THE *N*-BOC GROUP AS AN ACTIVATOR FOR THE α-LITHIATION OF CARBAMATES: SYNTHESIS OF 11-SUBSTITUTED DIBENZOXAZEPINES[1]

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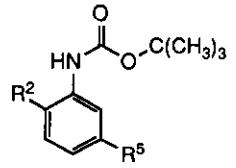
Abstract - A series of 11-substituted dibenzoxazepines was prepared *via* α-lithiation utilizing the *N*-Boc group as an activator. The *N*-Boc group directs metalation of **5** by n-BuLi to the benzylic C-11 carbon. For **6** which contains 1,3 interrelated directed metalation groups, metalation with *n*-BuLi occurs at both the 11- and 9- positions. The regioselectivity for the lithiation of **6** can be increased to a ratio of 97:3, by employing LDA as the base, thus providing a convenient and general route to 11-substituted 8-chloro-dibenzoxazepines. By the proper choice of the base, the regioselectivity of lithiation-substitution reactions in the pharmaceutically important heteroaromatic ring systems (**5**) and (**6**) can be controlled. The *N*-Boc group can be readily removed with mild acid treatment.

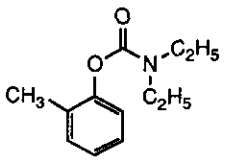
INTRODUCTION

The use of directing groups to facilitate α-lithiation of amines, followed by reaction with an electrophile has found wide application in a variety of synthetic transformations.[2,3] The *N*-Boc group has been utilized as an activator for directed lithiation of *N*-Boc-aniline (**1**).[4] Recently, Beak reported the directed α-lithiation of secondary amines using the *N*-Boc group.[5] The advantages of *N*-Boc as a directing group in α-lithiations are: 1) high yields of products functionalized alpha to the amino group, 2) the ease of preparation of the *N*-Boc derivatives, and 3) the ease of removal of the *N*-Boc group upon mild acid treatment.

There are relatively few examples of directed lithiation reactions using carbamate directing groups in which both benzylic and aryl protons are in competition for abstraction. The dilithiation of *N*-Boc-*o*-toluidine (**2**), and the 5-chloro analog (**3**), have been reported with *s*-BuLi or *t*-BuLi in THF, to provide the benzylic anions exclusively.[6] The *O*-diethylcarbamate of *o*-cresol (**4**), in which there are two possible positions for proton abstraction in the same molecule, has been deprotonated with *s*-BuLi/TMEDA and LDA.[7] With *s*-BuLi/TMEDA, deprotonation was observed at both the benzylic and aryl positions; with LDA, only benzylic deprotonation occurred.



1 R^2=H R^5=H
2 R^2=CH_3 R^5=H
3 R^2=CH_3 R^5=Cl



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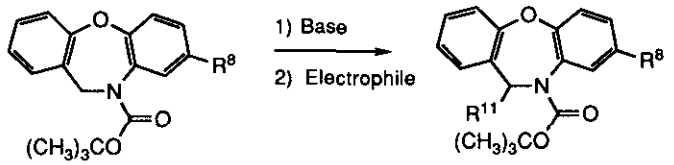
An interesting substrate for directed lithiation in which there are two possible sites of deprotonations, i.e. benzylic versus aryl, are the *N*-Boc-dibenzoxazepines (**5**) and (**6**). The dibenzoxazepine moiety has been incorporated into a variety of pharmacologically active substances, including analgesics, antipsychotic agents, and antidepressants.[8] We wish to report our studies on the directed lithiation of the dibenzoxazepine ring system.

RESULTS AND DISCUSSION

The *N*-Boc dibenzoxazepines (**5**) and (**6**) were synthesized using di-*t*-butyldicarbonate as the acylating agent.[9] The lithiation-substitution reactions were performed using a modification of Beak's procedure,[5] where THF was used instead of ether and *n*-BuLi or LDA were used instead of *s*-BuLi/TMEDA. Lithiation of **5** and **6** rapidly occurs with *n*-BuLi at -78°C in THF with no nucleophilic attack of *n*-BuLi at the carbonyl of the Boc group. It was reported that the dilithiation of *N*-Boc-aniline **1** occurred only with *s*-BuLi/TMEDA or *t*-BuLi/TMEDA, and that use of *n*-BuLi/TMEDA resulted in nucleophilic attack at the Boc carbonyl.[4] Even under forced conditions, the dilithiation of **1** did not occur with *n*-BuLi, or with *s*-BuLi in THF in the absence of TMEDA.[4] It is well known that addition of TMEDA leads to an increased basicity of organic lithium compounds while suppressing their nucleophilicity.[4b] The lithiation of *N*-Boc-*o*-toluidine (**2**) has been reported

with *s*-BuLi or *t*-BuLi in THF, in the absence of TMEDA.[6a] Yields of the products of lithiation of **5** and **6** followed by reaction with electrophiles are found in Table I. The regioselectivity of each lithiation-substitution reaction was determined by ^{1}H nmr.

Table I. Products from the lithiation-substitution reaction of *N*-Boc-dibenzoxazepines (**5** and **6**).



5 $R^8 = H$

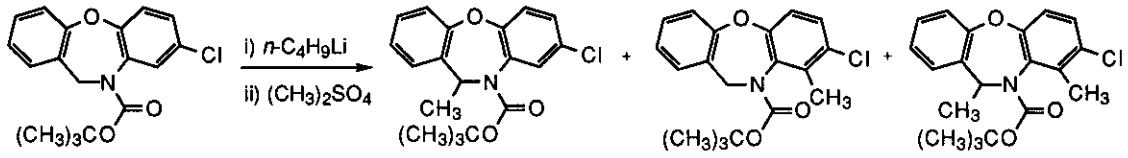
6 $R^8 = Cl$

Number	R^8	R^{11}	Base	Electrophile	Yield
7	H	TMS	n-BuLi	TMSCl	74%
8	H	Me	n-BuLi	Me_2SO_4	87%
9	H	Et	n-BuLi	EtI	97%
10	H	CO_2H	n-BuLi	CO_2	84%
11	H	CO_2Et	n-BuLi	$ClCO_2Et$	80%
12	Cl	Me	LDA	Me_2SO_4	69%
15	Cl	TMS	LDA	TMSCl	80%
16	Cl	CO_2H	LDA	CO_2	97%
17	Cl	$CH_2C_6H_5$	LDA	$BrCH_2C_6H_5$	44%

Two possible sites of deprotonation on 1,1-dimethylethyldibenz[*b,f*][1,4]-oxazepine-10(11*H*)-carboxylate (**5**) are the aryl position at C-9 and the benzylic position at C-11. The reaction of **5** with *n*-BuLi in THF at -78°C followed by the addition of a variety of electrophiles provides the 11-substituted *N*-Boc-dibenzoxazepines (**7-11**) in good to excellent yields. The regioselectivity of the deprotonation of this substrate produces exclusively 11-substituted *N*-Boc-dibenzoxazepines.

The 1,1-dimethylethyl 8-chlorodibenz[*b,f*][1,4]-oxazepine-10(11*H*)-carboxylate (**6**) also has two possible sites of deprotonation, the aryl position at C-9 and the benzylic position at C-11. Although there are no analogs in the literature that have these competing sites of deprotonation, there is a similar example reported in the literature. The 5-chloro-2-methyl-*N*-Boc-aniline (**3**) has been dilithiated with *s*-BuLi in THF, to provide only lithiation on the benzylic carbon.[6] When 1.2 equivalents of *n*-BuLi in THF were used to metalate (**6**) followed by CD_3OD

quench, deuterium incorporation occurred primarily at the 11-position as determined by the reduction in the ^{1}H nmr signal at 4.78 ppm. A 20% reduction in the ^{1}H nmr signal at 7.33 ppm for the C-9 proton was also observed. This suggests that the presence of the chloro substituent in **6** facilitates lithiation at the 9-position. This result is interesting but not surprising since cooperative lithiation effects of a 1,3 interrelated directed metalation group (DMG) are known, and the chloro group is a weak DMG.[3] Reaction of the anions of **6** with dimethyl sulfate, lead to a mixture of alkylated products as shown below.

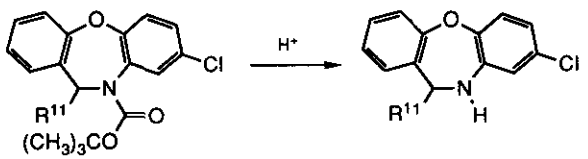


6 **12** **13** **14**

The reaction mixture was analyzed by hplc, mass spectroscopy, and ^{1}H nmr. The 11-methyl analog (**12**) was the major product (68.8%) but a significant amount of a product identified as 8-chloro-9-methyldibenzoxazepine (**13**) (17.4%) was present as well as a product identified as the 9,11-dimethyl analog (**14**) (11.8%). The structures have been assigned based on nmr and mass spectral data. The dimethyl analog (**14**) and the 11-methyl analog (**12**) could be separated from the mixture by preparative hplc; however, the 9-methyl analog (**13**) could not be separated from the mixture. When 1.0 equivalent of *n*-BuLi was used followed by treatment with dimethylsulfate, the three products (**12**, **13** and **14**) were produced in a ratio of 67.6%, 20.5% and 6.1%, respectively as determined by hplc.

In order to increase the metalation regioselectivity and to generate the 11-substituted dibenzoxazepines in a synthetically useful manner, a variety of bases were investigated. The use of the nonnucleophilic base LDA resulted in the formation of 11-position and 9-position products in a ratio of 97:3 respectively by ^{1}H nmr. Thus by choosing the appropriate base, the selectivity of the lithiation-substitution reaction on the dibenzoxazepine was controlled. This method was utilized to generate analogs (**12**,**15-17**), shown in Table 1, in yields of 44-97%.

Removal of the *N*-Boc group was effected by treatment with HCl or TFA as exemplified by **12**, **16** and **17** to provide **18-20**, as shown below. The 11-TMS analog (**15**) proved to be unstable to conditions required to remove the *N*-Boc group.



12	$R^{11} = CH_3$	**18**	$R^{11} = CH_3$
16	$R^{11} = CO_2H$	**19**	$R^{11} = CO_2H$
17	$R^{11} = CH_2C_6H_5$	**20**	$R^{11} = CH_2C_6H_5$

CONCLUSION

The *N*-Boc group directs metalation by *n*-BuLi to the benzylic C-11 carbon. For **6** which contains 1,3 interrelated DMG's, metalation with *n*-BuLi occurs at both the 11- and 9- positions. The regioselectivity for the lithiation of **6** can be increased to a ratio of 97:3, by employing LDA as the base, thus providing a convenient and general route to 11-substituted 8-chlorodibenzoxazepines. By the proper choice of the base, the regioselectivity of lithiation-substitution reactions in the pharmaceutically important heteroaromatic ring systems (**5**) and (**6**) can be controlled. The *N*-Boc group is readily removed with mild acid treatment.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H Nmr spectra were recorded on a Varian VXR 500, Varian VXR 400 or a General Electric QE 300 spectrometer at 500, 400 or 300 MHz respectively and the chemical shifts are reported relative to TMS. Peaks are assigned by multiplicity, coupling constant(s) in Hertz, and integration. Mass spectra were performed on a Finnigan-MAT Model 8430 mass spectrometer. Fast Atom Bombardment mass spectra (FABms) were obtained on a VG40-250 mass spectrometer. High-resolution mass spectra (HRms) were obtained on a Finnegan MAT 90 mass spectrometer with FAB or EI ionization. Analytical tlc was developed by staining with I_2 or visualization with uv light. Flash chromatography was performed according to the method of Still.[8] The analytical hplc was performed on a Supelco LC-18-DB 25 cm column with 75:25 MeCN:H_2O as solvent and a flow rate of 1 ml/min at 1500 psi. High performance liquid chromatography (hplc) separations were performed on a Waters Associates LC 2000 or a Prep 500A System with silica gel columns. Elemental analyses were performed on a Carlo Erba model 1106 or performed by Galbraith Laboratories, Inc. Unless otherwise noted, nonaqueous reactions were carried out in flame-dried glassware under a dry nitrogen or argon atmosphere. Anhydrous Na_2SO_4 or $MgSO_4$ was used to dry organic solutions. Unless otherwise noted, starting materials were

obtained from Aldrich chemical and were used without further purification. 10,11-Dihydrodibenz[*b,f*][1,4]-oxazepine and 8-chloro-10,11-dihydrodibenz[*b,f*][1,4] oxazepine were prepared as previously described.[9]

1,1-Dimethylethyl dibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (5). A solution of 10,11-dihydrodibenz[*b,f*][1,4]oxazepine (12.75 g, 65 mmol), di-*tert*-butyl dicarbonate (17 g, 78 mmol) and DMAP (1 g, 8 mmol) in THF (500 ml) was refluxed under a N_2 atmosphere for 24 h. The solvent was removed under reduced pressure to yield a yellow oil that was flash chromatographed on silica gel (10% EtOAc/hexane) to yield **5** as a white solid (16.3 g, 84.4%): mp 90-91°C; ir (KBr) 3431, 2980, 1705 cm^{-1}; ^1H nmr ($CDCl_3$, 400 MHz) δ 0.97 (s, 9H), 4.32 (s, 2H), 6.5-6.9 (m,8H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.51; H, 6.75; N, 4.59.

1,1-Dimethylethyl 8-chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (6). This reaction was performed as in **5**, using 8-chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepine (65 mmol) to yield **6** as a white solid (95.4%): mp 109-110°C; ^1H mmr ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 4.78 (s, 2H), 7.03 (m,1H), 7.15 (m,4H), 7.23 (m,1H), 7.33 (br s, 1H). Anal. Calcd for $C_{18}H_{18}NO_3Cl$: C, 65.16; H, 5.47; N, 4.22. Found: C, 64.78; H, 5.51; N, 4.13.

General Procedure for the Synthesis of 11-substituted *N*-Boc-dibenzoxazepines. To a cooled (-78°C) stirred solution of **5** (202 mg, 0.68 mmol) in THF (5 ml), was added a solution of *n*-BuLi (1.6 M, 0.50 ml, 0.82 mmol). Formation of the anion was observed as an orange solution. The mixture was stirred at -78°C for an additional 15 min, after which an electrophile (0.82 mmol) was added. The mixture was then removed from the cooling bath and allowed to warm to room temperature. After addition of water (2 ml), the mixture was extracted with ether (25 ml x 2) and the combined extracts were dried. The extracts were concentrated to give the crude product as an oil, which was purified by flash chromatography with 10% EtOAc/hexane.

1,1-Dimethylethyl 11-trimethylsilyldibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (7): white solid (74%): mp 95-97°C; ^1H nmr ($CDCl_3$, 400 MHz) δ -0.20 (s, 9H), 1.38 (s, 9H), 5.10 (m,1H), 6.87-7.25 (m,8H). Anal. Calcd for $C_{21}H_{27}NO_3Si$: C: 68.26, H: 7.36, N: 3.79. Found: C: 68.29; H: 7.62; N: 3.71.

1,1-Dimethylethyl 11-methyldibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (8): white solid (87%). mp 100-103°C; ^{1}H nmr ($CDCl_3$, 400 MHz) δ 1.34 (d, *J* =7 Hz, 3H), 1.43 (s, 9H), 5.70 (br, 1H), 7.0-7.3 (m, 8H). Anal. Calcd for $C_{19}H_{21}NO_3$: C: 73.29, H: 6.80, N: 4.50. Found C: 72.99; H: 6.96; N: 4.45.

1,1-Dimethylethyl 11-ethyldibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (9): white solid (97%). An analytical sample was crystallized from hexane. mp 111-114°C; ^{1}H nmr ($CDCl_3$, 400 MHz) δ 0.97 (t, *J* =7 Hz, 3H), 1.43 (S, 9H), 1.62 (m, 2H), 5.30 (br, 1H), 7.0-7.3 (m, 8H). Anal. Calcd for $C_{20}H_{23}NO_3$: C: 73.82, H: 7.12, N: 4.30. Found C: 73.65; H: 7.31; N: 4.29.

10-(1,1-Dimethylethyl) 11-hydrogen dibenz[*b,f*][1,4]oxazepine-10(11*H*),11-dicarboxylate (10): To a cooled (-78°C) stirred solution of **5** (202 mg, 0.68 mmol) in THF (5 ml), was added a solution of *n*-BuLi (1.6 M, 0.50 ml, 0.82 mmol). Formation of the anion was observed as an orange solution. The mixture was stirred at -78°C for 15 min and treated with anhydrous CO_2 gas, then slowly warmed to room temperature and diluted with HCl (2 ml, 1M). The mixture was then extracted with ethyl acetate (25 ml x 2) and the combined extracts were dried. The extracts were concentrated to give the product as a solid (290 mg), which was purified by crystallization from CH_2Cl_2 to yield **10** as a solid (190 mg, 84%). mp 181-182°C (decomp.); ^{1}H nmr ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H), 6.34 (br s, 1H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 6H). Anal. Calcd for $C_{19}H_{19}NO_5$: C: 66.85, H: 5.61, N: 4.10. Found C: 66.50; H: 5.63; N: 3.85.

11-Ethyl 10-(1,1-dimethylethyl) dibenz[*b,f*][1,4]oxazepine-10(11*H*),11-dicarboxylate (11): The crude product was obtained as an oil which crystallized on standing. The crystals were suspended in hexane and collected by filtration to yield **11** as a solid (80%). mp 105-107°C (decomp.); ^{1}H nmr ($CDCl_3$, 400 MHz) δ 1.10 (t, *J* = 7.1 Hz, 3H), 1.42 (s, 9H), 4.04 (q, *J* = 7.1 Hz, 2H), 6.30 (br s, 1H), 7.0-7.1 (m, 2H), 7.2-7.3 (m, 6H). Anal. Calcd for $C_{21}H_{23}NO_5$: C: 68.28, H: 6.28, N: 3.79. Found C: 68.03; H: 6.34; N: 3.62.

Reaction of 6 with *n*-BuLi followed by CD_3OD: To a cooled (-78°C) stirred solution of **6** (225 mg, 0.68 mmol) in THF (5 ml), was added a solution of *n*-BuLi (1.6 M, 0.50 ml, 0.82 mmol). Formation of the anion was observed as a red solution. The mixture was stirred at -78°C for 30 min and followed by the addition of CD_3OD (0.2 ml, 177 mg, 0.82 mmol). The reaction mixture was slowly warmed to 0°C and diluted with

water (2ml) and extracted with ether (35 ml). The ether layer was washed with brine (5 ml) and dried. The extract was concentrated to give the product (225 mg, 99.7%) as an oil; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.42 (s, 9H), 4.78 (s, 1 H), 7.03 (m,1H), 7.15 (m,4H), 7.23 (m,1H), 7.33 (br s, 0.67 H).

Reaction of 6 with 1.2 eq. *n*-BuLi followed by Me_2SO_4: The anion which was generated as above from **6** (225 mg, 0.68 mmol) was treated with dimethyl sulfate (77 ml, 0.82 mmol), to give the crude product (290 mg) as an oil. Analytical hplc showed the presence of three products in yields of 68.8%, 17.4% and 11.8%. Structure assignments were made by ^{1}H nmr as compounds (**12**), (**13**) and (**14**), respectively. The 9-methyl analog (**13**) could not be separated from **12** by preparative hplc. A sample of **14** was purified to 99% purity by preparative hplc; ^{1}H nmr ($CDCl_3$, 500 MHz) δ 1.28 (d, *J* =7.2, 3H), 1.38 (s, 9H), 2.35 (s, 3H), 5.80 (q, *J* =7.2, 1H), 7.0-7.4 (m, 6H); ms 359 (M·, 5), 303 (10), 244 (14), 57 (100); HRms calcd for $C_{20}H_{22}NO_3Cl$: 359.1288. Found: 359.1286.

Reaction of 6 with 1.0 eq. *n*-BuLi followed by Me_2SO_4: Reaction was run as above except treated with dimethyl sulfate (62 µl, 0.69 mmol), to give the crude product (227 mg, 97%) as an oil. Analytical hplc showed the presence of three compounds in yields of: **12**, 67.6%; **13**, 20.5% and **14**, 6.1%.

1,1-Dimethylethyl 8-chloro-11-methyldibenz[*b,f*][1,4]oxazepine-10-(11*H*)-carboxylate (12): To a cooled (-78°C) stirred solution of **6** (0.90 g, 2.72 mmol) in THF (54 ml), was added a solution of LDA (1.5 M, 1.99 ml, 2.99 mmol). The solution gradually became red-orange. The mixture was stirred at -78°C for 15 min and treated with dimethyl sulfate (0.41g, 3.26 mmol). The mixture gradually lightened and was slowly allowed to warm to room temperature and diluted with water (8 ml). The mixture was extracted with ether (100 ml x 2) and the combined extracts were dried and concentrated to give the crude product (0.98 g) as an oil. The product was purified by chromatography over silica gel with 1-3% EtOAc/hexane followed by reverse phase chromatography with 55-65% MeCN/water to yield **12** as a colorless oil (0.65 g, 69%); ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.31 (d, *J* = 7.2 Hz, 3H), 1,38(s, 9H), 5.5-5.7 (br m, 1H), 6.9-7.0 (m, 1H), 7.1-7.2 (m, 6H); ms 345 (M+, 94), 290 (100), 245 (74); HRms calcd for $C_{19}H_{20}NO_3Cl$: 345.1132. Found: 345.1139. Anal. Calcd for $C_{19}H_{20}NO_3Cl$: C, 65.99; H, 5.83; N, 4.05; Cl, 10.25. Found: C, 66.21; H, 6.05; N, 3.96; Cl, 10.49.

1,1-Dimethylethyl 8-chloro-11-trimethylsilyldibenz[*b,f*][1,4]oxazepine-10-(11*H*)-carboxylate (15): Reaction was run as **12** above. Treatment with chlorotrimethylsilane (0.35 g, 3.26 mmol) provided the crude product (1.1g) as an oil, which was purified by chromatography over silica with 0-3% EtOAc/hexane followed by reverse phase chromatography with 72% MeCN/water to yield **15** as a colorless solid (0.88 g, 80%): mp 76-77°C; ^{1}H nmr ($CDCl_3$, 300 MHz) δ -0.18 (s, 9H), 1.36 (s,9H), 5.01 (br s, 1H), 6.9-7.3 (m, 7 H); FABms 410 (M+Li, 18), 404 (M+H, 6), 348 (64), 302 (100); HRms calcd for $C_{21}H_{26}NO_3SiCl$: 403.1371. Found: 403.1376. Anal. Calcd for $C_{21}H_{26}NO_3SiCl$: C, 62.43; H, 6.49; N, 3.47; Cl, 8.78. Found C, 62.34; H, 6.64; N, 3.38; Cl, 9.24.

10-(1,1-Dimethylethyl) 11-hydrogen 8-chlorodibenz[*b,f*][1,4]oxazepine-10(11*H*) 11-dicarboxylate (16): To a cooled (-78°C) stirred solution of **6** (7.5 g, 22.6 mmol) in THF (400 ml), was added a solution of LDA (1.5 M, 15 ml, 22.5 mmol). The mixture was stirred at -78°C for 20 min and treated with CO_2 (solid), then slowly warmed to room temperature and concentrated under vacuum. To the residue was added EtOAc and HCl (1 M). The organic layer was washed with brine and dried. Removal of the solvent gave the crude product as an oil, which was purified by flash chromatography (1:9, MeOH:CH_2Cl_2) to yield **16** as a foam (8.3 g, 97%). ^{1}H Nmr ($CDCl_3$, 300 MHz) δ 1.43 (s, 9H), 6.31 (s, 1H), 7.0-7.2 (m, 4H), 7.3-7.4 (m, 3H), 8.64 (s br, 1H). Anal. Calcd for $C_{19}H_{18}NO_5Cl$: C: 60.72; H: 4.83; N: 3.73; Cl: 9.43. Found C: 60.80; H: 5.05; N: 3.69; Cl: 9.74.

1,1-Dimethylethyl 8-chloro-11-phenylmethyldibenz[*b,f*][1,4]oxazepine-10(11*H*)-carboxylate (17): To a cooled (-78°C) stirred solution of **6** (5.0 g, 15.0 mmol) in THF (500 ml), was added a solution of LDA (1.5 M, 11 ml, 16.5 mmol). After 20 min, benzyl bromide (1.9 ml, 15.9 mmol) was added, and the stirring was continued for 1 h at -78°C followed by room temperature overnight, the reaction was then quenched with H_2O. After most of the THF was removed under vacuum, the residue was dissolved in CH_2Cl_2, washed with H_2O and dried. Chromatography on silica gel (hexane) provided **17** (2.8 g, 44%) as a white solid. An analytical sample was obtained by further purification on reverse phase hplc with 70% CH_3CN/H_2O/0.05% TFA: mp 142-143°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 1.31 (s, 9H), 2.73 (dd, J = 15 Hz, J = 10.5 Hz, 1H), 3.03 (dd, J = 15 Hz, J = 6.3 Hz, 1H), 5.89 (br s, 1H), 6.70 (br s, 1H), 6.9-7.1 (m, 4H), 7.1-7.3 (m, 7H). FABms: m/z 428 $(M+Li)^+$. HRms calcd for $C_{25}H_{24}NO_3Cl$: 422.1523. Found 422.1521. Anal. Calcd for $C_{25}H_{24}NO_3Cl$: C, 71.17; H, 5.73; N, 3.32; Cl, 8.40. Found: C,71.31; H, 5.77; N, 3.28; Cl, 8.30.

8-Chloro-10,11-dihydro-11-methyldibenz[*b,f*][1,4]oxazepine (18): To a stirred solution of the crude product (**12**), (1.86 g) in 1,4-dioxane (5 ml) cooled to 0°C was added HCl/dioxane (10 ml, 4N). The solution was stirred at 0°C for 1.5 h and neutralized with sat. $NaHCO_3$. The mixture was extracted with ether (25 ml x 3). The combined extracts were washed with brine (25 ml), dried and concentrated to give the crude product as a tan oil (1.50 g). The product was purified by chromatography over silica gel with 0-5% EtOAc/hexane to yield **18** as a colorless solid (1.02g, 76%): mp 60-61°C; ^{1}H nmr ($CDCl_3$, 300 MHz) δ 1.64 (d, *J* = 6.8 Hz, 3H), 5.04 (q, *J* = 6.8 Hz, 1H), 6.50 (d, *J* = 2.4 Hz, 6.0 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 1H), 7.1-7.3 (m, 4H); ms 246 (m+H, 100), 230 (18); HRms calcd for $C_{14}H_{12}NOCl$: 245.0607. Found: 245.0600. Anal. Calcd for $C_{14}H_{12}NOCl$: C, 68.44; H, 4.92; N, 5.70; Cl, 14.43. Found: C, 68.30; H, 5.06; N, 5.65; Cl, 14.52.

8-Chloro-10,11-dihydrodibenz[*b,f*][1,4]oxazepine-11-carboxylic acid (19): A stirring solution of **16** (2.0 g, 5.3 mmol) in CH_2Cl_2 (15 ml), was cooled to 0°C followed by the addition of TFA (30 ml). The mixture was then slowly warmed to room temperature over 30 min and concentrated under vacuum. The material was taken up in MeOH (20 ml) and H_2O (20 ml) and purified by preparative hplc to give the crude product as an oil, which was triturated with hexane, and dried under vacuum, to yield **19** as a foam (1.0 g, 68.2 %). ^{1}H Nmr ($CDCl_3$, 300 MHz) δ 4.92 (s, 1H), 6.49 (dd, *J* =8.7, *J* =2.7 Hz, 1H), 6.70 (d, *J* =2.7 Hz, 1H), 6.79 (br s, 1H), 6.96 (d, *J* =8.4 Hz, 1H), 7.1-7.2 (m, 2H), 7.33 (dt, *J* =7.5, *J* =1.8 Hz, 1H), 7.43 (dd, *J* = 7.5, *J* =1.4 Hz, 1H), 12.68 (br s, 1H). Anal. Calcd for $C_{19}H_{18}NO_5Cl$: C: 60.72; H: 4.83; N: 3.73; Cl: 9.43. Found C: 60.80; H: 5.05; N: 3.69; Cl: 9.74.

8-Chloro-10,11-dihydro-11-phenylmethyldibenz[*b,f*][1,4]oxazepine (20): To **17** (2.2g, 5.2 mmol) in TFA/CH_2Cl_2 (1:1; 25 ml) was bubbled HCl gas for 1 h. The solvent was evaporated and the residue was dissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, followed by H_2O and dried. Purification *via* flash chromatography (10% EtOAc/hexane) provided **20** (1.1 g, 81%) as a white solid: mp 163-164°C; ^{1}H nmr ($CDCl_3$, 300 MHz): δ 3.29 (dd, *J* = 13.5 Hz, *J* = 5.4 Hz, 1H), 3.43 (dd, *J* = 13.5 Hz, *J* = 9.6 Hz, 1H), 4.57 (dd, *J* = 9.6 Hz, *J* = 5.4 Hz, 1H), 6.49 (d, *J* = 2.7 Hz, 1H), 6.65 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 1H), 7.0-7.1 (m, 3H), 7.19 (m, 3H), 7.2-7.4 (m, 4H). FABms: m/z 322 $(M+H)^+$. HRms calcd for $C_{20}H_{16}NOCl$: 322.0999. Found: 322.0980. Anal. Calcd for $C_{20}H_{16}NOCl$: C,74.65; H, 5.01; N, 4.35; Cl, 11.02. Found: C, 74.65; H, 5.07; N, 4.33; Cl, 11.30.

ACKNOWLEDGEMENTS

We would like to thank Dr. Donald W. Hansen Jr., Dr. Michael Vazquez, Professors Peter Beak, Anthony Barrett and Victor Snieckus for helpful discussions, Ms. Patricia Finnegan for aid in interpretation of nmr spectra, and Mr. Randy Fronek and Ms. Mamta Desai for chromatographic support.

REFERENCES AND NOTES

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Received, 18th October, 1993