A Comparatively Advantageous Route to Oxcarbazepine (Trileptal®) Based on Palladium-Catalyzed Arylations Free of Transmetallating Agents

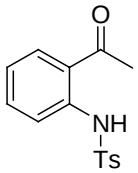
Mónica Carril, Raul SanMartin*, Fátima Churruca, Imanol Tellitu and Esther Domínguez*

Supporting Information

General Remarks. Toluene, dichloromethane, pyridine and chloroform were purchased from Scharlau Chemie and used without further purification. 2'-Aminoacetophenone, *p*-toluenesulfonyl chloride, potassium carbonate, methyl chloroformate, Xantphos and potassium phosphate were purchased from Aldrich and used without further purification. 1,2-Dibromobenzene, $Pd(OAc)_2$, cesium carbonate, chlorosulfonyl isocyanate were purchased from Acros Organics and used as received. BINAP was purchased from Avocado Organics and used without further purification. Concentrated sulfuric acid was purchased from NormaSolv and used as received. Redistilled water was employed in several palladium-catalyzed reactions, although non-distilled water afforded target compounds with comparable yiels.

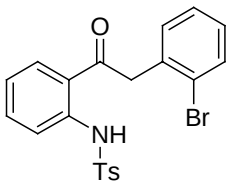
^1H and ^{13}C spectra were recorded in $CDCl_3$ solution in a Bruker AC-250. Chemical shifts are reported in ppm downfield (δ) from Me_4Si. IR spectra were recorded on a Perkin-Elmer 1600 FT infrared spectrophotometer and only noteworthy absorptions are listed. Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2 (silica gel 60 F_{254}, Merck), and the spots were located with UV light. Flash chromatography was carried out on SiO_2 (silica gel 60, Merck, 230-400 mesh ASTM). Drying of organic extracts during workup of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a Büchi rotatory evaporator. HRMS were performed by the *Centro de Apoio Científico Tecnológico á Investigación* (C.A.C.T.I.) in the University of Vigo, using VG Autospec M apparatus..

All reactions were carried out under argon except the synthesis of amine **5** which was performed in a reaction vessel open to the atmosphere.



1-[2-*N*-(4-Methylbenzenesulfonamido)phenyl]ethanone 6a

A solution of 2'-aminoacetophenone **3** (3 g, 21.75 mmol), *p*-toluenesulfonyl chloride (12 g, 61.77 mmol), pyridine (8 ml, 12.78 mmol) in CH_2Cl_2 (200 ml) was stirred overnight. The reaction mixture was washed twice with a saturated aqueous solution of $CuSO_4$ (2 x 150 ml) and once with water (150 ml). The organic layer was dried and concentrated *in vacuo* and the resulting residue was purified by crystallization from ethyl acetate to yield sulfonamide **6a** (6.034 g, 96%) as white needles, mp 148-150°C (EtOAc) (lit.[1] 147-148°C); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.36 (3H, s), 2.56 (3H, s), 7.06 (1H, td, *J* = 1.19, 7.72), 7.22 (2H, d, *J* = 7.93), 7.45 (1H, td, *J* = 1.19, 7.72), 7.68 (1H, dd, *J* = 1.19, 7.93), 7.74 (2H, d, *J* = 8.32), 7.79 (1H, dd, *J* = 1.19, 7.93), 11.46 (1H, s); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 21.4, 28.0, 118.8, 122.1, 122.5, 127.5, 129.5, 131.8, 134.8, 136.4, 139.9, 143.8, 202.4; FTIR (neat film, cm^{-1}) 3052.9, 1644.2; EIMS (*m/z*, %) 289 (M, 89), 155 (19), 134 (96), 120 (15), 106 (23), 91 (100); HRMS calcd for $C_{15}H_{15}NO_3S$, 289.0773; found, 289.0767.

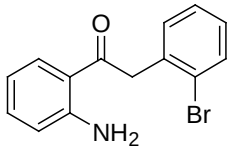


2-(2-Bromophenyl)-1-[2-*N*-(4-methylbenzenesulfonamido)phenyl]ethanone 7a.

A solution of sulfonamide **6a** (150 mg, 0.519 mmol), 1,2-dibromobenzene **4** (0.15 ml, 1.25 mmol), $Pd(OAc)_2$ (5.3 mg, 0.023 mmol), Xantphos (26.5 mg, 0.044 mmol), Cs_2CO_3 (243.6 mg, 0.74 mmol), toluene (2.6 ml) and water (0.5 ml) was heated at

[1] Kempter, G.; Schiewald, E. *J. Prakt. Chem.* **1965**, *28*, 169.

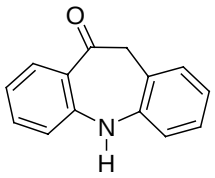
120°C. After 48 hours the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated *in vacuo*. The crude product was then purified by flash chromatography (CH_2Cl_2) to give starting material **6a** (22.1 mg) and deoxybenzoin **7a** (167,8 mg, 86%) as translucent prisms, mp 125-126°C (EtOAc); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 2.36 (3H, s), 4.40 (2H, s), 7.07-7.34 (6H, m), 7.48 (1H, td, *J* = 1.19, 7.93), 7.60 (1H, dd, *J* = 1.19, 7.93), 7.72 (2H, d, *J* = 8.32), 7.76 (1H, dd, *J* = 1.19, 8.72), 7.97 (1H, dd, *J* = 1.19, 7.93), 11. 32 (1H, s); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 21.4, 46.6, 119.1, 121.6, 122.7, 124.9, 127.1, 127.5, 129.0, 129.6, 131.1, 131.7, 132.7, 134.3, 135.0, 136.4, 140.2, 143.8, 200.4; FTIR (neat film, cm^{-1}) 3122.2, 1651.6; FAB-MS (*m/z*, %) 446 (MH+2, 75), 444 (MH, 78), 391 (80), 307 (25), 289 (23), 274 (95), 248 (31), 154 (100); HRMS calcd for $C_{21}H_{18}O_3SBr$, 443.0191; found, 443.0181.



1-(2-Aminophenyl)-2-(2-bromophenyl)ethanone 5

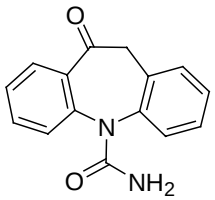
A solution of deoxybenzoin **7a** (1.1892 g, 2.678 mmol) in 20 ml of concentrated sulfuric acid was stirred at room temperature in an open vessel for 10 min (until complete solution of the substrate is visually observed). The reaction mixture was then poured onto an ice-water mixture (aprox. 200 ml). The resulting solution was allowed to reach room temperature and then was extracted with diethyl ether (3 x 150 ml). The organic layer was dried and the solvent was removed *in vacuo* to give amine **5** (736 mg, 95%) as pale yellow crystals, mp 84-86°C (Et_2O); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.46 (2H, s), 6.16 (2H, bs), 6.69-6.75 (2H, m), 7.14-7.34 (4H, m), 7.62 (1H, d, *J* = 7.53), 7.88 (1H, d, *J* = 7.92); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 46.2, 115.9, 117.4, 125.2, 127.4,

128.6, 131.0, 131.7, 132.7, 134.5, 135.6, 150.5, 198.4; FTIR (neat film, cm^{-1}) 3473.9, 3348.3, 1650.0; EIMS (*m/z*, %) 291 (M+2, 10), 289 (M, 9), 120 (100), 92 (15); HRMS calcd for $C_{14}H_{12}NOBr$, 291.0082; found, 291.0097.



10,11-Dihydro-5*H*-dibenz[*b,f*]azepin-10-one 8

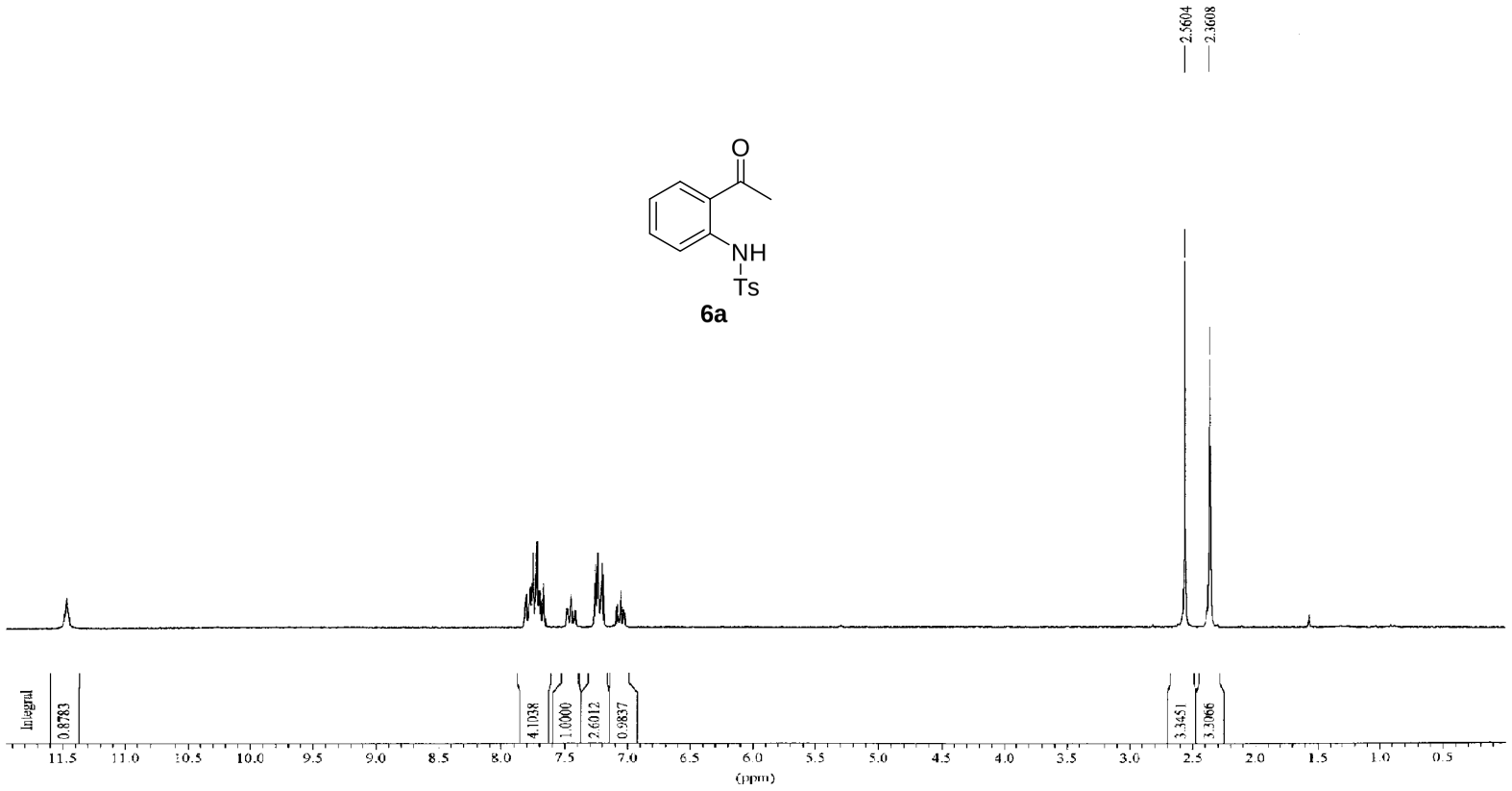
A solution of amine **5** (100.6 mg, 0.347 mmol), $Pd(OAc)_2$ (4 mg, 0.017 mmol), BINAP (17.4 mg, 0.027 mmol), previously ground K_3PO_4 (150 mg, 0.683 mmol), toluene (3.5 ml) and water (1.5 ml) was heated at 130°C. After 5 hours the reaction mixture was partitioned between water and dichloromethane. The organic layer was dried and concentrated *in vacuo*. The crude product was then purified by flash chromatography (5% Et_2O/CH_2Cl_2) to give azepinone **8** (66 mg, 91%) as yellow needles, mp 138-139°C (MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.84 (2H, s), 6.84 (1H, bs), 6.93 (1H, t, *J* = 7.53), 7.03-7.31 (5H, m), 7.41 (1H, td, *J* = 1.58, 7.53), 8.04 (1H, dd, *J* = 1.59, 8.33); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 49.3, 118.8, 119.2, 119.4, 123.9, 124.3, 124.8, 127.6, 129.9,130.5, 133.5, 141.3, 146.4, 189.6; FTIR (neat film, cm^{-1}) 3325.7, 3229.4, 3136.1, 3054.2, 2973.1, 1649.9; EIMS (*m/z*, %) 209 (M, 100), 180 (58), 120 (17); HRMS calcd for $C_{14}H_{11}NO$, 209.0841; found, 209.0847.



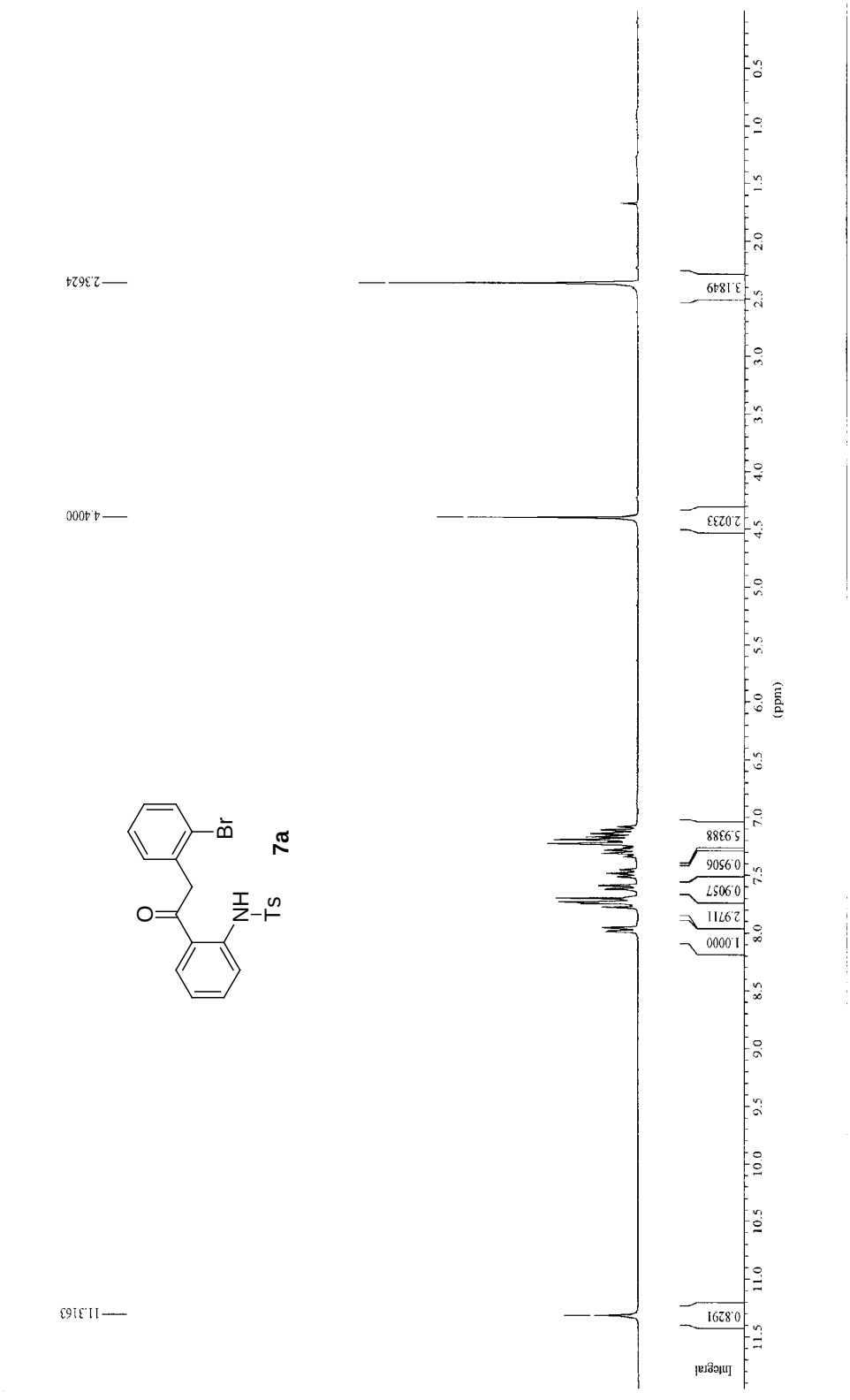
10,11-Dihydro-5-aminocarbonyl-dibenz[*b,f*]azepin-10-one (oxcarbazepine) 1

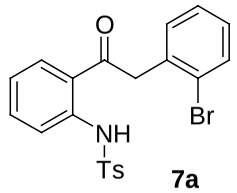
The patented procedure[2] for the carbamoylation of derivative **8** (66 mg, 0.316 mmol) was slightly modified, altering the amount of the chlorosulfonyl isocyanate reagent (3.6 eq.). The use of water instead of ice and the purification method (flash chromatography, 8% MeOH/CH_2Cl_2) were also slight modifications of the latter procedure. Thus, oxcarbazepine **1** (39.8 mg, 50%) was isolated as a white solid, mp 219-221°C (MeOH), (lit.[2] 224°C (MeOH)); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.85 (1H, d, *J* = 13.87), 4.45 (1H, d, *J* = 13.87), 4.97 (2H, bs), 7.31-7.68 (7H, m), 8.10 (1H, dd, *J* = 1.59, 7.93); ^{13}C NMR ($CDCl_3$, 63 MHz) δ 48.9, 127.3, 127.7, 128.6, 129.0, 129.3, 129.8, 130.1, 130.6, 133.9, 141.2, 143.0, 156.1, 157.3, 191.9; FTIR (neat film, cm^{-1}) 3459.8, 3330.6, 1678.1, 1648.7; EIMS (*m/z*, %) 252 (M, 47), 209 (86), 180 (100), 152 (23). HRMS calcd for $C_{15}H_{12}N_2O_2$, 252.0899; found, 252.0896.

[2] Milanese, A. PCT Int. Appl. WO 9621649, 1996; *Chem. Abstr*. **1996**, *125*, 195448.

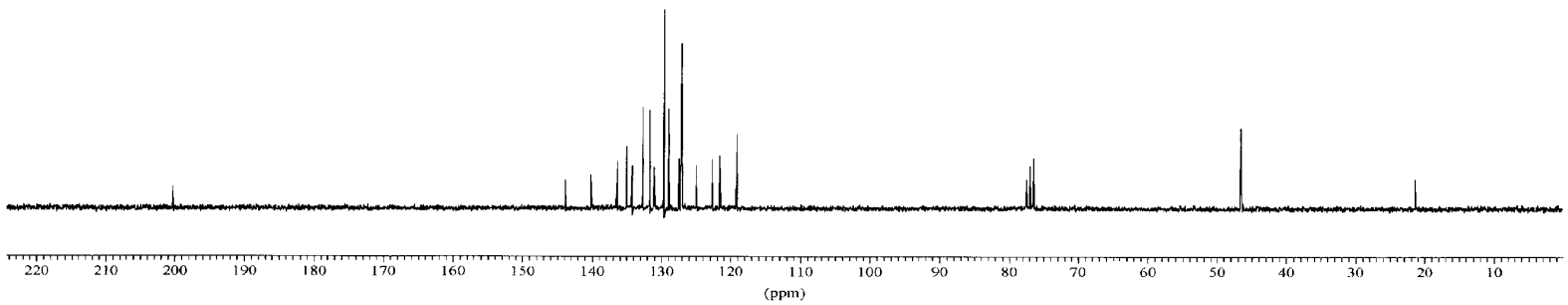

O
NH
Ts
6a
2.5604
2.3608
Integral
0.8783
4.1038
1.0000
2.6012
0.9837
3.3451
3.3066
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)

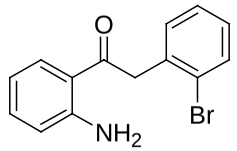
21.4234
28.0458
118.8180
122.1007
122.5288
127.1245
129.5508
131.8630
134.8516
136.3730
139.9126
143.8232
202.3685
(ppm)
6a


11.3163
4.4000
2.3624
Integral
0.8291
1.0000
2.9711
0.9057
0.9506
5.9388
2.0233
3.1849
(ppm)
Br
NH
Ts
O
7a

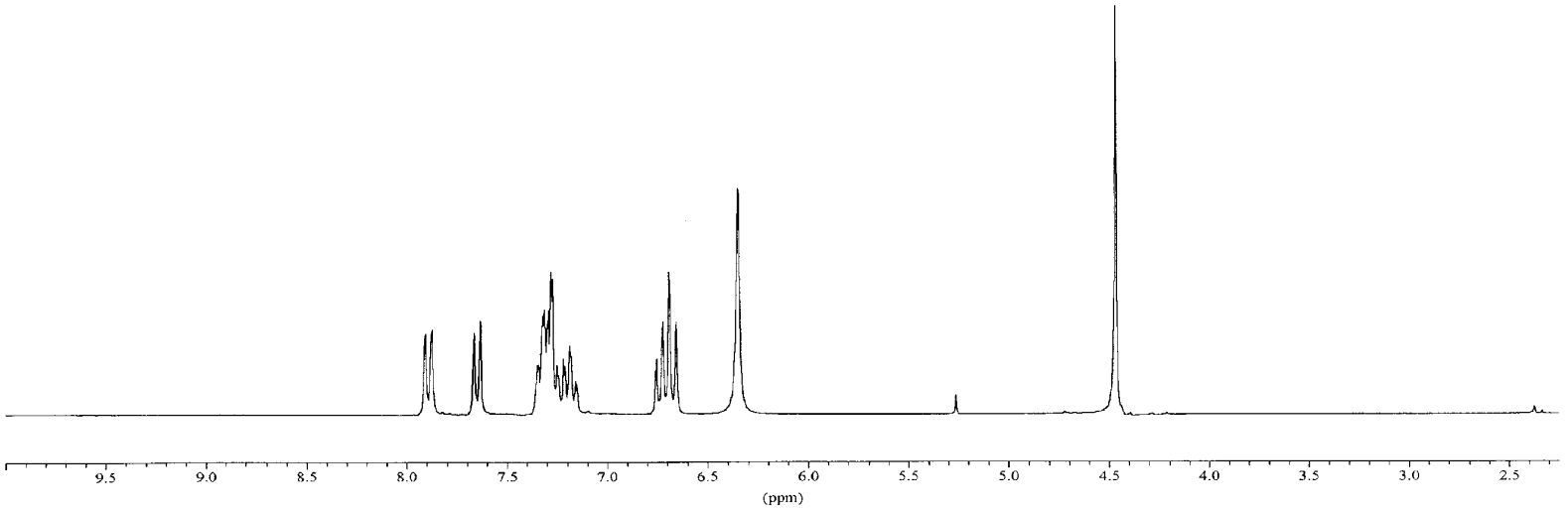

O
Br
NH
Ts

7a


220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
(ppm)



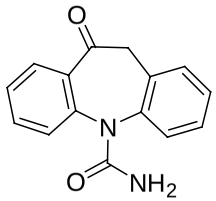
5



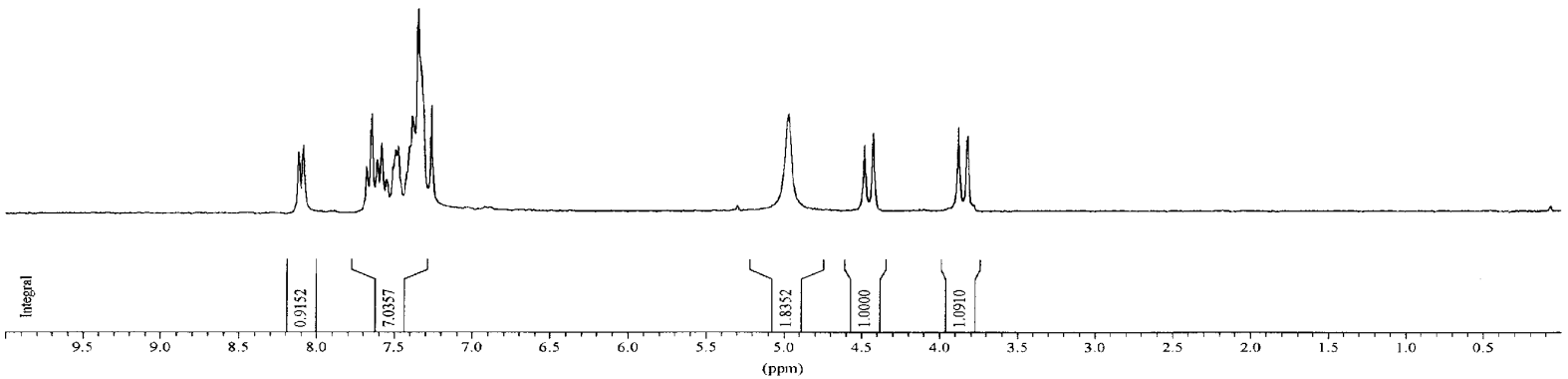
46.2573
198.3722
150.4741
135.6309
134.5462
132.6622
131.6917
131.0357
128.3...
127.4385
125.1835
117.4479
115.8779
Br
O
NH2
5
(ppm)

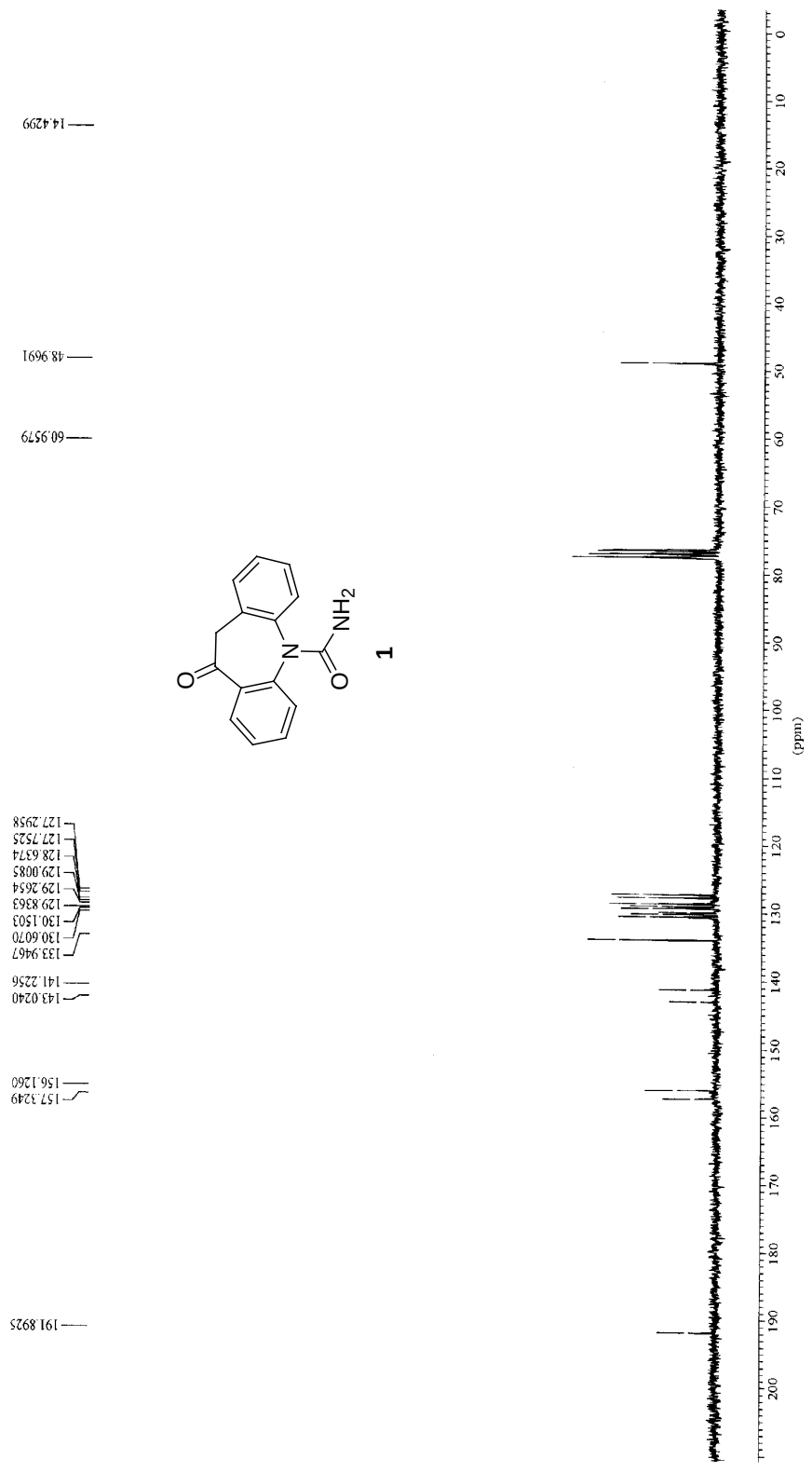
3.8375
2.2264
1.9278
4.9658
1.0017
1.0000
Integral
(ppm)
8

49.2831
8
118.8466
119.1606
119.3604
123.9561
124.3272
124.8410
127.5813
129.9219
130.4643
133.5186
141.3398
146.4208
189.5519
(ppm)


O
N
O
NH2

1


Integral
0.9152
7.0357
1.8352
1.0000
1.0910
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
(ppm)


191.8925
157.3249
156.1260
143.0240
141.2256
133.9467
130.6070
130.1503
129.8363
129.2654
129.0085
128.6374
127.7525
127.2958
60.9579
48.9691
14.4299
O
N
O
NH2
1
(ppm)