharmacological activity [9] to serve as a versatile drug for the treatment of CNS disturbances [10–20]. Moreover, 1,4-benzodiazepines are useful intermediates for the preparation of other fused ring system such as triazolo, imidazo, oxazino, or furano-benzodiazepines [21–27]. For example, imidazobenzodiazepines such as midazolam or climazolam and triazolobenzodiazepines such as alprazolam or triazolam possess pharmacological property.

Midazolam is an imidazobenzodiazepine and excellent medicinal compound that was first synthesized by Fryer and Walser in 1978 [28]. This important drug illustrated various pharmacological properties such as anesthetic, sedative, hypnotic, anticonvulsant, muscle relaxant, and anxiolytic activities. There are several multistep methods for the synthesis of this drug outlined in literature [29–36]. Although, different groups of researcher synthesized this clinical drug, none of these syntheses procedures can be scalable or expose a complex chemistry. The laboratory procedures for synthesis of midazolam have suffered from several problems, such as long reaction pathway, formation of various by-products, difficult separation by chromatography. Moreover, the technical and significant aspect of product purification is not specified. In fact, many of these procedures are not marketable and none of these syntheses are scalable commercially. More synthetic approach for midazolam starts from formation of seven-membered ring. Generally this ring closure accomplished via an intramolecular reaction from the corresponding α-(aminoacetamido)-benzophenone. In addition, the synthesis of the imidazole ring is a challenging step for the synthesis of imidazo[1,5-a][1,4]benzodiazepine family, for achievement to this purpose, several five or six step procedures have been reported in the literature. This step was highly affected the overall yield of these ring formation. The differences in imidazobenzodiazepines synthetic routes lie basically on how one approaches the formation of imidazole nucleus. Notably, the isocyanide reagents have been reported for synthesize of imidazobenzodiazepine structures [37–44]. Most of them have been achieved in low yield or require a multistep method. In some cases, the purification of the intermediates and target products with chromatography was necessary. Certainly, an earlier paper published the application of Tos-MIC for the preparation of midazolam and tricyclic benzodiazepines [45]. It is interesting to note that imidazobenzodiazepines have been manufactured by the reaction of isocyanides with an in situ intermediate formed of the benzodiazepine, preferably the iminophosphate or iminochloride derivatives [37, 46–48]. But the product has been obtained in moderate yields (15–30%). Here, a novel method utilizing two valuable isocyanides for synthesizing midazolam and novel tricyclic benzodiazepines has been described. In this methodology, a one-pot annulation process has been employed using tosylmethyl isocyanide (Tos-MIC) and ethyl isocyanoacetate reagents. This synthetic sequence not yet described in literature.

Results and discussion

In this research, the possibility of synthesizing midazolam via two methods has been considered. Our goal is to illustrate an optimized process that would yield midazolam and its analogues within the shortest sequence and maximum yield. Toward this goal, several patent and literature routes have been investigated and an efficient and simple process for midazolam was devised. The method suggested for the synthesis of midazolam is shown below (Scheme 1).

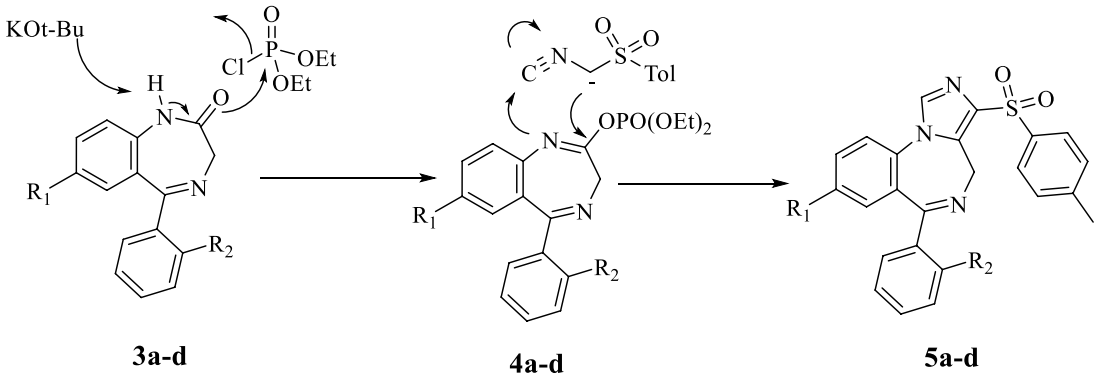
In the first step, the synthesis of benzodiazepine nucleus is described. Benzodiazepine nucleus (**3a**) was synthesized according to a published literature [49–54]. Starting with 2-amino-5-chloro-2′-fluorobenzophenone (**1a**), a commercial available compound, was treated with bromoacetyl bromide in dichloromethane to yield the intermediate, 2-(2-bromoacetamido)-5-chloro-2′-flourobenzophenone (**2a**) in good yield. The cyclization of amide (**2a**) could be carried out in the presence of liquid ammonia, methanolic ammonia, ammonia in a mixture of CH_2Cl_2 and EtOAc, hexamethylenetetramine (HMTA), sodium azide and others. However, formation of 1,4-benzophenone ring is not a clean reaction and several by-products formed. Although cyclization of the aforementioned amide is described in many literatures, the most reported routes for this goal carried out with methanolic ammonia. The utility of ammonia gas led to significant amounts of product. The highest yield was achieved by employing in situ formation of ammonia gas in methanol. Benzophenones (**1a–c**) with different substitution such as Cl, NO_2 in the ring and substitution such as F, Cl in other ring derivatives to the desired 1,4-benzodiazepin-2-one (**3a–c**) in 70–87% yields in this process. In the case of benzophenones with halogen substitution, cyclization of amide intermediates to benzodiazepines (**3a-b**) can be performed with ammonia gas in scale-up amount. However, when this cyclization was employed for amide intermediate with -NO_2 substitution, no cyclized product was observed. The NO_2-substituted



Scheme 1 Synthesis of midazolam

amide (**2c**) reacted with HMTA to give the benzodiazepine (**3c**) with no difficulty in 87% yield. The para-chloro aniline also used as starting material in this study. We have tried to synthesis 2-amino-5-chlorobenzophenone via the acylation of para-chloro aniline with benzoyl chloride by using Friedel–Crafts reaction. Incorporation of the acetyl moiety was accomplished with $ZnCl_2$ as Lewis acid at 195–205 °C. The corresponding benzoyl chloride functions as protecting group and reactant. Initially para-chloroaniline reacts with the benzoyl chloride at low temperature to form an amide, then the temperature was gradually increased to 195–205 °C and nucleophilic attack from the ring electrons to the acyl carbon. In the second step, imidazole ring formation start from insertion of a carbon nucleophile on position 2 of the benzodiazepine. Numerous studies and several stepwise methods for carbon–carbon bond forming on amide group of benzodiazepines have been investigated. For this purpose the secondary amide in the 1,4-benzodiazepine ring must be activated via conversion to an appropriate intermediate such as thioamides [55, 56], N-nitrosoamidines [26, 57], imidoyl halides [39, 58, 59] and others, then the carbon–carbon bond formation of them with carbanion led to generation of target compound. Certainly, the application of Tos-MIC for this goal and preparation of midazolam and tricyclic benzodiazepine had been developed in the literature [48]. In previous research, the carbanion of Tos-MIC has been generated with butyllithium then condensation with 1,4-benzodiazepine *N*-nitrosoamidines gives entry to target imidazobenzodiazepines. However, this process takes some drawbacks, for instance the separation of the product accomplished with chromatography which was critical for large-scale reactions. In addition, the formation of tricyclic benzodiazepine proceeds after four steps from initial benzodiazepine. Moreover, butyllithium is very sensitive and difficult-to-handle compared to other bases, its application involved the low-temperature for prevented side reactions. Furthermore the *N*-nitrosoamidines derivatives are stable intermediates which were prepared after three steps reaction from initial 1, 4-benzodiazepin-2-one. The one-pot imidazo-annulation of benzodiazepine with diethyl chlorophosphate had been reported in the literature [60–62]. All these process accomplished via the reaction of enol phosphonate with ethyl isocyanoacetate in the presence of different bases (NaH, LDA or potassium tert-butoxide). We have focused on improving this one-pot annulation reaction. In these synthetic methods, the condensation of in situ-formed iminophosphate derivatives with carbanion of Tos-MIC or ethyl isocyanoacetate gives entry to imidazobenzodiazepines. For this purpose, the intermediate enol phosphonate generated by reaction of 1,4-benzodiazepin-2-one with diethyl chlorophosphate in the presence of potassium *tert*-butoxide in dry THF at − 20 °C. Then, isocyanides were added portionwise to a solution of enol phosphonate in aforementioned reaction condition. This procedure is carried out more easily compared to previous work [48]. This improved one-pot method required neither the application of the sensitive base butyllithium nor does it require the purification of the products with chromatography. The initial benzodiazepines (**3a**–**d**) were converted in one-step into the midazolam intermediates and its analogues (**5a**–**d**). The mechanism of this reaction is shown in Scheme 2. Moreover, some of the target products were successfully precipitated from diethyl ether (Table 1).

This is the first time that an enol phosphonate and Tos-MIC reagent are used for preparation of the imidazobenzodiazepines family. In route I, at first the monoanion of Tos-MIC is generated by reaction with potassium tert-butoxide in moderate condition. The reaction temperature was kept in − 20 °C and lower temperature was not needed for this process. In addition, potassium tert-butoxide is a mild and safer base that is not used with Tos-MIC for this ring closing. In the next step for synthesizing of midazolam, methylation of compound **5a** carried out with one equivalent of butyl lithium, followed by the addition of methyl iodide. Elimination of the tosyl group on imidazobenzodiazepine **6a** was performed by reaction with Na–Hg amalgam. In the second



Scheme 2 Plausible mechanism for the formation of **5a-d**

Table 1 Preparation of target imidazo[1,5-a][1,4]benzodiazepines

Entry	Product	R_1	R_2	Time (h)	Yield (%)[a]
1	**5a**	Cl	F	5	60
2	**6a**	Cl	F	24	90
3	**7a**	Cl	F	4	72[b]
4	**5e**	Cl	F	6	60
5	**6e**	Cl	F	4	98
6	**7e**	Cl	F	4	83
7	**8e**	Cl	F	2	70
8	**7a**	Cl	F	24	90[c]
9	**5b**	Cl	H	5	80
10	**5c**	NO_2	F	5	62
11	**5d**	NO_2	Cl	5	85

[a]Isolated yield

[b]Yield of **7a** by desulfonylation of **6a** with 10% Na–Hg amalgam

[c]Yield of **7a** after reaction of **8e** with MeI

method (route II), midazolam synthesized using the ethyl isocyanoacetate which is commonly used for the synthesis of some imidazobenzodiazepines. It is a relatively different method in which for the synthesis of midazolam and desmethyl midazolam has been reported. Benzodiazepine nucleus (**3a**) was used as the starting material for this synthetic route. The imidazole ring closure on benzodiazepine is carried out similarly to above modified one-pot reaction. The carbanion of ethyl isocyanoacetate condensed with less stable iminophosphates intermediate to give the target imidazobenzodiazepine framework (**5e**). After workup, the desired imidazo product was precipitated from diethyl ether. The ethyl ester moiety on the imidazole ring hydrolyzes to carboxylic acid via basic condition. Lastly, the process for decarboxylation of the imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic acid was carried out in high boiling solvent such as *N,N*-dimethylacetamide, mineral oil [63]. In another research, decarboxylation of this ligand performed in n-butanol at high pressure and temperature [64]. However, decarboxylation reaction of this compound led to formation of the isomer impurity that affected the yield of the product [65]. In order to prevent the formation of impurity, this problem is overcome by the conversion of intermediate (**6e**) to its salt [66]. Acid hydrolysis of the derivative (**6e**) can be performed by dissolving in an inorganic acid in the presence of alcohol at ambient temperature. The thermal decarboxylation of the salt (**7e**) in NMP to avoid the formation of the isomer impurity and significant percentage of desmethyl midazolam (**8e**) prepared. Finally, methylation at position 2 of the imidazole ring can be proceed with butyllithium at − 78 °C, followed by addition of methyl iodide in excellent yield.

Experimental section

General

All the chemicals were 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 Spectrum-100 FT-IR spectrometer. IR spectra of liquids were recorded as thin films on NaCl plates. The ^{1}HNMR and ^{13}CNMR spectra were determined using TMS as an internal reference with an Avance FT NMR spectrometer operating at 250 and 60 MHz, respectively. Mass spectra were recorded on an 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 were accomplished using a Perkin-Elmer 2400 Elemental Analyzer.

2-(2-Bromoacetamido)-5-chloro-2′-fluorobenzophenone (2a)

To a solution of 2-amino-5-chloro-2′-fluorobenzophenone **1a** (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 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}HNMR (250 MHz, $CDCl_3$, δppm): 4.24 (s, 2H), 7.17–7.35 (m, 2H), 7.49–7.64 (m, 4H), 8.72 (d, 1H, J = 7.5), 11.96 (s, 1H). ^{13}CNMR (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.

2-(2-Bromoacetamido)-5-chlorobenzophenone (2b)

This product was prepared from **1b** 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} (–CH2), 3221 cm^{-1} (N-H). ^{1}HNMR (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, 1H, J = 10), 11.33 (s, 1H). ^{13}CNMR (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-(2-Chloroacetamido)-5-nitro-2′-fluorobenzophenone (2c)

To a solution of 2-amino-5-nitro-2′-fluorobenzophenone **1c** (0.52 g, 2 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C was added dropwise chloroacetyl chloride (0.63 mL, 8 mmol). 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 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}HNMR (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}CNMR (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.

Amidobenzodiazepine: general procedure

A solution of α-(haloacetamido)-benzophenone (1.0 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 heated under reflux overnight and cooled to room temperature. The solvent was removed under vacuum to yield combined organic layers as a yellow-white solid. This combined organic layer was washed with cool toluene for further purification (yields 70–85%).

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

A solution of 2-(2-bromoacetamido)-5-chloro-2′-fluorobenzophenone **2a** (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 heated under reflux overnight and cooled to room temperature. The solvent was evaporated under vacuum to yield combined organic layers 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}HNMR (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}CNMR (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 (3b)

This product was prepared from **2b** 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}HNMR (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}CNMR (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-Nitro-5-(2-fluorophenyl)-1,3-dihydro-2H-benzo[e][1,4]diazepin-2-one (3c)

A mixture of hexamine (0.631 g, 4.5 mmol) and ammonium chloride (0.201 g, 3.75 mmol) in ethanol (50 ml) was heated at 70 °C for 1 h. After this time, the 2-(2-chloroacetamido)-5-nitro-2′-fluorobenzophenone **2c** (0.505 g, 1.5 mmol) was added slowly and the reaction mixture was refluxed for 4 h. The resultant yellow solution was evaporated under vacuum. The solid residue was dissolved in water (40 ml) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over Na_2SO_4 and concentrated to dryness under vacuum. The desired yellow product **3c** obtained in good yield. Yield: 0.391 g (1.3 mmol, 87%); Mp: 200–203 °C. IR (ν_{max}, KBr): 1342, 1534 cm^{-1} (NO_2), 1698 cm^{-1} (C=O), 2925, 2964 cm^{-1} (-CH_2-), 3096 cm^{-1} (N-H). ^{1}HNMR (250 MHz, $CDCl_3$, δ ppm): 4.39 (s, 2H), 6.97–7.04 (t, 1H), 7.20–7.30 (m, 2H), 7.43–7.46 (q, 1H), 7.57–7.63 (t, 1H), 8.07 (s, 1H) 8.24–8.27 (d, 1H), 10.33 (s, 1H). ^{13}CNMR (62.5 MHz, $CDCl_3$, δ ppm): 56.7, 116.3, 116.6, 122.2, 124.8, 124.9, 126.1, 126.4, 126.6, 128.2, 131.5, 133.0, 133.1, 142.5, 143.2, 158.4, 162.4, 166.6, 171.4.

Tosylimidazo[1,5-a][1,4]benzodiazepines (5): general procedure

To a stirred solution of amidobenzodiazepine (1 mmol) in dry THF (20 mL) at 0 °C under argon, *t*-BuOK (1.1 mmol) was

added portionwise. After a further 20 min at 0 °C, the reaction mixture was cooled to − 20 °C with stirring. Diethyl chlorophosphate (1.4 mmol) was added dropwise over 5 min. After stirring this mixture at 0 °C for 30 min, the reaction flask 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 room temperature 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 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, washed with Et_2O (50 mL). The desired product **5** obtained in good yields. (Overall yield 70–85%).

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

t-BuOK (0.86 g, 7.7 mmol) was added portionwise to a solution of amidobenzodiazepine **3a** (2.02 g, 7 mmol) in dry THF (120 mL) at 0 °C under argon. After 20 min at 0 °C, the mixture was cooled to − 20 °C with stirring, then diethyl chlorophosphate (1.41 ml, 9.8 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 (1.5 g, 7.7 mmol) was added portionwise, 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 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, washed with Et_2O (50 mL). The desired light yellow-white product **5a** 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), 6.98–7.05 (m, 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-(4-toluenesulfonyl)-4H-imidaz o[1,5-a][1,4]benzodiazepine (5b)

This product was prepared from **3b** according to the general procedure described above to afford after washing with diethyl ether (50% hexanes–EtOAc). Yield: 0.632 g (1.41 mmol, 80%); yellow-orange solid. Mp: 157–159 °C. IR (ν_{max}, KBr): 609 cm^{-1} (C-Cl), 1145, 1324 cm^{-1} (S=O), 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 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 **3c** 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): 1154, 1321 cm^{-1} (S=O), 1354, 1531 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, 1 H), 7.23–7.34 (m, 3 H), 7.50–7.55 (dd, 1 H), 7.74–7.78 (d, 2 H), 7.99–8.03 (d, 3 H), 8.22 (s, 1 H), 8.47–8.51 (d, 1 H), ^{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)-4 *H*-imidazo[1,5-a][1,4]benzodiazepine (5d)

t-BuOK (0.246 g, 2.2 mmol) was added portionwise to a stirred solution of clonazepam **3d** (0.631 g, 2 mmol) in dry THF (40 mL) at 0 °C under argon. After 20 min at 0 °C, 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 portionwise, 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 phases concentrated in 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 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.

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

To a solution of **5a** (0.341 g, 0.729 mmol) in dry THF (20 ml) at − 78 °C, n-Butyllithium (0.45 mL, solution 1.7 M in hexanes, 0.765 mmol) was added dropwise under argon gas. After stirring the mixture at − 78 °C for 15 min, the methyl iodide (0.2 ml, 2.92 mmol) was added dropwise. The resulting black solution was stirred vigorously for 4 h at − 78 °C. After this time, the resultant green mixture was then 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 vacuum. The resulting solid residue was purified by chromatography on silica gel (20:80 EtOAc: Petroleum ether). The desired white product **6a** obtained with an overall yield of 90% (0.314 g). Mp: 269–271 °C. IR (ν_{max}, KBr): 1610 cm^{-1} (S=O). ^{1}HNMR (250 MHz, $CDCl_3$, δ ppm): 2.37 (s, 3H), 2.50 (s, 3H), 3.97 (d, 1H, J = 13), 6.10 (d, 1H, J = 13), 7.01 (m, 1H), 7.27 (m, 4H), 7.37 (d, 1H, J = 7.5), 7.46 (m, 1H), 7.58 (d, 1H. J = 7.5), 7.72 (m, 1H), 8.00 (d, 2H, J = 7.5).^{13}CNMR (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.

Midazolam (7a): 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine

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. ^{1}HNMR (250 MHz, DMSO, δ ppm): 2.85 (s, 3H), 4.22 (d, 1H, J = 13), 5.27 (d, 1H, J = 13), 7.29–7.41 (m, 3H), 7.58–7.76 (m, 3H), 7.94 (m, 1H), 8.10 (m, 1H) .^{13}CNMR (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)-4*H*-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylate (5e)

t-BuOK (0.427 g, 3.81 mmol) was added portionwise to a stirred solution of amidobenzodiazepine **3a** (1 g, 3.46 mmol) in dry THF (80 mL) at 0 °C under argon. After 30 min at 0 °C, the mixture was cooled to − 20 °C with stirring, then diethyl chlorophosphate (0.7 ml, 4.85 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 ethyl isocyanoacetate (0.42 ml, 3.81 mmol) was added dropwise, followed by the addition of *t*-BuOK (0.466 g, 4.16 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 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, washed with Et_2O (50 mL) to give most of the desired tricyclic systems **3e**. The mother liquor was further purified by chromatography on silica gel (40:60 EtOAc:petroleum ether) to afford additional product. The desired light yellow-white (pale yellow) product **5e** obtained with an overall yield of 60% (0.79 g). IR (ν_{max}, KBr): 2928, 2960 cm^{-1} (-C_2H_5) 1563, 1613 cm^{-1} 2(C=N), 1722 cm^{-1} (C=O).^{1}HNMR (250 MHz, $CDCl_3$, δ ppm): 1.34 (t, 3H, J = 7.5), 4.03 (br s, 1H), 4.33 (q, 2H, J = 7.5), 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}CNMR (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.

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

The ester **5e** (1.0 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 room temperature for 4 h. 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 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} 2(C=O),

2400–3600 cm^{-1} (O-H). ^{1}HNMR (250 MHz, DMSO, δ 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}CNMR (62.5 MHz, $CDCl_3$, δ ppm): 45.0, 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, 162.2, 164.5.

5-(Aminomethyl)-1-{4-chloro-2-[(2-fluorophenyl) carbonyl]phenyl}-1*H*-imidazole-4-carboxylic acid dihydrochloride (7e)

The tricyclic acid **6e** (1 g, 2.81 mmol) from the previous step was dissolved in EtOH (80 mL) at room temperature and 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 addition of the acid solution. The reaction mixture was stirred for 4 h. The resultant salt was filtered under vacuum, 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)-4*H*-imidazo[1,5-a][1,4] benzodiazepine (8e)

The dihydrochloride salt **7e** (1.0 g, 2.23 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 room temperature with stirring. 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), washed with water (2 × 40 ml). The combined organic phases were dried over Na_2SO_4, evaporated in vacuum and the resulting crude mixture was chromatographed to afford **8e** as a yellow product with an overall yield of 70% (0.488 g). IR (ν_{max}, KBr): 758 cm^{-1} (C-Cl), 3080 cm^{-1} (CH arom), 1487, 1606 cm^{-1} (C=C arom), ^{1}HNMR (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}CNMR (62.5 MHz, $CDCl_3$, δ ppm): 45.5, 116.1, 116.4, 123.8, 124.5, 126.2, 127.8, 127.9, 129.9, 130.3, 131.1, 132.0, 132.1, 132.3, 132.5, 133.2, 133.7, 134.8, 158.2, 162.2, 164.4.

Midazolam (7a): 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine

To a solution of **8e** (1.0 g, 3.2 mmol) in dry THF (40 ml) at − 78 °C, n-butyllithium (1.89 mL, solution 1.7 M in hexanes, 3.2 mmol) was added dropwise under argon gas. After stirring the mixture at − 78 °C for 15 min, the methyl iodide (0.4 ml, 6.4 mmol) was added dropwise. The resulting black solution was stirred vigorously for 4 h at − 78 °C. Then, 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 vacuo. The resulting solid residue was purified by chromatography on silica gel (20:80 EtOAc:petroleum ether). The desired white product **7a** obtained with an overall yield of 90% (0.938 g). ^{1}HNMR (250 MHz, DMSO, δ ppm): 2.85 (s, 3H), 4.22 (d, 1H, J = 13), 5.27 (d, 1H, J = 13), 7.29–7.41 (m, 3H), 7.58–7.76 (m, 3H), 7.94 (m, 1H), 8.10 (m, 1H) .^{13}CNMR (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.

Conclusion

We have presented two different and improved multistep methods for the synthesis of midazolam and its analogous. These synthetic methods included the formation of an imidazole ring fused in the 1,2-position benzodiazepines which had been developed from a one-pot annulation process. This procedure permitted the carbon–carbon bond forming reaction and condensation of the less stable iminophosphates with mono-anion of tosylmethyl isocyanide or ethyl isocyanoacetate under basic (moderate) conditions. In the first method (route I), tosylmethyl isocyanide (Tos-MIC) was used and the number of synthetic steps are decreased to 5 step in comparison to previous report and the overall yield of this method was 29%. In the second method (route II), the synthesis of midazolam with ethyl isocyanoacetate was accomplished in 6 step with 82% yield.

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Affiliations

Mohammad Javad Taghizadeh[1] · Gholam reza malakpouri[1] · Abdollah Javidan[1,2]

✉ Mohammad Javad Taghizadeh
mohammadjavadtaghizadeh31@yahoo.com

[1] Department of Chemistry, Faculty of Science, University of Imam Hossein, Tehran, Islamic Republic of Iran

[2] Eyvanekey University, Eyvanekey, Islamic Republic of Iran