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A Short Route to Midazolam via Michael Addition to a Nitroolefin

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ABSTRACT: A new approach to midazolam through Michael addition of 2-aminobenzophenone with a nitroolefin as a key step is reported. We devised a telescoped four-step synthesis using only one single protecting group, resulting in an excellent atom economy.

KEYWORDS: *midazolam, Michael addition, intramolecular cyclization, nitroolefins, 1,4-benzodiazepine*

1. INTRODUCTION

Midazolam is a fast- and short-acting benzodiazepine,[1] which was first synthesized by Fryer and Walser. They registered a patent in 1976[2] and subsequently published the synthesis route in 1978.[3] Benzodiazepines represent a class of biologically active compounds of great interest to medicine and the pharmaceutical industry due to their diverse therapeutic properties. Midazolam, in particular, is well-known for its anxiolytic, muscle relaxant, anticonvulsant, sedative, and hypnotic properties.[1,4,5] It acts primarily at the synaptic level through the benzodiazepine-γ-aminobutyric acid ($GABA_A$) receptor complex containing a chloride ion channel. Besides its pharmacological activities, midazolam was the first water-soluble benzodiazepine, a property that contributes to its rapid absorption, especially in comparison to older representatives of the class such as diazepam or lorazepam.[6] Its superior solubility is attributed to midazolam's imidazole ring, which enables salt formation due to its relative basicity. In addition, it is reported that midazolam forms a pH-dependent equilibrium between the ring-open and ring-closed form of the 7-membered heterocyclic ring. At acidic pH, the ring is open and highly water-soluble. As soon as the midazolam is absorbed and exposed to physiological pH, the ring structure closes and becomes lipophilic.[6,7] The ring-closing form of midazolam crosses the blood-brain barrier readily, which leads to a rapid onset of action, resulting in a fast absorption rate and rapid excretion with a half-life of typically around 2 h.[6−8]

The first synthetic approaches of midazolam were conducted by Fryer and co-workers from Roche in the 1970s (Scheme 1).[3,9,10] They found two different pathways to synthesize their key starting material **6** from 2-aminobenzophenone **3** in two or three steps in good yields. Compound **6** is converted in four steps to key intermediate **2**, involving difficult-to-handle reagents, such as methylamine gas or Raney nickel, and a potentially carcinogenic nitrosamine intermediate. Compound **2** undergoes an intermolecular cyclization with triethyl orthoacetate to give the imidazole scaffold in intermediate **10**. The last step of the synthesis of Fryer et al. is the dehydrogenation with MnO_2 to give midazolam **1** as the free base.

A new synthesis of midazolam was reported by Wang et al. in 2023.[8] Their key step is a one-pot reductive amination−deprotection−cyclization process between 2-aminobenzophenone **11** and Boc-protected 1,3-diaminopropan-2-one **12**, followed by an intermolecular cyclization and oxidative dehydrogenation reaction (see Scheme 2). In addition to the synthetic route shown in Scheme 2, they also developed a scalable process for the preparation of midazolam hydrochloride in five steps, with a total yield of 26.5%. Compared to previously reported methods, their protocol offers significant improvements in safety and cost efficiency.

Our synthetic approach aimed at high atom economy by minimizing the use of protecting groups while keeping the step count low. The central concept was to use a Michael addition as the key step for the formation of key intermediate **2** (Scheme 3). For this purpose, nitroolefin **14** was chosen as a Michael acceptor, paired with the well-established starting material 2-aminobenzophenone **3**. Starting material **3** is commercially available and can be obtained by a Friedel−Crafts reaction of 4-chloroaniline (**15**) and 2-fluorobenzoic acid chloride (**16**).[11] As in numerous previously reported routes, the present synthetic pathway to midazolam also begins with benzophenone **3**. The proposed route consists of three main steps to form intermediate **3**: Michael addition, reduction of the nitro group, and Boc-deprotection. Compared to the strategy by Wang et al., our route utilizes only one Boc-protecting group and ketal protection/deprotection of the benzophenone carbonyl should be avoided.[8]

2. RESULTS AND DISCUSSION

Synthesis of Nitroolefin 14. We aimed at a synthesis of midazolam with minimal protecting group usage that does not require expensive transition metals like palladium. The key step

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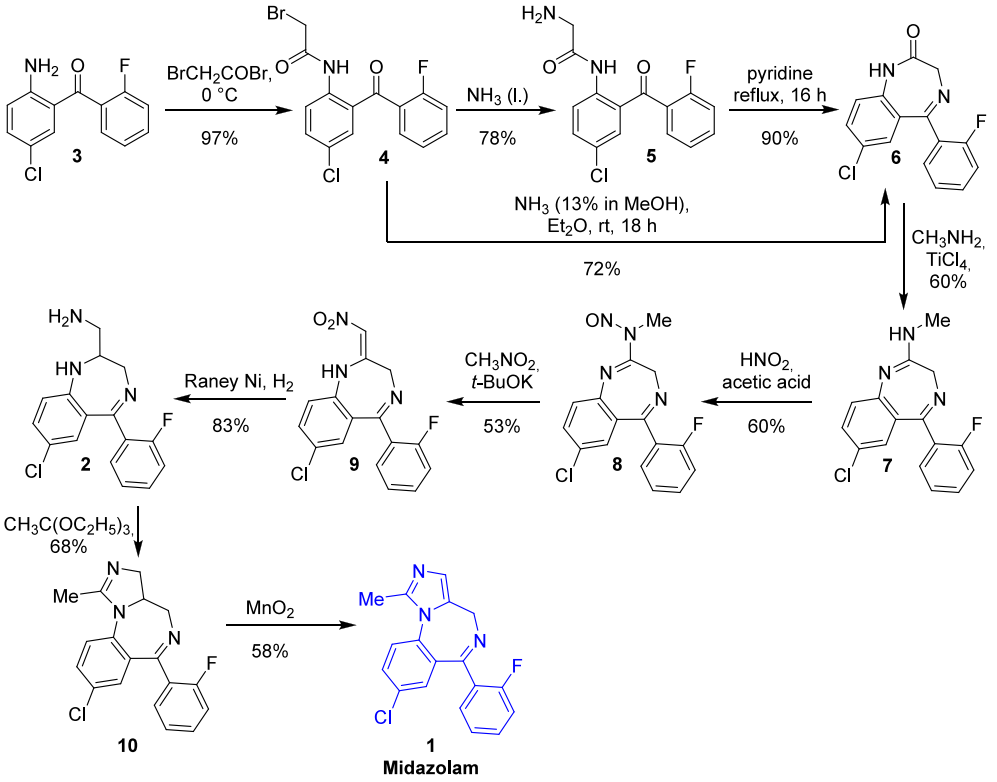
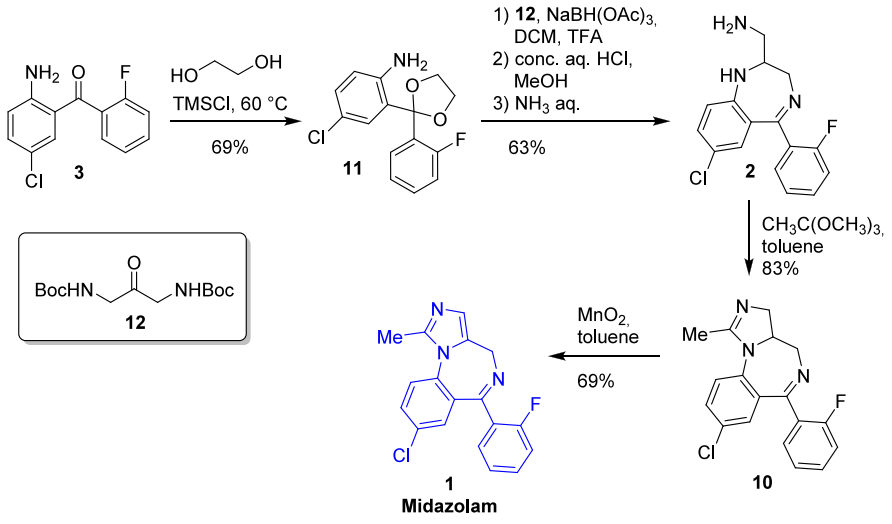
Scheme 1. Fryer's and Roche's Original Synthesis of Midazolam[3,9,10]



Scheme 2. Third-Generation Synthesis Process of Wang et al.[8]



is a Michael addition between 2-aminobenzophenone **3** and a nitroolefin **14**. The nitroolefin precursor **14** is synthesized in four steps starting from 2-aminoethanol (Scheme 4). In the first step, 2-aminoethanol is protected by using di-*tert*-butyl dicarbonate,[12] followed by oxidation of the alcohol to the corresponding aldehyde **19** in a Parikh−Doering reaction; compound **19** is subsequently purified by filtration over a short pad of silica.[13] Aldehyde **19** is then transformed in a Henry reaction with nitromethane to alcohol **20**,[14] followed by dehydration according to a protocol of Fioravanti et al.[14] Nitroolefin **14** is obtained as the *E*-isomer, with an overall yield of 39% over four steps.[14] The synthesis route can be shortened to two or three steps, as compounds **18** and **19** are commercially available. For the TGA and DSC data of compounds **14** and **20**, see the Supporting Information.

Elaboration of the Midazolam Synthesis. A key step of this synthesis is the formation of the seven-membered ring of the midazolam structure. Starting from known 2-amino-benzophenone **3**, which is reacted with nitroolefin **14** in a Michael addition to yield product **13** (see Scheme 5). Solvents and temperatures for the addition step were screened and optimized (Supporting Information). Promising conditions involved the reaction in the melt at 85 °C; however, the reaction mixture solidified before reaching full conversion. To address this issue, two equivalents of 1,4-dioxane were added to permit stirring. Due to the almost complete conversion, the

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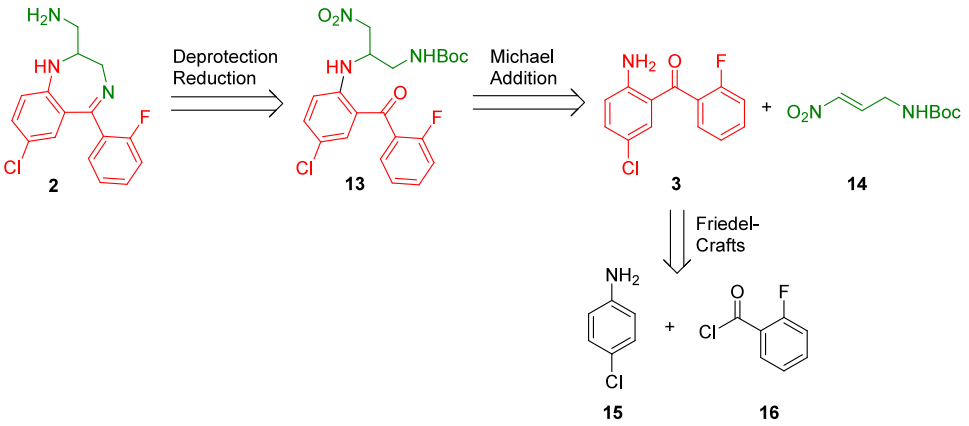
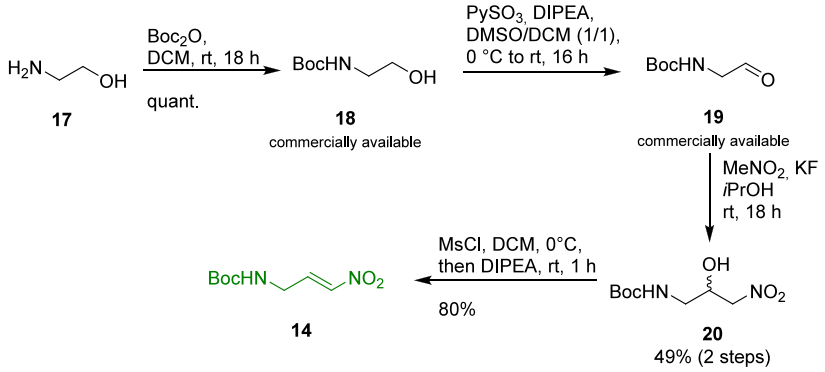
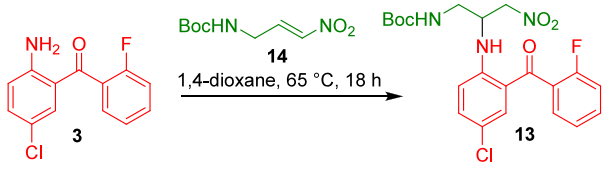
Scheme 3. Retrosynthesis for the Formation of Key Intermediate 2.[11]



Scheme 4. Synthesis of Nitroolefin 14[12−14]



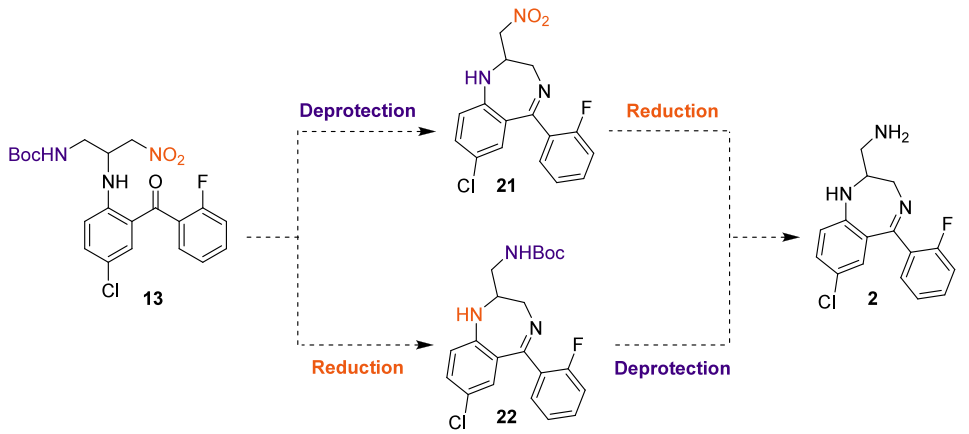
Scheme 5. Michael Addition of Aminobenzophenone 3 to Nitroolefin 14



crude reaction mixture was carried forward directly to the next step.

With the crude material **13** in hand, the next goal was to close the seven-membered ring. There are two possible pathways, either Boc-deprotection or nitro group reduction, to generate the free amino group, which closes the ring via imine formation with the benzophenone carbonyl. One route involved Boc-deprotection first, followed by nitro group reduction. Alternatively, nitro reduction could be carried out first, followed by Boc removal (Scheme 6). Initial experiments demonstrated that Boc deprotection of compound **13** to nitroalkane **21** proceeded smoothly. However, the subsequent reduction of the nitro group was challenging. Conditions reported in the literature, reduction using Raney nickel as applied in the synthesis of **2**, could not be directly transferred from substrate **9** (synthesis of Walser et al.) to substrate **21**. As a result, the focus shifted to the alternative pathway, in which

Scheme 6. Pathways for the Formation of Key Intermediate 2



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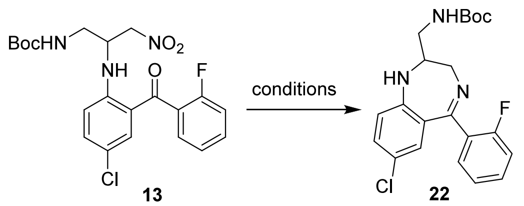
the nitro group was reduced prior to Boc-deprotection. Various reaction conditions were tested to achieve the reduction of the nitro group.

The tested reaction conditions are summarized in Table 1. The reduction with Raney nickel was, in this case, also unsuccessful.[3] The use of palladium on carbon (not preferred as a catalyst) resulted in the dechlorination of the starting material. In addition, the reduction with $NiCl_2$ and $NaBH_4$[15] resulted in a complex mixture without traces of the desired product. Zinc and iron were tested as reducing agents, as well. The reduction with zinc and acetic acid gave the desired product in a mixture with side products.[16,17] One of the side reactions is the reduction of the ketone to the corresponding alcohol. The reduction with iron and acetic acid[18] gave the best results, and full conversion to the desired product could be achieved with seemingly no side product formation. Telescoping the Michael addition, nitro group reduction, followed by ring closure, proved to be a successful strategy. The yield over this combined transformation is between 50 and 60%.

Table 1. Reduction of Compounds 13 to 22 (Tested Reaction Conditions and Results)



entry	conditions	conversion of 13 [%][a]	comment
1	$NiCl_2 \cdot 6\ H_2O$, $NaBH_4$, EtOH, rt		side product formation
2	Zn, AcOH, THF/MeOH (9/1) rt	>50	slow reaction (4 days), side product formation, reduction of the ketone
3	Zn, AcOH, rt		side product formation
4	H_2, Raney-Ni, EtOH, rt		
5	H_2 (1 bar),10% Pd/C, MeOH/AcOH (1%), rt, 1 mL/min[b]		dechlorination
6	Fe, NH_4Cl, MeOH/H_2O (1/0.75), reflux, 18 h	quant.	side product formation
7	Fe, AcOH, THF/MeOH (2/1), 65 °C, 18 h	quant.	

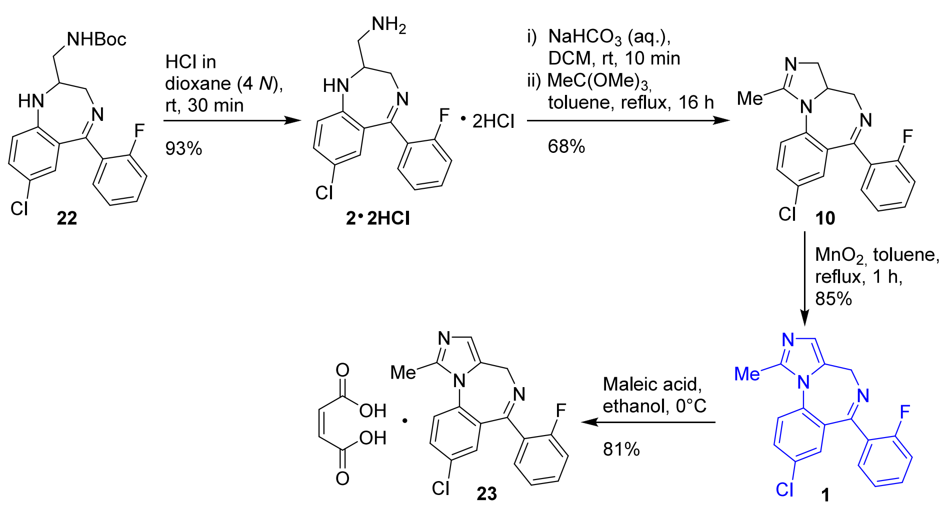
[a]Determined by LC-MS (254 nm). [b]Experiment with the H-Cube Mini Plus (ThalesNano).

After ring closure to compound **22**, only deprotection is required to obtain the known intermediate **2**. The cleavage of the Boc-group was performed using hydrogen chloride in 1,4-dioxane. The primary amine **2** was precipitated directly from the reaction mixture as its dihydrochloride salt **2·2HCl2 2HCl** by the addition of diethyl ether. The subsequent steps followed established procedures reported in the literature (Scheme 7). Formation of the imidazole ring was accomplished via reaction with trimethyl orthoacetate in toluene at 100 °C. The synthesis of the final product midazolam was achieved by the oxidation with manganese dioxide,[3] in a yield of 85% (HPLC purity 96%). As some minor impurities were visible in the ^{1}H NMR spectrum, the midazolam was precipitated by the salt formation with maleic acid. The salt was obtained with a yield of 81%. Further scale-up should improve the yield, as you can see in the results of Wang et al.[8]

■ CONCLUSIONS

In conclusion, a new route for the synthesis of midazolam (**1**) with a Michael addition to nitroolefin **14** as the key step was developed (see Scheme 8). The required nitroolefin **14** was synthesized in four steps from inexpensive 2-aminoethanol, but the route can be further shortened to just two steps when starting from commercially available aldehyde **19**. Compared to previously reported methods, which use 5−11 steps, we shortened the route from benzophenone **3** to midazolam (**1**) to only four steps through telescoping, with an overall yield of 32% and very high purity. Unlike the process described by Wang et al.,[8] our route does not require the ketal protection and subsequent deprotection of the benzophenone carbonyl. In addition, nitroolefin **14** also requires only one Boc-protecting group compared to ketone **12** used by Wang et al.[8] The use of fewer protecting groups leads to a better atom economy in our synthesis. Another benefit of our route in comparison to published approaches is the use of iron as a

Scheme 7. Deprotection to Key Intermediate 2 and Known Synthesis Steps to Midazolam (1).[3,8]



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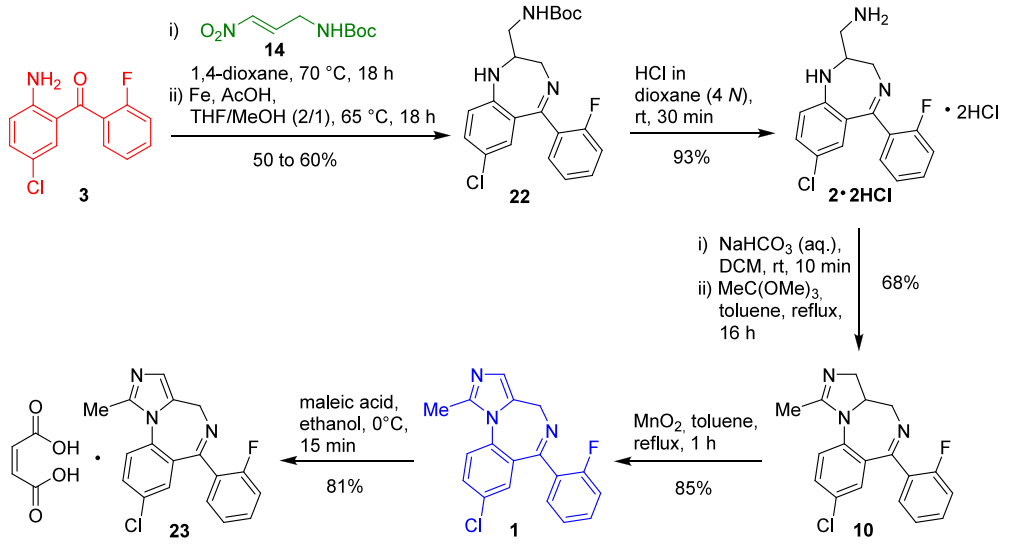
Scheme 8. Overview of the Presented Synthesis Route[3,8]



reductant, which is more cost-effective and easier to handle than the potentially pyrophoric Raney nickel. While far from being optimized for large-scale production, particularly with respect to the choice of solvents and purification operations, the presented route offers an attractive perspective on a short and efficient approach to an important benzodiazepine-type API.

EXPERIMENTAL SECTION

All of the chemicals employed were commercially available and used without prior purification. Anhydrous solvents were taken from a solvent purification system under a nitrogen atmosphere. NMR spectra were recorded on a Bruker Avance-III HD instrument (^{1}H NMR: 300 MHz, ^{13}C NMR: 75 MHz) or a Bruker Avance-III HD instrument (^{1}H NMR: 400 MHz, ^{13}C NMR: 101 MHz, ^{19}F NMR: 377 MHz) with a 5 mm BBFO probe. The chemical shifts δ were expressed in ppm downfield from tetramethyl silane (^{1}H NMR, ^{13}C NMR). Deuterated solvents ($CDCl_3$, DMSO-d_6) served as an internal reference. The reported signal multiplicities were abbreviated as follows: s br = broad singlet, s = singlet, d = doublet, t = triplet. Coupling constants J are reported in Hz. ESI-MS spectra were recorded on a 1260-series Infinity II HPLC system (Agilent Technologies) with a binary pump and integrated diode array detector coupled to an LC/MSD Infinity lab LC/MSD (G6125B LC/MSD) mass spectrometer. For high-resolution (HR) mass spectra, an Agilent 6545 Q-TOF spectrometer and a suitable external calibrant were used. IR spectroscopy was conducted on a Bruker Tensor 27 FTIR spectrometer using a diamond ATR unit. Thin-layer chromatography was performed on Merck F_{254} silica gel plates. Spots were visualized with UV-light (λ = 254 nm) or stained with the appropriate reagents. Melting ranges were determined in open glass capillaries on a melting point measuring device type MP30 from Mettler Toledo.

***tert*-Butyl (2-Hydroxyethyl)carbamate (18).** According to a procedure by Helmchen et al.,[12] a solution of Boc_2O (6.42 g, 29.43 mmol, 1.00 equiv) in DCM (20 mL) was added slowly to a solution of 2-aminoethanol (2.00 g, 32.74 mmol, 1.11 equiv) in DCM (10 mL) under a nitrogen atmosphere at 0 °C. The reaction mixture was stirred for 18 h at rt and then washed with sat. $NaHCO_3$ solution (60 mL). The organic phase was dried with Na_2SO_4 and concentrated in vacuo. The product was obtained as a colorless oil (4.75 g, 29.47 mmol, quant.) and used in the next synthesis step without further purification. R_f (SiO_2) = 0.46 (cyclohexane/EtOAc, 1/1), IR (ATR): ν = 3340, 2977, 2933, 1685, 1277, 1521, 1366, 1169, 1067, 866 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (s, 1H, NH), 3.67 (t, J = 5.1 Hz, 2H), 3.26 (q, J = 4.9 Hz, 2H), 2.82 (s, 1H, OH), 1.43 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.0, 79.8, 62.6, 43.3, 28.5 ppm. ESI-HRMS: calcd for $[C_7H_{15}NNaO_3 + H]^+$, m/z = 184.0944; found, m/z = 184.0949.

***tert*-Butyl (2-Oxoethyl)carbamate (19).** According to a procedure by Ann Hallinan et al.,[13] to a solution of alcohol **18** (4.75 g, 29.43 mmol, 1.00 equiv) in DCM (40 mL) was added DIPEA (10.00 mL, 58.86 mmol, 2.00 equiv) and sulfur trioxide-pyridine complex (9.36 g, 58.86 mmol, 2.00 equiv) dissolved in DMSO (40 mL) at 0 °C. After removing the ice bath, the reaction mixture was stirred for 16 h at rt and then added to ice-cold brine (250 mL). The aqueous phase was extracted with Et_2O (2 × 300 mL). The combined organic phases were washed with cold 1 M $KHSO_4$ solution (200 mL), cold water (2 × 200 mL), and cold brine (200 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated under vacuum. The crude product was filtered through a pad of silica gel, and the aldehyde was eluted from the silica gel with DCM/EtOAc (4/1). The solvent was removed, and the product was obtained as an orange oil (4.29 g, 26.95 mmol). Aldehyde **19** is not particularly stable and was used directly in the next step.

***tert*-Butyl (2-Hydroxy-3-nitropropyl)carbamate (20).** According to a modified procedure by Tardella et al.,[14] to a solution of aldehyde **19** (4.29 g, 26.95 mmol, 1.00 equiv) in *i*-PrOH (30 mL) was added nitromethane (8.22 g, 134.74 mmol, 5.00 equiv) and KF (31.4 mg, 0.54 mmol, 0.02 equiv). The reaction mixture was stirred for 18 h at rt, the solvent was removed, and the residue was dissolved in DCM (60 mL) and washed with brine (60 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography (cyclohexane/EtOAc; 3/1). The product was obtained as a colorless solid (3.17 g, 24.39 mmol, 49%, last 2 steps). R_f (SiO_2) = 0.53 (cyclohexane/EtOAc, 1/1), T_m = 49.3 − 55.9 °C. IR (ATR): ν

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= 3399, 2981, 2940, 1659, 1526, 1380, 1348, 1167, 1118, 643 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.02 (s, 1H, NH), 4.56−4.34 (m, 3H), 3.80 (s, 1H, OH), 3.46−3.20 (m, 2H), 1.44 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.3, 80.8, 78.3, 68.7, 43.8, 28.4 ppm. ESI-HRMS: calcd for $[C_9H_{17}N_2O_7 + HCOO]^-$, m/z = 265.1041; found, m/z = 265.1044.

***tert*-Butyl (*E*)-(3-Nitroallyl)carbamate (14).** According to a procedure by Tardella et al.,[14] methanesulfonyl chloride (0.78 g, 6.86 mmol, 1.20 equiv) was added to a solution of nitro alcohol **20** (1.26 g, 5.72 mmol, 1.00 equiv) in DCM (40 mL) at 0 °C and stirred for 20 min. Then DIPEA (2.48 mL, 14.25 mmol, 2.50 equiv) was added, and the cooling was removed. The reaction solution was stirred for 1 h at rt and then washed with water (40 mL), 2 M HCl solution (2 × 40 mL), and sat. NH_4Cl solution (40 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Cyclohexane/EtOAc) to give the product as a yellowish solid (0.92 g, 4.57 mmol, 80%). R_f (SiO_2) = 0.67 (cyclohexane/EtOAc, 1/1), T_m = 45.0 − 50.3 °C. IR (ATR): ν = 3337, 2979, 1690, 1521, 1392, 1248, 1159, 1055, 902, 516 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.27−7.17 (m, 1H), 7.05 (dt, J = 13.4, 1.8 Hz, 1H), 4.82 (s, 1H), 4.06−3.96 (m, 2H), 1.45 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.7, 140.2, 139.2, 80.7, 38.6, 28.4 ppm. ESI-HRMS: calcd for $[C_8H_{14}N_2NaO_4 + H]^+$, m/z = 225.0846; found, m/z = 225.0845.

***tert*-Butyl (2-((4-Chloro-2-(2-fluorobenzoyl)phenyl)-amino)-3-nitropropyl)carbamate (13).** Amino benzophenone **3** (0.22 g, 0.90 mmol, 1.00 Äq equiv) and nitroolefin **14** (0.20 g, 0.90 mmol, 1.10 equiv) were stirred together with 1,4-dioxane (0.4 mL) for 18 h at 70 °C. The mixture was cooled to rt and the raw material purified by reversed-phase flash chromatography (ACN/H_2O). The product was obtained as a yellow oil (195 mg, 0.43 mmol, 48%). R_f (SiO_2) = 0.16 (Cyclohexane/EtOAc, 4/1). IR (ATR): ν = 2980, 2925, 1701, 1628, 1555, 1510, 1272, 1243, 1160, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 9.04 (d, J = 8.3 Hz, 1H, NH), 7.55−7.47 (m, 1H), 7.45−7.36 (m, 2H), 7.33 (t, J = 2.5 Hz, 1H), 7.29−7.23 (m, 1H), 7.17 (ddd, J = 9.6, 8.4, 1.0 Hz, 1H), 6.96 (d, J = 9.1 Hz, 1H), 4.94 (s, 1H), 4.71−4.56 (m, 3H), 3.52 (dt, J = 14.5, 5.5 Hz, 1H), 3.36 (dt, J = 14.4, 6.3 Hz, 1H), 1.45 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.2, 159.1 (d, J = 250.5 Hz), 156.3, 148.7, 136.1, 134.4, 132.6 (d, J = 8.1 Hz), 129.9 (d, J = 3.3 Hz), 127.8 (d, J = 16.1 Hz), 124.4 (d, J = 3.7 Hz), 120.8, 119.5, 116.4 (d, J = 21.6 Hz), 113.7, 80.6, 76.6, 51.2, 42.5, 28.4 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.04 to −113.16 (m) ppm. ESI-HRMS: calcd for $[C_{21}H_{23}ClFN_3O_5 + H]^+$, m/z = 452.1383; found, m/z = 452.1376.

This procedure was only followed for characterization purposes and was superseded by the telescoped procedure including reduction of the nitro group; see below.

***tert*-Butyl ((7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-benzo[e][1,4]diazepin-2-yl)methyl)carbamate (22) (Telescoped Procedure from 3).** Amino benzophenone **3** (0.73 g, 2.92 mmol, 1.00 equiv) and nitroolefin **14** (0.65 g, 3.20 mmol, 1.10 equiv) were stirred together with 1,4-dioxane (0.52 g, 5.84 mmol, 2.00 equiv) for 18 h at 70 °C. The mixture was cooled to rt and dissolved in THF (30 mL) and MeOH (15 mL). To this solution were added iron powder (2.44 g, 43.80 mmol, 15.00 equiv) and acetic acid (2.63 g, 43.80 mmol,15.00 equiv), and the reaction mixture was stirred for 18 h at 65 °C. The mixture was filtered over Celite and rinsed with EtOAc (100 mL). The filtrate was washed with sat. $NaHCO_3$ solution (60 mL) and brine (60 mL) and dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (Cyclohexane/EtOAc). The product was obtained as yellow oil (0.59 g, 1.46 mmol, 50%). R_f (SiO_2) = 0.20 (Cyclohexane/EtOAc, 1/1). IR (ATR): ν = 3339, 2977, 1690, 1614, 1510, 1483, 1451, 1253, 1165, 732. cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.48−7.34 (m, 2H), 7.19 (td, J = 7.5, 1.1 Hz, 1H), 7.15−7.01 (m, 2H), 6.87 (d, J = 2.5 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 4.99 (t, J = 5.4 Hz, 1H), 4.81 (s, 1H), 4.14−4.03 (m, 1H), 4.01−3.81 (m, 2H), 3.48−3.34 (m, 1H), 3.30−3.16 (m, 1H), 1.45 (s, 9H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.1, 160.4 (d, J = 250.1 Hz), 157.2, 145.7, 131.5, 131.4, 131.3, 131.1, 130.5, 129.36 (d, J = 13.0 Hz), 124.33 (d, J = 3.3 Hz), 122.5 (d, J = 7.4 Hz), 120.6, 116.27 (d, J = 21.7 Hz), 80.2, 64.8, 54.1, 45.2, 28.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −114.03 to −114.16 (m) ppm. ESI-HRMS: calcd for $[C_{21}H_{24}ClFN_3O_2 + H]^+$, m/z = 404.1536; found, m/z = 404.1525.

(7-Chloro-5-(2-fluorophenyl)-2,3-dihydro-1*H*-benzo-[e][1,4]diazepin-2-yl)methanamine Dihydrochloride 2·2HCl. The carbamate **20** (0.54 g, 1.33 mmol, 1.00 equiv) was dissolved in 4*N* HCl in 1,4-dioxane (10 mL) and stirred for 30 to 45 min at rt. The hydrochloride was precipitated by the slow addition of Et_2O (30 mL). The suspension was cooled to 0 °C and stirred for 5 min. The yellow solid was filtered off and washed with Et_2O (20 mL). The hydrochloride was dried in vacuo at 40 °C and obtained as a yellow solid (0.47 g, 1.24 mmol, 93%). R_f (SiO_2) = 0.15 (DCM/MeOH, 4/1, free base). IR (ATR): ν = 2858, 1612, 1483, 1450, 1346, 1216, 1169, 842, 770, 614 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = δ 9.35 (s, 1H, NH), 8.63 (s, 3H, $NH_{2/3}$), 7.90−7.73 (m, 1H), 7.70 (td, J = 7.5, 1.7 Hz, 1H), 7.56 (dd, J = 9.2, 2.3 Hz, 1H), 7.53−7.46 (m, 2H), 7.32 (d, J = 9.3 Hz, 1H), 6.83 (dd, J = 2.4, 1.1 Hz, 1H), 4.33 (s, 1H), 4.06 (d, J = 3.9 Hz, 2H), 3.11 (s, 1H), 2.98 (s, 1H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 170.9, 158.9 (d, J = 251.4 Hz), 150.1, 136.2, 135.2 (d, J = 8.5 Hz), 132.2, 132.0, 125.2, 125.1, 122.5, 120.2, 116.5 (d, J = 20.6 Hz), 110.9, 57.46, 49.9, 40.5 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = − 113.06 ppm. APCI-HRMS: calcd for $[C_{16}H_{15}ClFN_3$ + H (free base)$]^+$, m/z = 304.1011; found, m/z = 304.0995.

8-Chloro-6-(2-fluorophenyl)-1-methyl-3a,4-dihydro-3*H*-benzo[f]imidazo[1,5-*a*][1,4]diazepine (10). According to a modified procedure by Wang et al.,[8] the hydrochloride **2** 2HCl (0.22 g, 0.58 mmol, 1.00 equiv) was suspended in DCM (20 mL) and stirred together with sat. $NaHCO_3$ solution (20 mL) was kept for 10 min at rt. The phases were separated, the aqueous phase was extracted with DCM (20 mL), and the combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in toluene (2.5 mL), and trimethyl orthoacetate (0.32 g, 2.62 mmol, 4.50 equiv) was added. The mixture was stirred at 110 °C for 16 h. The solvent was removed in vacuo, and the raw material was purified by flash chromatography (DCM/MeOH). The product was obtained as a colorless oil (0.13 g, 0.39 mmol, 68%). R_f (SiO_2) = 0.13 (DCM/MeOH, 4/1). IR (ATR): ν = 2932, 2864, 1610, 1559, 1477, 1451, 1260, 1211, 824, 743 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 7.68 (dd, J = 8.4, 2.5 Hz, 1H), 7.65−7.52 (m, 2H), 7.49 (d, J = 8.4 Hz, 1H), 7.32 (td, J = 7.5, 1.1 Hz, 1H), 7.23 (ddd, J = 11.3, 8.2, 1.0 Hz, 1H), 7.13 (d, J = 2.4 Hz, 1H), 4.75−4.58 (m, 1H), 3.96−3.81 (m, 2H), 3.72 (dd, J = 14.1, 7.3 Hz, 1H), 3.38 (dd, J = 11.7,

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4.4 Hz, 1H), 1.62 (s, 3H). ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 165.6, 160.9, 160.3 (d, J = 249.4 Hz), 138.0, 137.5, 132.8, 132.6, 132.5, 131.7, 131.3, 131.2, 128.6 (d, J = 1.4 Hz), 126.8 (d, J = 10.8 Hz), 124.8 (d, J = 3.3 Hz), 116.2 (d, J = 21.8 Hz), 71.3, 56.1, 53.6, 13.9 ppm. ^{19}F NMR (282 MHz, DMSO-d_6): δ = −112.41 to −112.66 (m) ppm. ESI-HRMS: calcd for $[C_{18}H_{16}ClFN_3 + H]^+$, m/z = 328.1011; found, m/z = 328.1009. The spectroscopic data are in accordance with the literature.[8]

8-Chloro-6-(2-fluorophenyl)-1-methyl-4*H*-benzo[f]-imidazo[1,5-*a*][1,4]diazepine (1, Midazolam). According to a procedure by Walser et al.,[3] **10** (0.17 g, 0.52 mmol, 1.00 equiv) was dissolved in dry toluene (3 mL), and manganese dioxide (0.68 g, 7.80 mmol, 15.00 equiv) was added. The suspension was heated to reflux for 1 h until the reaction was completed. The mixture was cooled to rt, and the reaction mixture was filtered with Celite. The filter cake was rinsed with EtOAc (40 mL). The filtrate was concentrated in vacuo to give the product as a beige solid (0.15 g, 0.44 mmol, 85%, purity 96%). R_f (SiO_2, free base) = 0.39 (DCM/MeOH, 95/5). IR (ATR): ν = 1612, 1485, 1452, 1414, 1311, 1213, 1103, 999, 824, 766 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.82−7.72 (m, 2H), 7.59 (td, J = 7.6, 1.9 Hz, 1H), 7.55−7.48 (m, 1H), 7.30 (td, J = 7.5, 1.1 Hz, 1H), 7.25−7.15 (m, 2H), 6.86 (d, J = 0.9 Hz, 1H), 5.06 (d, J = 12.9 Hz, 1H), 4.02 (d, J = 12.9, 1H), 2.46 (s, 3H) ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 163.3, 159.5(d, J = 249.0 Hz), 143.9, 134.2, 133.1, 132.41 (d, J = 8.5 Hz), 131.5, 131.4, 131.2, 131.1(d, J = 1.9 Hz), 128.8, 127.20 (d, J = 11.6 Hz), 126.7, 124.61 (d, J = 3.6 Hz), 122.2, 116.02 (d, J = 21.2 Hz), 45.2, 14.2 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −112.06 to −112.27 (m) ppm. ESI-HRMS: calcd for $[C_{18}H_{13}ClFN_3 + H]^+$, m/z = 326.0855; found, m/z = 326.0843. The spectroscopic data are in accordance with the literature.[5]

Midazolam (**1**, 100 mg) was dissolved in 1 mL of ethanol, and maleic acid (0.07 g, 0.61 mmol, 2.00 equiv) dissolved in 1 mL of ethanol was added at 0 °C. The mixture was stirred for 15 min. The salt was prepared by the slow addition of ether (20 mL). The solvent was decanted, and more ether was added. This process was repeated 3 times. The remaining ether was removed under a vacuum. The midazolam maleate salt **23** was obtained as a colorless solid (0.11 g, 0.24 mmol, 81%). ^{1}H NMR (300 MHz, DMSO-d_6): δ = 7.96−7.77 (m, 2H), 7.71−7.47 (m, 2H), 7.39−7.27 (m, 3H), 7.22 (ddd, J = 11.0, 8.3, 1.1 Hz, 1H), 6.16 (s, 2H), 5.14 (d, J = 13.1 Hz, 1H), 4.10 (dd, J = 13.1, 1.1 Hz, 1H), 2.60 (s, 3H). ppm. ^{13}C NMR (75 MHz, DMSO-d_6): δ = 167.0, 163.5, 159.7 (d, J = 249.5 Hz), 144.5, 134.6, 132.9, 132.7 (d, J = 8.8 Hz), 132.5, 132.1, 131.8, 131.5, 131.3 (d, J = 1.9 Hz), 129.1, 127.0, 127.0 (d, J = 11.4 Hz), 124.7 (d, J = 3.3 Hz), 119.3, 116.2 (d, J = 21.5 Hz), 44.8, 13.6 ppm. ^{19}F NMR (282 MHz, $CDCl_3$): δ = −113.45 (ddd, J = 11.2, 7.6, 5.3 Hz) ppm. The spectroscopic data are in accordance with the literature.[19]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.5c00320.

Optimization studies, chromatograms, NMR spectra, DSC, and TGA data (PDF)

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Notes

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