JOC Article

New Synthesis of 1,3-Dihydro-1,4-benzodiazepin-2(2*H*)-ones and 3-Amino-1,3-dihydro-1,4-benzodiazepin-2(2*H*)-ones: Pd-Catalyzed Cross-Coupling of Imidoyl Chlorides with Organoboronic Acids

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Received December 17, 2002

A new approach to the synthesis of 1,4-benzodiazepines and 3-amino-1,4-benzodiazepines, which employs the Pd-catalyzed cross-coupling reaction of an imidoyl chloride with an organometallic reagent as the key step, is described. A five-step synthesis of a key intermediate is described and it is shown that in only four further steps (three couplings and a TFA-mediated BOC-deprotection) a wide variety of N1-, C3-amino-, C5-carbon-, or nitrogen-substituted 1,4-benzodiazepines can be synthesized.

Introduction

The 1,4-benzodiazepine skeleton (**I**, Figure 1) is one of medicinal chemistry's most widely used motifs. First discovered in the 1960s,[1] there are many marketed pharmaceutical agents (e.g. Diazepam) that contain a 1,4-benzodiazepine. These function principally as GABA receptor agonists for CNS clinical indications such as anxiety, insomnia, muscle spasm, epilepsy and convulsions.

The slightly more functionalized 3-amino-1,4-benzodiazepine skeleton (**II**, Figure 1), first highlighted as a component of a nonpeptidic CCK antagonist,[2] has gained recognition as a "privileged structure"[3] and has been used in a number of medicinal chemistry programs in many therapeutic settings (for example, CCK,[4] bradykinin,[5] farnesyl transferase,[6] PDE IV,[7] and IKS-mediated cardiac arythmia[8]). Most recently, several publications,[9] including our own,[10] have described the use of acylated 3-amino-benzodiazepines (e.g. **III**, Figure 1) as highly potent γ-secretase inhibitors (with potential for the nonpalliative treatment of Alzheimer's Disease[11]).

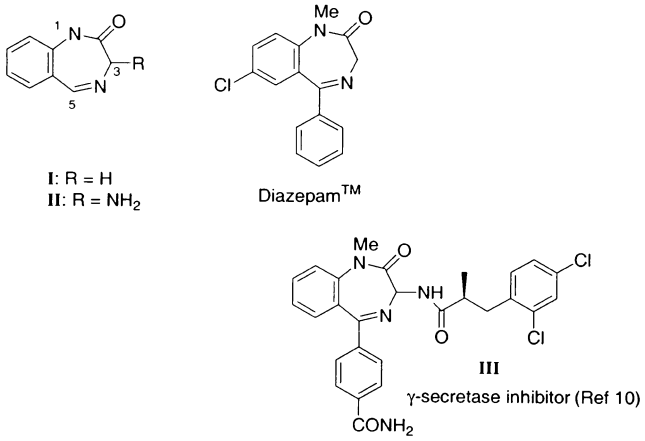

FIGURE 1. 1,4-Benzodiazepin-2(2*H*)-ones and 3-amino-1,4-benzodiazepin-2(2*H*)-ones.

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Published on Web 03/07/2003

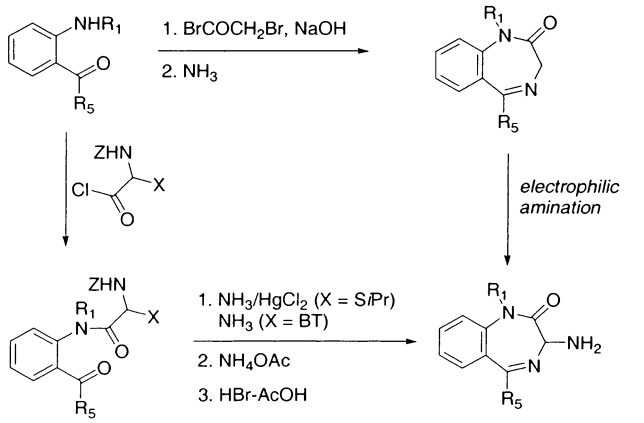


FIGURE 2. General strategies for the synthesis of 1,4-benzodiazepin-2(2*H*)-ones and 3-amino-1,4-benzodiazepin-2(2*H*)-ones.[12]

There are a number of commonly employed and efficient synthetic routes to 1,4-benzodiazepines and 3-amino-1,4-benzodiazepines,[12] which are broadly summarized in Figure 2. The major limitation with these routes is that the C-5 substituent and, to a lesser extent, the N-1 substituent are established at an early stage in the synthesis. This is clearly not ideal for the preparation of analogues containing diversity at either of these positions. One exception related to the work described in this article is contained in a Sanofi patent,[13] which describes the nucleophilic addition of two organomanganese reagents (cyclohexylmanganese and phenylmanganese) to the C-5 imidoyl chloride of a simple 1,4-benzodiazepine.

Accordingly, it was surmized that a more convergent approach to 1,4-benzodiazepines and 3-amino-1,4-benzodiazepines may well be realized through a Pd(0)-catalyzed sp^2 cross-coupling reaction of an imidoyl halide (haloimidate) or triflate with a suitable organometallic C-5 substituent (stannane, organozinc, or boronic acid) (**2** → **1**, Figure 3). In principle, **2** should be available by functionalization of bis(lactam) **3**.

Examples of carbon−carbon bond formations involving Pd(0)-catalyzed reactions of imidoyl halides or triflates are surprisingly rare, given the vast numbers of examples that involve alkenyl halides or triflates, or 2-halo- (or triflyl-) pyridines. A few examples of sp^2−sp couplings of imidoyl chlorides with alkynyl stannanes,[14,15] alkynyl cuprates,[16] and alkynes[17] are known, including an elegant approach to the synthesis of the semicorrins.[18,19] The sp^2−

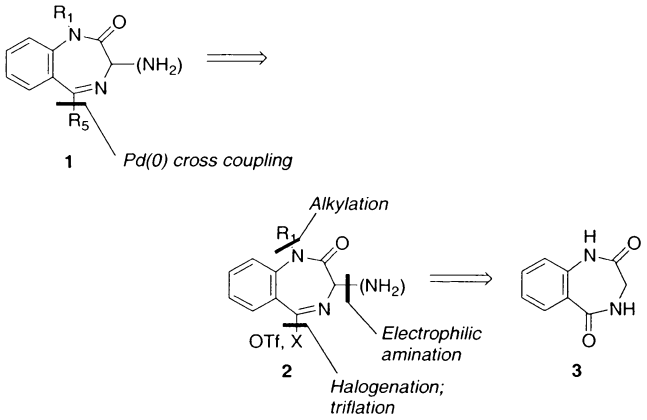
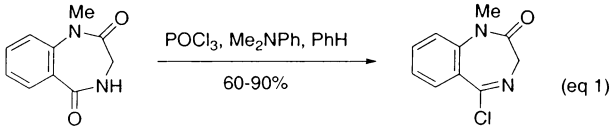


FIGURE 3. Retrosynthesis of 1,4-benzodiazepin-2(2*H*)-ones and 3-amino-1,4-benzodiazepin-2(2*H*)-ones.

sp^2 coupling of an imidoyl triflate with 2-pyridylzinc chloride has been investigated by Shiraishi and co-workers[20] and Davis has reported a single example of a Kumada coupling of a Grignard reagent with an imidoyl chloride, although even a slight variation to the structure of the imidoyl chloride caused the reaction to fail.[21] In contrast, a number of examples of Pd(0)-catalyzed cross-couplings of the isomeric lactam-derived ketene aminal triflates[22] and phosphates[23] have been reported. In this contribution, we describe the successful execution of the retrosynthesis described in Figure 3 and present a new and efficient route to a very versatile intermediate from which almost any N1-, N3-, C5-substituted benzodiazepine can be made in only four additional steps.

Results and Discussion

As a model substrate for the key cross-coupling reaction, **5** was prepared from **4**[25] following the efficient procedure described by Wade and co-workers (eq 1).[24]



The cross-coupling reaction of **5** with a representative arylborane [2-(3-pyridyl)-1,3,2-dioxaborinane] to make **6** (Table 1) was investigated under a variety of conditions utilized for the Suzuki reaction. Initial results with the

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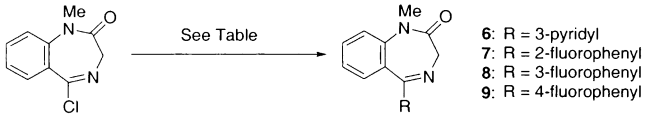
TABLE 1. Reaction of Imidoyl Chloride 5 with Boronic Acids under Various Conditions[e]



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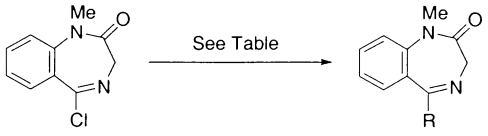
entry	Pd (equiv)	ligand/base (equiv)	reaction conditions	product (%)
1	$Pd(OAc)_2$ (0.01)	**L**[a] (0.02), KF (3)	THF, rt, 20 h	**6** (0)
2	$Pd(OAc)_2$ (0.1)	**L**[a] (0.2), KF (3)	THF, rt, 24 h	**6** (0)
3	$Pd(OAc)_2$ (0.01)	**L**[a] (0.02), K_3PO_4 (2)	toluene, 100 °C, 24 h	**6** (0)
4	$Pd(OAc)_2$ (0.1)	**L**[a] (0.2), K_3PO_4 (2)	toluene, 100 °C, 20 h	**6** (0)
5	$Pd_2(dba)_3$ (0.1)	P^tBu_3(0.2), Cs_2CO_3 (2)	dioxane, 80 °C, 24 h	**6** (31)
6	$Pd(PPh_3)_4$ (0.1)	K_3PO_4 (2)	DMF, 100 °C, 3 h	**6** (87)
7	$Pd(PPh_3)_4$ (0.1)	Na_2CO_3 (2)	H_2O−DME, 100 °C, 0.5 h	**6** (89)
8	$Pd(PPh_3)_4$ (0.1)	Na_2CO_3 (2)	H_2O−DME, RT, 10 d	**6** (91)
9	$Pd(OAc)_2$ (0.1)	PPh_3 (0.2), Cs_2CO_3 (2)	DMF, 100 °C, 2 h	**6** (95)
10[b]	$Pd(OAc)_2$ (0.1)	PPh_3 (0.2), Cs_2CO_3 (2)	DMF, 100 °C, 2 h	**7** (44)
11[c]	$Pd(OAc)_2$ (0.1)	PPh_3 (0.2), Cs_2CO_3 (2)	DMF, 100 °C, 2 h	**8** (22)
12[d]	$Pd(OAc)_2$ (0.1)	PPh_3 (0.2), Cs_2CO_3 (2)	DMF, 100 °C, 2 h	**9** (0)

[a] **L** = 2-(di-*tert*-butylphosphino)biphenyl. [b] 2-Fluorobenzeneboronic acid was used. [c] 3-Fluorobenzeneboronic acid was used. [d] 4-Fluorobenzeneboronic acid was used. [e] Reactions were performed on a 1 mmol scale with 2-(3-pyridyl)-1,3,2-dioxaborinane; yields are based on isolated, purified material.

catalyst/ligand system employed by Buchwald[26] for the cross-coupling of aryl chlorides were not encouraging (entries 1−4), with either starting material being recovered unchanged or decomposition occurring. Under conditions first described by Fu,[27] an isolated yield of 31% was obtained (entry 5). However, with $Pd(PPh_3)_4$ and either K_3PO_4[28] (entry 6) or aqueous Na_2CO_3[29] as the base, the yield of **6** was increased greatly with essentially clean and complete conversion occurring rapidly at 100 °C (entry 7). The success of the latter reaction was somewhat surprising as imidoyl chlorides are normally unstable to aqueous conditions. The reaction with Na_2CO_3/H_2O-DME (entry 8) also went to completion at room temperature but required a reaction time of over 10 days. From this initial screen, palladium(II) acetate-PPh_3-Cs_2CO_3[30] appeared to be the best conditions, yielding **6** in 95% isolated yield. However, this yield was not reproducible and on changing the structure of the boronic acid even modestly (entries 10−12) the isolated yields of **7**−**9** were disappointingly low.

Fortunately, the original conditions[29] for the Suzuki coupling (entry 7) worked reliably with a wide variety of aromatic and heteroaromatic boronic acids to give compounds **7**−**14** (entries 1−8, Table 2), even with a reduced amount of $Pd(PPh_3)_4$ (1 mol %). It was also pleasing to find that the Castro−Stevens sp−sp^2 coupling of **5** with phenylacetylene worked well to give **15** and an sp^2−sp^3 coupling with an organozinc reagent afforded **16** (Table 2, entries 9 and 10). The Stille reaction of **5** with tri(*n*-butyl)vinyltin (entry 11) also proceeded well to give the 1-azadiene **17**, but this was unstable to chromatography. Unfortunately, attempts to form an organometallic species from **5** were unsuccessful: bis(pinacolato)diboron, (dppf)$PdCl_2$, KOAc, dioxane, 80 °C[31] gave the 5-acetoxy derivative; and pinacolborane, (dppf)$PdCl_2$, $AsPh_3$, Et_3N[32] led to reduction. Attempts to form the organozinc with commercially available Rieke zinc were also unsuccessful.

TABLE 2. Reaction of Imidoyl Chloride 5 with Various Organometallics[f]



5 7-17

entry	organometallic[a]	product (%)
1	2-fluorobenzeneboronic acid	**7** (99)
2	3-fluorobenzeneboronic acid	**8** (95)
3	4-fluorobenzeneboronic acid	**9** (97)
4	3-methoxybenzeneboronic acid	**10** (90)
5	4-methoxybenzeneboronic acid	**11** (82)
6	4-nitrobenzeneboronic acid	**12** (66)
7	2-thiopheneboronic acid	**13** (94)
8	benzo[*b*]thiophene-2-boronic acid	**14** (98)
9	phenylacetylene[b]	**15** (68)
10	6-ethoxy-6-oxohexylzinc bromide[c]	**16** (76)
11	tri(*n*-butyl)vinylstannane[d]	**17**[e]

[a] Reaction conditions: Na_2CO_3 (2 equiv), $Pd(PPh_3)_4$ (0.01 equiv), 80 °C, DME−H_2O unless otherwise stated. [b] Reaction conditions: $PdCl_2(PPh_3)_2$, CuI, Et_3N, PPh_3, 90 °C. [c] Reaction conditions: $PdCl_2(PPh_3)_2$, THF, rt. [d] Reaction conditions: $Pd_2(dba)_3$, $PtBu_3$, CsF, dioxane, 100 °C. [e] Reaction product unstable to chromatography. [f] Reactions were performed on a 1 mmol scale; yields are based on isolated, purified material.

Having defined reliable conditions for the Suzuki coupling and demonstrated the effectiveness of a range of other cross-coupling reactions on chloroimidate **5**, we next turned our attention to applying the same reaction conditions to the more challenging 3-amino-1,4-benzodiazepines.

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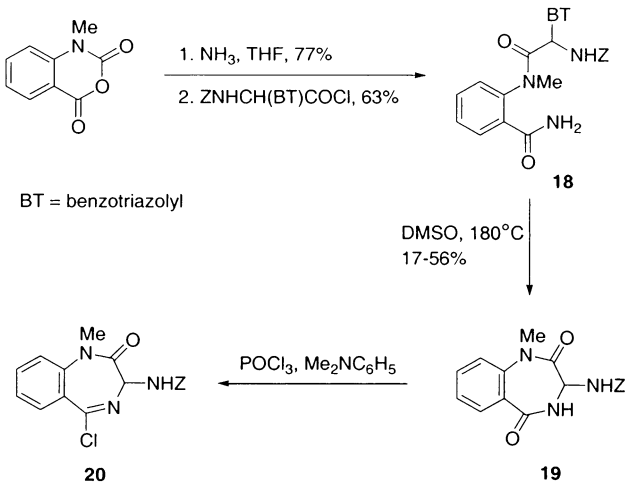
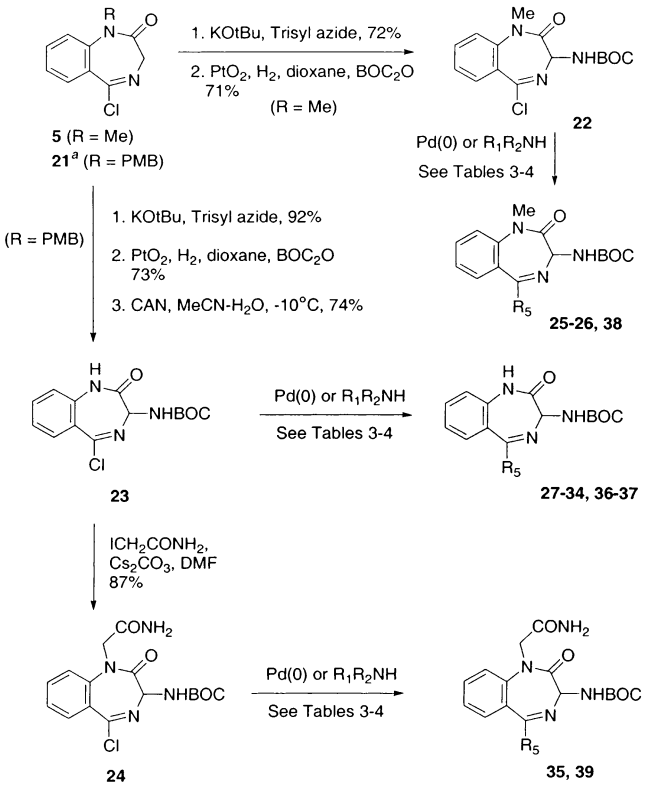
SCHEME 1. Synthesis of Imidoyl Chloride 20



SCHEME 2. Synthesis and Reaction of 3-Amino-5-chloro-1,4-benzodiazepines

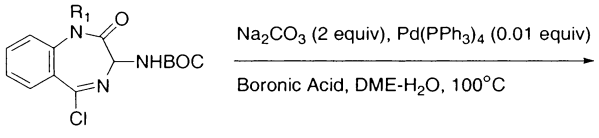


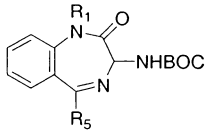
[a] Prepared by alkylation of **3** (ref 12) and imidoyl chloride formation (64%) (see Experimental Section).

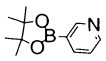
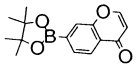
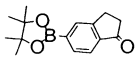
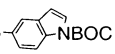
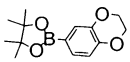
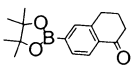
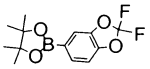
Surprisingly, the 3-amino-5-chloro-1,4-benzodiazepine or, at the inception of this work, 3-amino-1,4-benzodiazepin-2,5-dione frameworks were not known compounds.[33] Our first generation synthesis of a 3-amino-1,4-benzodiazepin-2,5-dione is shown in Scheme 1. Reaction of *N*-methyl anthranilamide with the acid chloride of α-benzotriazolyl-CBZ-glycine under conditions described by Sherrill and Sugg[12f] gave **18**, which underwent thermal cyclization (180 °C, DMSO) with the elimination of benzotriazole to form **19**. Bis(lactam) **19** was selectively converted to the imidoyl chloride **20** in high yield by treatment with $POCl_3$ and *N*,*N*-dimethylaniline at reflux for 5 h, followed by an aqueous workup and chromatography. Alternatively the reaction can be performed in only a few minutes by refluxing **19** in neat $POCl_3$, although on a practical scale the workup is more difficult. Once pure, **20** was stable in a stoppered flask at room temperature for several months. Although the cyclization reaction was efficient on a small scale (56% isolated yield), attempts to scale it up or optimize the reaction conditions were repeatedly unsuccessful. In particular, the reaction always failed when the N1 substituent was a hydrogen atom. Given that the N1 position is a valuable point of diversity, we sought an alternative solution.

(33) A synthesis of 3-amino-3,4-dihydro-1-methyl-1*H*-1,4-benzodiazepine-2,5-dione is described by Wu et al., WO 9828268.

TABLE 3. Reaction of Imidoyl Chlorides 22−24 with Various Boronic Acids[b]

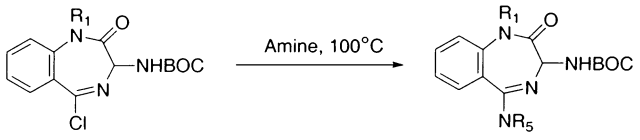




Entry	R_1	Boronic Acid	Yield %
1	Me		**25** (88)
2	Me		**26**(93)[a]
3	H	4-chlorobenzeneboronic acid	**27** (70)
4	H	5-quinolyl boronic acid	**28** (72)
5	H		**29** (51)
6	H		**30** (77)
7	H	3,4-(methylenedioxy)-benzeneboronic acid	**31** (77)
8	H		**32** (67)
9	H		**33** (52)
10	H	4-(trifluoromethyl)-benzene boronic acid	**34** (44)
11	CH_2CONH_2		**35** (82)[a]

[a] Overall yield following deprotection of the BOC group with TFA-DCM. [b] Yields are based on isolated, chromatographically pure material. Noncommercially available boronates were made from the corresponding bromides or triflates by the Miyaura protocol (ref 31).

TABLE 4. Reaction of Imidoyl Chlorides 22−24 with Various Amines[a]



22-24 36-39

entry	R_1	amine	product (%)
1	H	morpholine	**36** (76)
2	H	azetidine	**37** (81)
3	Me	piperidine	**38** (64)
4	CH_2CONH_2	morpholine	**39** (84)

[a] Yields are based on isolated, chromatographically pure material.

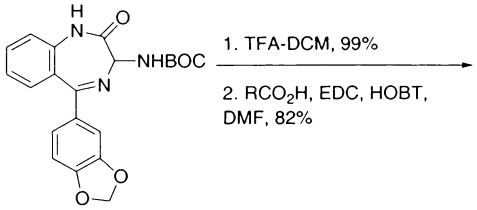
Our second generation approach, based on the electrophilic azidation of **5** (R = Me) or **21** (R = PMB), was more reliable and is shown in Scheme 2. The azidation[8] of **5** proceeded well to give the azide in good isolated yield. Reduction of the azide functionality to give **22** was achieved by hydrogenation with PtO_2 under a slight pressure of hydrogen in the presence of a modest excess of $(BOC)_2O$. Other methods (PPh_3-H_2O-MeOH; TMSI) or hydrogenation in the absence of $(BOC)_2O$ were unsuccessful.

Application to the synthesis of **21** worked equally well and on removal of the PMB protecting group with ceric ammonium nitrate at −10 °C **23** was obtained reliably (and on a multigram scale) in 60−80% yield. Imidoyl chloride **23** can be selectively alkylated at the N1 position with iodoacetamide (and with other simple alkylating agents—data not shown) to give **24**.

A variety of cross-coupling reactions were performed on imidoyl chlorides **22**−**24** with use of the conditions defined in our earlier study, and the results are shown in Table 3. From these results, it can be seen that the yields of **25**−**33** are generally good, even with unusual and functionalized boronic acids (entries 1−11). It is noteworthy that the cross-coupling reaction proceeds well either with or without functionality at the N1 position, thereby allowing the N1 and C5 substituents to be introduced in either order.

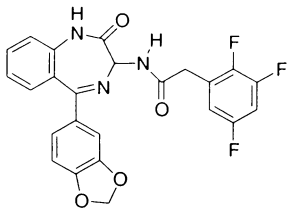
In a further exploration of the reactivity of imidoyl chlorides **22**−**24**, a variety of simple secondary amines were reacted with **22**−**24** to give **36**−**39** as shown in Table 4. The products, amidinobenzodiazepines, are often more water-soluble and brain penetrant than typical benzodiazepines.[30,34] Previous syntheses of amidinobenzodiazepines have involved formation of the C3-unsubstituted amidine, followed by electrophilic amination and reduction;[35] this new route would appear to be an attractive, more convergent, alternative.

Finally, to illustrate the use of these new strategies in preparing biologically active benzodiazepines, the BOC group was readily removed from **31** with TFA, and acylation with a representative phenylacetic acid proceeded uneventfully to give **40** in high yield (eq 2).



31

(eq 2)



40

Conclusion

A new approach to the synthesis of 1,4-benzodiazepines and 3-amino-1,4-benzodiazepines, which utilizes the cross-coupling reaction of an imidoyl chloride as the key step, has been described. A five-step synthesis of **23** allows access to virtually any N1-, C3-acylamino, C5-carbon-, or nitrogen-substituted benzodiazepine from commercially available starting materials via four further transformations (a Pd(0)-catalyzed cross-coupling, an alkylation, a TFA-mediated BOC-deprotection, and an acylation). We believe this work refreshes the benzodiazepine field by the application of modern cross-coupling reactions and will assist in the future preparation of biologically active benzodiazepines.[41]

Experimental Section

General Considerations. Melting points are uncorrected. Unless otherwise noted, all reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. Solutions were evaporated under reduced pressure with a rotary evaporator. Flash column chromatography was performed on silica gel (40−63 μm mesh). Starting materials were obtained commercially and used as received.

2*H*-1,4-Benzodiazepin-2-one, 5-chloro-1,3-dihydro-1-methyl- (5):[36] A solution of **4** (25 g, 0.13 mol), *N*,*N*-dimethylaniline (33 mL, 0.26 mol), $POCl_3$ (12.2 mL, 0.13 mol), and benzene (250 mL) was refluxed for 7 h, then allowed to cool overnight. The reaction mixture was cooled to 0 °C, treated with ice water (100 mL), and stirred for 30 min until the reaction mixture reached room temperature. The reaction mixture was poured into more water and ether. The organic layer was separated, washed with water and brine, dried ($MgSO_4$), filtered, and evaporated. Trituration with ether gave **5** (21.8 g, 80%) as a white solid: mp 185−187 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 7.82 (1H, dd, J = 7.8, 1.5 Hz), 7.58 (1H, ddd, J = 7.4, 7.4, 0.8 Hz), 7.32−7.27 (2H, m), 4.63 (1H, br s), 3.27 (1H, br s), 3.41 (3H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 37.2,

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(35) Reference 12e and references therein.

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58.1, 123.0, 126.6, 129.1, 131.2, 134.6, 144.2, 159.3, 170.6. MS: 209 $(M + H)^+$. Anal. Calcd for $C_{10}H_9OClN_2$: C 57.57, H 4.35, N 13.43. Found: C 57.25, H 4.48, N 13.39.

General Procedure for the Cross-Coupling of Imidoyl Chlorides with Boronic Acids (General Procedure A). 2*H*-1,4-Benzodiazepin-2-one, 5-(3-pyridyl)-1,3-dihydro-1-methyl- (6): A mixture of the imidoyl chloride **5** (200 mg, 0.96 mmol) was treated with 2-(3-pyridyl)-1,3,2-dioxaborinane (188 mg, 1.15 mmol), $Pd(PPh_3)_4$ (11.1 mg, 0.01 mmol), 2 N aqueous Na_2CO_3 (1.5 mL), and DME (2.5 mL), degassed with nitrogen, and heated at 80 °C for 120 min. The reaction mixture was cooled, extracted with ethyl acetate, washed with brine, dried, filtered, and evaporated to give the crude product. Purification by flash column chromatography (5% MeOH−CH_2Cl_2) gave **6** (219 mg, 91%) as a white powder: mp 240−242 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.79 (1H, d, J = 1.4 Hz), 8.68 (1H, dd, J = 4.8, 1.4 Hz), 8.03 (1H, ddd, J = 7.9, 1.9. 1.9 Hz), 7.59 (1H, ddd, J = 7.3, 7.3, 1.7 Hz), 7.38 (1H, d, J = 8.3 Hz), 7.37−7.34 (1H, m), 7.31 (1H, dd, J = 7.8, 1.7), 7.24 (1H, dd, J = 7.9, 7.9 Hz), 4.86 (1H, d, J = 10.6 Hz), 4.12 (1H, d, J = 10.6 Hz), 3.43 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 169.6, 168.0, 151.5, 150.2, 144.1, 137.0, 134.4, 132.4, 130.0, 127.7, 124.5, 123.9, 122.2, 57.3, 34.8. MS: 252 $(M + H)^+$.

2*H*-1,4-Benzodiazepin-2-one, 5-(2-fluorophenyl)-1,3-dihydro-1-methyl- (7):[37] Following general procedure A, **7** was obtained in 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.67−7.01 (8H, m), 4.86 (1H, d, J = 10.7 Hz), 3.81 (1H, d, J = 10.7 Hz), 3.44 (3H, s). MS: 269 $(M + H)^+$. Anal. Calcd for $C_{16}H_{13}ON_2F$: C 71.63, H 4.83, N 10.13. Found: C 71.48, H 4.88, N 10.44.

2*H*-1,4-Benzodiazepin-2-one, 5-(3-fluorophenyl)-1,3-dihydro-1-methyl-(8): Following general procedure A, **8** was obtained in 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.59−7.13 (8H, m), 4.82 (1H, d, J = 10.7 Hz), 3.78 (1H, d, J = 10.7 Hz), 3.42 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 170.2, 169.0 (d, J = 2.5 Hz), 162.6 (d, J = 246.5 Hz), 144.1, 140.9 (d, J = 6.9 Hz), 131.6, 130.24, 129.8 (d, J = 8.1 Hz), 128.2, 125.4 (d, J = 3.2 Hz), 124.0, 121.2, 117.3 (d, J = 21.5 Hz), 116.3 (d, J = 22.8 Hz), 57.0, 34.8. MS: 269 $(M + H)^+$. Anal. Calcd for $C_{16}H_{13}ON_2F$: C 71.63, H 4.83, N 10.13. Found: C 71.05, H 4.69, N 10.17.

2*H*-1,4-Benzodiazepin-2-one, 5-(4-fluorophenyl)-1,3-dihydro-1-methyl- (9):[38] Following general procedure A, **9** was obtained in 97% yield. ^{1}H NMR (360 MHz, $CDCl_3$): 7.64−7.05 (8H, m), 4.79 (1H, d, J = 10.7 Hz), 3.76 (1H, d, J = 10.7 Hz), 3.42 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 170.3, 168.9, 164.2 (d, J = 250.6 Hz), 144.1, 134.99, 134.96, 131.64, 131.55, 131.53, 130.3, 128.5, 123.9, 121.1, 115.3, 115.1, 56.9, 34.8. MS: 269 $(M + H)^+$. Anal. Calcd for $C_{16}H_{13}ON_2F \cdot 0.1H_2O$: C 71.15, H 4.85, N 10.37. Found: C 71.32, H 4.79, N 10.15.

2*H*-1,4-Benzodiazepin-2-one, 5-(3-methoxyphenyl)-1,3-dihydro-1-methyl- (10):[39] Following general procedure A, **10** was obtained in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.55 (1H, ddd, J = 7.4, 7.4, 1.6 Hz), 7.53−7.26 (4H, m), 7.21−7.14 (1H, m), 7.10 (1H, ddd, J = 7.7, 7.7, 1.2 Hz), 7.02−6.99 (1H, m), 4.81 (1H, d, J = 10.7 Hz), 3.84 (3H, s), 3.77 (1H, d, J = 10.7 Hz), 3.41 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 169.8, 169.5, 159.5, 144.0, 140.2, 132.0, 130.2, 129.8, 128.3, 124.3, 122.4, 122.0, 116.6, 114.4, 57.1, 55.6, 34.6. MS: 281 $(M + H)^+$. Measured M^+ 280.12117(±0.0016).

2*H*-1,4-Benzodiazepin-2-one, 5-(4-methoxyphenyl)-1,3-dihydro-1-methyl- (11): Following general procedure A, **11** was obtained in 82% yield as a white solid: mp 151−152 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 7.59−7.52 (3H, m), 7.35−7.32 (2H, m), 7.21−7.17 (1H, m), 6.92−6.89 (2H, m), 4.76 (1H, d, J = 10.7 Hz), 3.85 (3H, s), 3.74 (1H, d, J = 10.7 Hz), 3.41 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 170.1, 168.9, 161.4, 144.0, 131.9, 131.3, 131.2, 130.3, 128.4, 124.3, 122.0, 114.1, 56.9, 55.8, 34.6. MS: 281 $(M + H)^+$. Anal. Calcd for $C_{17}H_{16}O_2N_2$: C 72.84, H 5.75, N 9.99. Found: C 72.48, H 5.88, N 9.57. Measured M^+ 280.12117(±0.0013).

2*H*-1,4-Benzodiazepin-2-one, 5-(4-nitrophenyl)-1,3-dihydro-1-methyl- (12): Following general procedure A, **12** was obtained in 66% yield as a white solid: mp 196−200 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 8.24 (2H, d, J = 9.1), 7.83 (2H, d, J = 9.1 Hz), 7.66−7.61 (1H, m), 7.43 (1H, d, J = 8.4 Hz), 7.27−7.24 (2H, m), 4.89 (1H, d, J = 10.5 Hz), 3.84 (1H, d, J = 10.5 Hz), 3.45 (3H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 171.5, 170.1, 150.7, 146.2, 146.0, 133.9, 132.3, 131.7, 129.5, 126.0, 125.2, 123.3, 59.2, 36.8. MS: 296 $(M + H)^+$. Measured M^+ 295.09569(±0.001).

2*H*-1,4-Benzodiazepin-2-one, 5-(2-thienyl)-1,3-dihydro-1-methyl-(13):[40] Following general procedure A, **13** was obtained in 94% yield. ^{1}H NMR ($CDCl_3$, 360 MHz): 7.58−7.22 (7H, m), 4.73 (1H, d, J = 10.9 Hz), 3.77 (1H, d, J = 10.9 Hz), 3.39 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$), 170.6, 164.9, 143.6, 141.5, 131.3, 130.0, 129.02, 129.00, 128.1, 125.8, 123.9, 121.0, 56.6, 34.8. MS: 257 $(M + 1)^+$. Anal. Calcd for $C_{14}H_{12}ON_2S$: C 65.60, H 4.72, N 10.93, S 12.51. Found: C 65.82, H 5.12, N 10.57, S 12.30.

2*H*-1,4-Benzodiazepin-2-one, 5-(2- benzo[*b*]thiophenyl)-1,3-dihydro-1-methyl- (14): Following general procedure A, **14** was obtained in 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.87−7.26 (9H, m), 4.79 (1H, d, J = 10.9 Hz), 3.84 (1H, d, J = 10.9 Hz), 3.41 (3H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 170.5, 164.5, 144.3, 143.6, 141.2, 139.5, 131.7, 129.9, 128.4, 127.6, 126.1, 124.7, 124.6, 124.2, 122.5, 121.3, 56.9, 34.9. MS: 307 $(M + 1)^+$. Anal. Calcd for $C_{18}H_{14}ON_2S$ $(0.1H_2O)$: C 70.15, H 4.58, N 9.09, S 10.40. Found: C 69.97, H 4.85, N 8.71, S 10.06.

2*H*-1,4-Benzodiazepin-2-one, 5-(phenylalkynyl)-1,3-dihydro-1-methyl- (15): A solution of chloroimidate **5** (250 mg, 1.20 mmol), phenylacetylene (147 mg, 1.44 mmol), CuI (6 mg), PPh_3 (84 mg), and $PdCl_2(PPh_3)_2$ (42 mg) in triethylamine (2 mL) was stirred at 90 °C overnight. The reaction mixture was partitioned between ethyl acetate and water. The organic phase was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by column chromatography (hexane/ethyl acetate 6:4) gave **15** (224 mg, 68%) as a white foam. ^{1}H NMR (360 MHz, $CDCl_3$): 7.94−7.91 (1H, m), 7.59−7.54 (3H, m), 7.40−7.26 (5H, m), 4.8 (1H, br s), 3.8 (1H, br s), 3.41 (1H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 170.9, 158.0, 144.4, 134.1, 133.8, 131.6, 131.3, 130.9, 130.3, 126.3, 123.1, 123.0, 93.5, 89.5, 59.2, 37.0. MS: 275 $(M + H)^+$. Measured M^+ 274.11061(±0.0021).

2*H*-1,4-Benzodiazepin-2-one, 5-(6-ethoxy-6-oxohexyl)-1,3-dihydro-1-methyl- (16): A solution of **5** (250 mg, 1.20 mmol) in THF (3 mL) was treated with $Pd(PPh_3)_2Cl_2$ (84 mg, 0.12 mmol) and 6-ethoxy-6-oxohexylzinc bromide (0.5 M in THF, 3.6 mL) and stirred at room temperature for 20 h. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with brine, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by column chromatography (hexane/ethyl acetate 1:1 → 3:7) gave **16** (186 mg, 49%), and unchanged starting material (95 mg, 38%). ^{1}H NMR (360 MHz, $CDCl_3$): 7.51−7.21 (4H, m), 4.56 (1H, d, J = 10.9 Hz), 4.10 (1H, q, J = 7.2 Hz), 3.61 (1H, d, J = 10.9 Hz), 3.36 (3H, s), 2.79 (2H, m), 2.24 (2H, m), 2.24 (2H, t, J = 7.5 Hz), 1.58 (4H, m), 1.33 (2H, m), 1.23 (3H, t, J = 7.2 Hz). MS: 317 $(M + H)^+$.

{**Benzotriazol-2-yl-[(2-carbamoyl-phenyl)-methyl-carbamoyl]-methyl**}**-carbamic acid benzyl ester (18):** A solution of 2-(benzotriazol-1-yl)-*N*-(benzyloxycarbonyl)glycine (Katritzky et al.[42]) (50 g, 0.15 mol) in THF (300 mL) at 0 °C was treated slowly with oxalyl chloride (2.0 M in CH_2Cl_2, 81 mL, 0.16 mol) and DMF (1 mL). The reaction mixture was stirred at 0 °C for 2 h, then treated with a solution of 2-(methylamino)benzamide (23 g, 0.15 mol) and 4-methylmorpholine (38 mL, 0.35 mol) in THF (100 mL). The reaction mixture was stirred overnight at 40 °C, then filtered. The residue was partitioned between water and warm ethyl acetate. The aqueous layer was extracted three times with ethyl acetate. The combined extracts were combined with the original filtrate, dried ($MgSO_4$), filtered and evaporated in

(42) Katritzky, A. R.; et al. *J. Org. Chem*. **1990**, *55*, 2206

vacuo. Trituration with ethyl acetate gave **18** as a white powder (23 g, 33%), mp 68−75 °C. The mother liquors were evaporated and purified by column chromatography to give a further quantity of **18** (21 g, 30%). ^{1}H NMR (400 MHz, DMSO): 9.3 (1H, d), 8.8 (1H, d), 8.15−6.90 (15H, m), 4.92−4.75 (2H, m), 3.12 (3H, d, J = 4.2 Hz).

(1-Methyl-2,5-dioxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-carbamic acid benzyl ester (19): Compound **18** (23 g, 0.05 mol) was added to DMSO (500 mL) at 180 °C. The reaction mixture was stirred at 180 °C for 20 min, cooled to room temperature, and diluted with 1 M NaOH (aq) and ether. The aqueous phase was extracted with ethyl acetate (five times) and the combined organic phases were washed with brine, dried, filtered and evaporated. Purification by column chromatography gave **19** (5.8 g, 34%) as a yellow solid, mp 143−145 °C. ^{1}H NMR (400 MHz, DMSO): 8.74 (1H, br d), 7.74−7.32 (10H, m), 5.21 (1H, dd, J = 7.8, 4.7), 5.07 (2H, s), 3.39 (3H, s). ^{13}C NMR (100 MHz, DMSO): 35.9, 59.5, 66.6, 123.1, 126.4, 128.3, 128.5, 128.9, 129.0, 129.9, 133.1, 137.0, 140.4, 155.6, 166.4, 168.1. MS: 340 $(M + H)^+$. Anal. Calcd for $C_{18}H_{17}O_4N_3$: C 63.71, H 5.05, N 12.38. Found: C 63.25, H 5.01, N 12.26. Measured M^+ 339.121 (±0.0002).

(1-Methyl-5-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*e*][1,4]diazepin-3-yl)-carbamic acid benzyl ester (20): A solution of **19** (1.1 g, 3.24 mmol) in $POCl_3$ (3 mL) was heated at 90 °C for 10 min. The reaction mixture was cooled, diluted with ethyl acetate, and poured into ice-cold $NaHCO_3$ solution. The organic phase was washed with $NaHCO_3$ solution (twice) and brine (twice), dried ($MgSO_4$), filtered, and evaporated in vacuo. Flash column chromatography (hexane/ethyl acetate 2:1) gave **20** as a white foam (950 mg, 82%). ^{1}H NMR (360 MHz, $CDCl_3$) 7.84 (1H, d, J = 7.9 Hz), 7.60 (1H, t, J = 7.3 Hz), 7.36−7.26 (7H, m), 6.59 (1H, d, J = 8.3 Hz), 5.22 (1H, d, J = 8.3 Hz), 5.13 (1H, d, J = 12.3 Hz), 5.09 (1H, d, J = 12.3 Hz), 3.44 (3H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 37.8, 69.0, 70.3, 123.5, 127.4, 129.7, 129.9, 130.0, 130.3, 131.2, 135.2, 137.9, 142.9, 156.1, 157.4, 167.8. MS: 380 $(M + Na)^+$. Anal. Calcd for $C_{18}H_{16}O_3N_3Cl$: C 60.42, H 4.51, N 11.74. Found: C 60.40, H 4.44, N 11.23. Measured M^+ 357.08801(±0.0010).

2*H*-1,4-Benzodiazepin-2-one, 5-chloro-1,2-dihydro-1-(4-methoxybenzyl)- (21): Step 1. A suspension of **3** (30 g, 0.17 mol), 4-methoxybenzyl chloride (23 mL, 0.17 mol), and Cs_2CO_3 (165 g, 0.51 mol) in DMF (750 mL) was stirred overnight at room temperature. The reaction mixture was filtered. The filtrate was evaporated in vacuo and the resulting residue partitioned between water and ethyl acetate. The aqueous layer was extracted with ethyl acetate, and the combined organic layers were dried, filtered, and evaporated in vacuo. Trituration with hexane gave the alkylated lactam (25 g). Further product was obtained by column chromatography (2.5% MeOH−CH_2Cl_2) of the mother liquors to give a total yield of 35 g (69%). ^{1}H NMR (400 MHz, $CDCl_3$) 8.75 (1H, t, J = 5.6 Hz), 7.63 (1H, dd, J = 1.6, 7.8 Hz), 7.54−7.46 (2H, m), 7.29−7.25 (1H, m), 7.03 (2H, d, J = 6.6 Hz), 6.80 (2H, d, J = 6.6 Hz), 5.25 (1H, br d, J = 10 Hz), 4.87 (1H, br d, J = 10 Hz), 3.85−3.77 (1H, m), 3.68 (3H, s), 3.59−3.50 (1H, m). MS: 439 $(M + H)^+$.

Step 2. A solution of the foregoing compound (4.3 g, 0.014 mol), *N*,*N*-dimethylaniline (3.7 mL, 0.029 mol), $POCl_3$ (1.35 mL, 0.014 mol), and benzene (30 mL) was refluxed for 7 h, then allowed to cool overnight. The reaction mixture was cooled to 0 °C, treated with ice water (15 mL), and stirred for 30 min until the reaction mixture reached room temperature. The reaction mixture was poured into more water and ether. The organic layer was separated, washed, dried, filtered, and evaporated. Purification by chromatography (CH_2Cl_2/hexane/ethyl acetate 1:1:0.1) gave **21** (3.5 g, 77%). ^{1}H NMR (360 MHz NMR, d_6-DMSO): 7.73 (1H, d, J = 7.5 Hz), 7.61−7.57 (2H, m), 7.34−7.30 (1H, m), 6.99 (2H, d, J = 8.6 Hz), 6.81 (2H, d, J = 8.6 Hz), 5.3 (1H, br d), 4.9 (1H, br d), 4.45 (1H, br d), 3.85 (1H, br d), 3.68 (3H, s).

(1-Methyl-5-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (22): Step 1. A solution of **5** (3.4 g, 0.016 mol) (WO 9514473) was dissolved in dry THF (120 mL) and cooled to −78 °C. A solution of KOtBu (1.0 M in THF, 19 mL) was added dropwise. The solution was warmed to −30 °C, held at that temperature for 5 min, then re-cooled to −78 °C. The reaction mixture was treated with a solution of trisyl azide (5.56 g, 0.018 mol) in THF (60 mL). After 5 min, glacial acetic acid (8.5 mL) was added and the reaction mixture was left to warm to room temperature overnight. The solvent was partially removed in vacuo and the residue was taken up in ethyl acetate−brine−water. The organic layer was separated, washed with brine, dried, filtered, and evaporated. Purification by flash column chromatography (hexane/ethyl acetate 7:3) gave the azide (2.3 g, 57%). ^{1}H NMR (400 MHz, $CDCl_3$): 7.84 (1H, dd, J = 7.9, 1.4 Hz), 7.64 (1H, ddd, J = 7.5, 7.5, 1.5 Hz), 7.37−7.31 (2H, m), 4.41 (1H, s), 3.47 (3H, s).

Step 2. A solution of the foregoing azide (0.67 g, 2.69 mmol) in dioxane (20 mL) was treated with BOC_2O (0.63 g, 2.96 mmol) and PtO_2 (20.6 mg, 0.13 mmol) and hydrogenated at 40 psi at room temperature for 4 h. The reaction mixture was filtered through Hyflo, washing with ethyl acetate. The reaction mixture was evaporated in vacuo and purified by column chromatography (5% ethyl acetate−CH_2Cl_2) to give **22** (0.58 g, 67%) as a white powder: mp 197−200 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 7.84 (1H, dd, J = 7.9, 1.4 Hz), 7.62−7.58 (1H, m), 7.35−7.28 (2H, m), 6.32 (1H, d, J = 8.8 Hz), 5.20 (1H, d, J = 8.8 Hz), 3.45 (3H, s), 1.44 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$) 166.7, 155.2, 153.7, 141.8, 134.2, 128.9, 127.1, 125.8, 122.9, 79.4, 69.2, 35.9, 28.5. Anal. Calcd for $C_{15}H_{18}ClN_3O_3$: C 55.64, H 5.60, N 12.98. Found: C 54.94, H 5.58, N 12.87. MS: 324 $(M + H)^+$. Measured M^+ 323.10366 (±0.0014).

(5-Chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-carbamic acid *tert*-butyl ester (23): Step 1. A solution of **21** (24 g, 0.08 mol) was dissolved in THF (500 mL), cooled to −78 °C, and treated with a solution of KOtBu (1.0 M in THF, 122 mL, 0.122 mol). The reaction mixture was stirred for 30 min at −78 °C, then was treated with a solution of trisyl azide (28 g, 0.096 mol) in THF (100 mL) and stirred at −78 °C for 40 min. The reaction mixture was treated with acetic acid (70 mL), warmed to room temperature, and stirred overnight. The reaction mixture was evaporated partially in vacuo, taken up in ethyl acetate−water, washed, dried ($MgSO_4$), filtered, and evaporated in vacuo. Purification by chromatography gave the azide (25 g, 92%). ^{1}H NMR (360 MHz, $CDCl_3$): 7.77 (1H, d, J = 8.5 Hz), 7.67−7.64 (2H, m), 7.40−7.35 (1H, m), 6.96 (2H, d, J = 6.6 Hz), 6.82 (2H, d, J = 6.6 Hz), 5.33 (1H, d, J = 15.5 Hz), 4.97 (1H, d, J = 15.5 Hz), 3.68 (3H, s), 3.35 (1H, s).

Step 2. A solution of the foregoing azide (25 g, 0.70 mol) in dioxane (300 mL) was treated with BOC_2O (25 g, 0.105 mol) and PtO_2 (2.5 g, 0.011 mol) and hydrogenated at 40 psi at room temperature for 3.5 h. The reaction mixture was filtered through Hyflo and purified by column chromatography to give the BOC-carbamate (22 g, 73%). ^{1}H NMR (360 MHz NMR, d_6-DMSO) 7.95 (1H, d, J = 8.7 Hz), 7.78−7.68 (3H, m), 7.41−7.36 (1H, m), 6.93 (2H, d, J = 8.6 Hz), 6.78 (2H, d, J = 8.6 Hz), 5.37 (1H, d, J = 15.5 Hz), 5.10 (1H, d, J = 8.7 Hz), 4.89 (1H, d, J = 15.5 Hz), 3.67 (3H, s), 1.39 (9H, s).

Step 3. A solution of the foregoing compound (5 g, 0.012 mol) was dissolved in acetonitrile (225 mL) and water (85 mL) and cooled to −15 °C. A solution of ceric ammonium nitrate (50 g, 0.091 mol) in water was added in three portions and the reaction mixture was stirred for 2 h, then diluted with ethyl acetate and water. The organic layer was washed with water and brine. Purification by a combination of trituration and chromatography (CH_2Cl_2/hexane/ethyl acetate 1:1:0.3) gave the deprotected chloroimidate **23** (2.7 g, 74%) as a white solid, mp 204−206 °C. ^{1}H NMR (400 MHz NMR, DMSO) 11.03 (1H, s), 7.85−7.82 (2H, m), 7.68−7.64 (1H, m), 7.37−7.33 (1H, m), 7.24−7.22 (1H, m), 4.98 (1H, d, J = 8.7 Hz), 1.39 (9H, s).

^{13}C NMR (100 MHz, $CDCl_3$) 166.7, 155.2, 153.7, 138.0, 134.1, 129.8, 125.3, 124.7, 121.8, 79.3, 69.1, 28.5. Anal. Calcd for $C_{14}H_{16}O_3N_3Cl$: C 54.29, H 5.21, N 13.57. Found: C 54.20, H 5.26, N 13.44. Measured M^+ 309.08801(±0.0015).

(1-(Ethylcarboxamido)-5-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (24): A solution of **23** (600 mg, 1.94 mmol) in DMF (10 mL) was treated with iodoacetamide (394 mg, 2.12 mmol) and cesium carbonate (1.9 g, 5.83 mmol) and stirred at room temperature for 1 h. The reaction mixture was diluted with ethyl acetate and brine, washed, dried, filtered, and evaporated. Purification by column chromatography (CH_2Cl_2/ethyl acetate 1:1) gave the alkylated chloroimidate **24** (620 mg, 87%) as a white solid :mp 204−207 °C. ^{1}H NMR (400 MHz NMR, DMSO): 7.91−7.83 (2H, m), 7.77−7.72 (1H, m), 7.65 (1H, s), 7.48−7.43 (2H, m), 7.20 (1H, s), 5.08 (1H, d), 4.46 (1H, d), 4.33 (1H, d), 1.38 (9H, s). ^{13}C NMR (100 MHz, DMSO): 169.3, 166.0, 155.2, 141.3, 134.1, 128.8, 127.6, 126.1, 123.1, 79.5, 68.9, 51.5, 28.5. MS: 367 $(M + H)^+$. Anal. Calcd for $C_{16}H_{19}O_4N_4Cl$: C 52.39, H 5.22, N 15.27. Found: C 51.63, H 5.07, N 15.50.

(1-Methyl-5-(3-pyridyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (25): Following general procedure A, **25** was obtained in 88% yield as a white solid: mp 238−240 °C. ^{1}H NMR (360 MHz, DMSO) 8.69 (2H, br s), 7.91 (1H, d, J = 8.0 Hz), 7.85 (1H, d, J = 7.5 Hz), 7.78−7.66 (2H, m), 7.49 (1H, dd, J = 4.9, 7.8 Hz), 7.36−7.34 (2H, m), 5.07 (1H, d, J = 7.5 Hz), 3.38 (3H, s), 1.39 (9H, s). ^{13}C NMR (90 MHz, DMSO) 30.4, 37.2, 71.7, 80.9, 124.6, 125.7, 126.8, 129.7, 131.6, 134.7, 135.5, 138.9, 145.1, 152.1, 153.6, 157.1, 166.7, 169.8. MS: 367 $(M + H)^+$. Anal. Calcd for $C_{20}H_{22}O_3N_4$: C 65.56, H 6.05, N 15.29. Found: C 65.34, H 6.06, N 15.05. Measured M^+ 366.16918(±0.0014).

(1-Methyl-5-(7-chromanoyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (26): Following general procedure A and deprotection of the BOC group with TFA−CH_2Cl_2, **26** was obtained in 77% yield as a pale yellow solid: mp 162−165 °C. ^{1}H NMR (360 MHz, DMSO) 8.34 (1H, d, J = 6.1 Hz), 8.13 (1H, d, J = 8.7 Hz), 7.76−7.65 (4H, m), 7.37−7.31 (2H, m), 6.41 (1H, d, J = 6.1 Hz), 4.6 (1H, vbr s), 4.54 (1H, s), 3.40 (3H, s). ^{13}C NMR (100 MHz, DMSO) 176.5, 169.8, 163.8, 157.9, 156.0, 143.46, 143.45, 132.7, 129.7, 128.0, 126.2, 125.7, 125.5, 124.7, 122.6, 119.7, 113.0, 71.1, 35.2. MS: 333 $(M + H)^+$. Measured M^+ 333.11134(±0.0017).

(5-(4-Chlorophenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (27): Following general procedure A, **27** was obtained in 70% yield as a white solid: mp 189−191 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 9.03 (1H, s), 7.56−7.48 (3H, m), 7.35 (1H, s), 7.33 (1H, s), 7.31 (1H, dd, J = 7.4, 1.2 Hz), 7.19 (2H, t, J = 7.6 Hz), 6.37 (1H, d, J = 8.6 Hz), 5.31−5.29 (1H, m), 1.49 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 169.0, 166.6, 155.3, 137.5, 137.0, 136.9, 132.3, 131.2, 131.0, 128.5, 127.3, 124.2, 121.6, 80.3, 68.7, 28.4. MS: 330 $(M - {}^tBu + H)^+$. Measured M^+ 385.11931(±0.0004).

(5-(5-Quinolyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*]-[1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (28): Following general procedure A, **28** was obtained in 72% yield as a white solid: mp 211−214 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 10.10 (1H, s), 9.11 (1H, d, J = 1.1 Hz), 8.29 (1H, s), 8.13 (1H, d, J = 8.4 Hz), 7.79 (1H, d, J = 8.1 Hz), 7.75 (1H, t, J = 8.1 Hz), 7.55 (2H, t, J = 7.7 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.29 (1H, d, J = 8.1 Hz), 7.19 (1H, t, J = 7.5 Hz), 6.56 (1H, d, J = 8.4 Hz), 5.41 (1H, d, J = 8.4 Hz), 1.51 (9H, s). ^{13}C NMR (360 MHz, $CDCl_3$): 170.9, 167.3, 157.2, 152.6, 150.4, 139.8, 139.7, 134.4, 133.0, 132.8, 132.5, 131.0, 130.5, 129.1, 128.81, 128.76, 126.2, 123.8, 82.2, 70.9, 30.2. MS: 403 $(M + H)^+$. Measured M^+ 402.16918(±0.0002).

(5-(5-(1-Indanoyl))-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo-[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (29): Following general procedure A, **29** was obtained in 51% yield as a white solid: mp 233−234 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 9.20 (1H, s), 7.17 (1H, s), 7.15 (1H, s), 6.99 (1H, t, J = 7.5 Hz), 6.91 (1H, d, J = 8.1 Hz), 6.75−6.60 (2H, m), 5.90 (1H, d, J = 8.4 Hz), 4.79 (1H, d, J = 8.4 Hz), 2.58 (2H, d, J = 6.3 Hz), 2.17 (2H, t, J = 5.8 Hz), 0.94 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 207.9, 170.2, 168.6, 156.6, 156.3, 145.6, 139.7, 139.0, 133.7, 132.2, 130.5, 129.4, 128.5, 125.5, 124.6, 123.0, 81.6, 70.1, 37.8, 29.6, 27.0. MS: 406 $(M + H)^+$. Measured M^+ 405.16885(±0.0004).

(5-(5-(1-*tert*-Butoxycarbonyl)indolyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (30): Following general procedure A, **30** was obtained in 77% yield as a white solid: mp 155−159 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 9.86 (1H, s), 8.10 (1H, d, J = 8.8 Hz), 7.75 (1H, s), 7.60 (1H, d, J = 3.5 Hz), 7.49 (2H, d, J = 8.1 Hz), 7.33 (1H, d, J = 7.7 Hz), 7.21 (1H, d, J = 8.1 Hz), 7.14 (1H, t, J = 7.5 Hz), 6.55 (1H, d, J = 3.5 Hz), 6.50 (1H, d, J = 8.4 Hz), 5.34 (1H, d, J = 8.4 Hz), 1.66 (9H, s), 1.50 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 171.4, 170.0, 157.2, 151.3, 139.6, 138.3, 135.3, 133.8, 133.3, 132.2, 129.9, 128.7, 128.1, 125.7, 124.9, 123.4, 116.5, 109.5, 85.9, 81.9, 70.5, 30.2, 30.0. MS: 491 $(M + H)^+$. Measured M^+ 490.22161(±0.0018).

(5-(3,4-Methylenedioxyphenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (31): Following general procedure A, **31** was obtained in 77% yield as a white solid: mp 206−207 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 9.01 (1H, s), 7.53−7.49 (1H, m), 7.38 (1H, dd, J = 6.7, 1.2 Hz), 7.20−7.14 (3H, m), 6.98 (1H, dd, J = 1.8, 8.0 Hz), 6.76 (1H, d, J = 8.2 Hz), 6.35 (1H, d, J = 8.6 Hz), 6.01 (2H, dd, J = 1.4, 8.0 Hz), 5.27 (1H, d, J = 8.6 Hz), 1.48 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$) 169.3, 166.8, 155.3, 149.8, 147.8, 137.5, 133.0, 132.0, 131.3, 127.7, 125.2, 124.0, 121.4, 109.8, 107.7, 101.5, 80.1, 68.5, 28.4. MS: 396 $(M + H)^+$, 418 $(M + Na)^+$, 340 $(M - {}^tBu + H)^+$. Anal. Calcd for $C_{21}H_{21}O_5N_3$: C 63.79, H 5.35, N 10.63. Found: C 63.45, H 5.41, N 10.37. Measured M^+ 395.14811(±0.0014).

(5-(3,4-Ethylenedioxyphenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (32): Following general procedure A, **32** was obtained in 67% yield as a white solid: mp 162−164 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 9.89 (1H, s), 7.45 (1H, t, J = 7.5 Hz), 7.35 (1H, d, J = 7.7 Hz), 7.17−7.14 (2H, m), 7.09 (1H, d, J = 1.8 Hz), 7.03 (1H, dd, J = 2.1, 8.4 Hz), 6.81 (1H, d, J = 8.4 Hz), 6.49 (1H, d, J = 8.4 Hz), 5.26 (1H, d, J = 8.4 Hz), 4.23 (4H, d, J = 7.0 Hz), 1.47 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 171.4, 168.7, 157.2, 147.7, 145.0, 139.6, 133.9, 133.7, 133.0, 129.4, 125.6, 125.4, 123.3, 120.9, 118.7, 81.8, 70.4, 66.4, 66.0, 30.2. MS: 410 $(M + H)^+$, 354 $(M - {}^tBu + H)^+$. Measured M^+ 409.16376(±0.0006).

(5-(4-α-Tetrolyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*]-[1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (33): Following general procedure A, **33** was obtained in 52% yield as a white solid: mp 241−244 °C. ^{1}H NMR (360 MHz, $CDCl_3$): 9.29 (1H, s), 8.00 (1H, d, J = 8.1 Hz), 7.56 (2H, s), 7.35−7.30 (1H, m), 7.23 (1H, s), 7.20 (1H, s), 6.43 (1H, d, J = 8.1 Hz), 5.33 (1H, d, J = 8.4 Hz), 2.97 (2H, d, J = 5.3 Hz), 2.68 (2H, t, J = 6.1 Hz), 2.15 (2H, d, 6.0), 1.49 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$): 199.9, 170.6, 169.1, 157.2, 146.3, 144.6, 139.4, 135.6, 134.2, 132.9, 132.0, 130.0, 129.1, 128.9, 126.1, 123.4, 82.2, 70.7, 41.0, 31.5, 30.2, 24.9. MS: 420 $(M + H)^+$, 364 $(M - {}^tBu + H)^+$. Measured M^+ 419.1845(±0.0004).

(5-(4-(Trifluoromethyl)phenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (34): Following general procedure A, **34** was obtained in 44% yield as a white solid: mp 236−238 °C. ^{1}H NMR (360 MHz, $CDCl_3$) 9.11 (1H, s), 7.12 (4H, q, J = 8.4 Hz), 7.00 (1H, t, J = 7.4 Hz), 6.74−6.63 (3H, m), 5.87 (1H, d, J = 8.4 Hz), 4.80 (1H, d, J = 8.1 Hz), 0.95 (9H, s). ^{13}C NMR (90 MHz, $CDCl_3$) 170.3, 167.3, 156.6, 143.1, 139.0, 133.7, 133.6 (q, J = 33.0 Hz), 132.1, 131.5, 128.3, 126.5 (q, 3.4), 126.4, 125.1 (q, 272.8), 125.5, 123.0, 81.6, 70.1, 29.6. MS: 420 $(M + H)^+$, 364 $(M - {}^tBu + H)^+$. Anal. Calcd for $C_{21}H_{20}F_3O_3N_3$: C 60.14, H 4.81, N 10.02. Found: C 60.31, H 4.84, N 9.82. Measured M^+ 419.14567(±0.0027).

(1-Ethylcarboxamido-5-(3,4-(difluoromethylenedioxy)-phenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (35): Following general procedure A and deprotection of the BOC group with TFA−CH_2Cl_2, **35** was obtained in 82% yield. ^{1}H NMR (400 MHz, DMSO): 7.66−7.60 (1H, m), 7.56 (1H, s), 7.53−7.46 (3H, m), 7.35 (1H, dd, J = 8.4, 1.7 Hz), 7.31−7.26 (2H, m), 7.12 (1H, s), 4.47 (1H, d, J = 16.8 Hz), 4.42 (1H, d, J = 16.8 Hz), 4.36 (1H, s), 2.6 (2H, br s). ^{13}C NMR (100 MHz, DMSO) 167.62, 167.61, 140.62, 133.8, 130.0, 127.39, 127.32, 124.6, 122.7, 120.6, 108.8, 108.0, 68.4, 47.9. MS: 389 $(M + H)^+$. Measured M^+ 388.09831(±0.0004).

General Procedure for the Reaction of Imidoyl Chlorides with Amines (General Procedure B). (5-Morpholinyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (36): A solution of the chloroimidate **23** (0.9 g, 2.90 mmol) was treated with morpholine (3 mL) and heated in a sealed tube for 2 h at 100 °C. The reaction mixture was evaporated in vacuo. Purification by column chromatography gave the amidine **36** (0.8 g, 76%) as a white solid: mp 244−246 °C. ^{1}H NMR (400 MHz, DMSO): 10.46 (1H, s), 7.60−7.53 (2H, m), 7.28−7.14 (3H, m), 4.73 (1H, d, J = 9.5 Hz), 3.72−3.54 (4H, m), 3.13−2.99 (4H, m), 1.36 (9H, s). ^{13}C NMR (100 MHz, DMSO): 172.8, 163.0, 157.1, 141.1, 134.1, 131.4, 126.1, 125.5, 124.2, 80.6, 68.7, 68.1, 50.6, 30.4. MS: 361 $(M + H)^+$. Anal. Calcd for $C_{18}H_{24}O_4N_4$: C 59.99, H 6.71, N 15.55. Found: C 59.83, H 6.56, N 15.18. Measured M^+ 360.17975(±0.0009).

(5-Azetidinyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)-carbamic acid *tert*-butyl ester (37): Following general procedure B, **37** was obtained in 81% yield as a white solid: mp 222−224 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 8.52 (1H, s), 7.48−7.42 (2H, m), 7.18 (1H, t, J = 7.4 Hz), 7.09 (1H, d, J = 7.4 Hz), 6.01 (1H, d, J = 8.5 Hz), 5.12 (1H, d, J = 8.5 Hz), 4.08 (2H, q, J = 7.9 Hz), 3.71 (2H, q, J = 7.9 Hz), 2.23 (2H, qn, J = 7.9 Hz), 1.42 (9H, s). ^{13}C NMR (100 MHz, $CDCl_3$): 171.4, 161.4, 155.3, 136.7, 131.6, 129.1, 124.4, 123.2, 121.7, 79.7, 66.0, 51.7, 28.3, 16.0. MS: 331 $(M + H)^+$. Anal. Calcd for $C_{17}H_{22}O_3N_4$: C 61.80, H 6.71, N 16.96. Found: C 61.69, H 6.70, N 16.41. Measured M^+ 330.16918(±0.0016).

(1-Methyl-5-piperidinyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (38): Following general procedure B, **38** was obtained in 64% yield as a white solid: mp 230−232 °C. ^{1}H NMR (400 MHz, DMSO: 7.65−7.60 (1H, m), 7.56−7.51 (2H, m), 7.37−7.33 (1H, m), 7.09 (1H, d, J = 8.6 Hz), 4.74 (1H, d, J = 8.6 Hz), 3.30 (3H, s), 3.23−3.13 (4H, m), 1.66−1.52 (4H, m), 1.50−1.35 (2H, m), 1.36 (9H, s). ^{13}C NMR (100 MHz, DMSO) 24.5, 25.5, 28.5, 34.7, 48.5, 66.7, 66.7, 78.7, 122.9, 125.4, 126.4, 128.7, 131.9, 142.9, 155.0, 160.6, 170.4. MS: 373 $(M + H)^+$. Anal. Calcd for $C_{20}H_{28}O_3N_4$: C 64.49, H 7.58, N 15.04. Found: C 63.99, H 7.55, N 14.62. Measured M^+ 372.21613(±0.0012).

(1-Ethylcarboxamido-5-morpholinyl-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-carbamic acid *tert*-butyl ester (39): Following general procedure B, **39** was obtained in 84% yield as a white solid: mp 267−269 °C. ^{1}H NMR (360 MHz, DMSO): 7.60−7.47 (4H, m), 7.36−7.32 (1H, m), 7.11−7.06 (2H, m), 4.87 (1H, d, J = 8.6 Hz), 4.52 (1H, d, J = 16.8 Hz), 4.32 (1H, d, J = 16.8 Hz), 3.69−3.57 (4H, m), 3.25−3.15 (4H, m), 1.35 (9H, s). ^{13}C NMR (90 MHz, DMSO) 30.4, 50.1, 51.5, 68.0, 68.2, 80.6, 125.3, 127.5, 128.6, 130.6, 133.8, 144.2, 156.9, 162.8, 171.2, 171.5. MS: 418 $(M + H)^+$. Anal. Calcd for $C_{20}H_{27}O_5N_5$: C 57.54, H 6.52, N 16.68. Found: C 57.40, H 6.29, N 16.12. Measured M^+ 417.20121(±0.0009).

(5-(3,4-Methylenedioxyphenyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)-2,4,5-(trifluorophenyl)-acetamide (40): Step 1. A solution of benzodiazepine **31** (100 mg, 0.25 mmol) in DCM (5 mL) and TFA (1 mL) was stirred at room temperature for 2 h, evaporated in vacuo, azeotroped with toluene, and purified by ion exchange chromatography to give the amine in quantitative yield. ^{1}H NMR (360 MHz, DMSO):10.62 (1H, br s), 7.57 (1H, t, J = 7.1 Hz), 7.31−6.84 (6H, m), 6.08 (2H, d, J = 3.1 Hz), 4.20 (1H, s), 2.7 (2H, vbr s). ^{13}C NMR (90 MHz, DMSO) 72.4, 103.9, 110.0, 110.9, 123.5, 125.1, 126.8, 129.0, 132.4, 133.9, 135.2, 141.1, 149.7, 151.3, 166.1, 172.8. MS: 296 $(M + H)^+$.

Step 2. A solution of the foregoing amine (75 mg) in DMF (4 mL) was treated with EDC (58 mg), HOBT (41 mg), and 2,3,5-trifluorophenylacetic acid (53 mg) and stirred at room temperature for 2 h. The reaction mixture was diluted with ethyl acetate, washed with citric acid solution, sodium bicarbonate solution, and brine, and dried ($MgSO_4$). Evaporation and purification by column chromatography gave **40** as a white solid (118 mg, 82%): mp 251−254 °C. ^{1}H NMR (400 MHz, DMSO): 10.82 (1H, s), 9.44 (1H, d, J = 7.8 Hz), 7.62 (1H, t, J = 7.3 Hz), 7.44−6.89 (9H, m), 6.11 (2H, d, J = 2.6 Hz), 5.19 (1H, d, J = 7.8 Hz), 3.81 (2H, s). ^{13}C NMR (100 MHz, DMSO): 35.1, 68.5, 102.1, 104.4 (d, J = 20 Hz), 104.7 (d, J = 21 Hz), 108.2, 109.0, 113.6 (d, J = 24 Hz), 121.8, 123.6, 125.2, 126.8, 127.3, 127.4, 130.8, 132.5, 132.7, 139.1, 147.9, 149.8, 166.4, 168.3, 168.8. ^{19}F NMR (400 MHz, DMSO): −116.43 (d, J = 15.5 Hz), −135.54 (d, J = 23.3 Hz), −147.29 (dd, J = 15.5, 23.3 Hz). MS: 468 $(M + H)^+$. Anal. Calcd for $C_{24}H_{16}O_4N_3F_3$: C 61.67, H 3.45, N 8.99. Found: C 61.64, H 3.51, N 8.75. Measured M^+ 467.10929(±0.0011).

Acknowledgment. We thank Professor István Markó (Université Catholique de Louvain, Belgium) for useful discussions, Drs. Ute Gerhard and Steve Thomas for measuring the high-resolution mass spectral data, and Dr. Russell Mortishire-Smith for assistance in preparing the Supporting Information.

Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**, **6**, **10**−**12**, **15**, **19**, **20**, and **22**−**40**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026860A