HETEROCYCLES, Vol. 55, No. 6, 2001, pp. 1057 – 1062, Received, 20th February, 2001

OXIDATION OF *2*-AMINO-*2'*-HYDROXYBENZOPHENONE *N*-ACYLHYDRAZONES: SYNTHESIS OF 6-SUBSTITUTED DIBENZAZEPIN-11-ONES

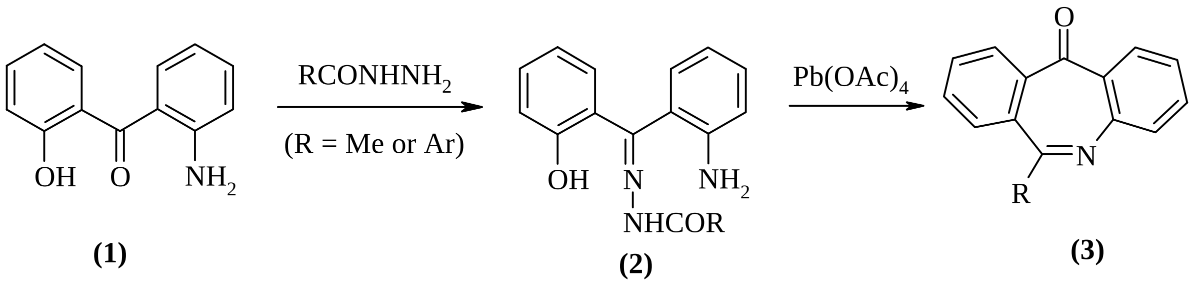
Antigoni Kotali,[a*] Efthymia Lazaridou,[a] Vassilios P. Papageorgiou,[a] and Philip A. Harris[b]

[a]Laboratory of Organic Chemistry, College of Engineering, University of Thessaloniki, Thessaloniki, GR-54006, Greece

[b]GlaxoSmithKline, Five Moore Drive, P.O. Box 13398, Research Triangle Park, North Carolina, 27709-3398, USA

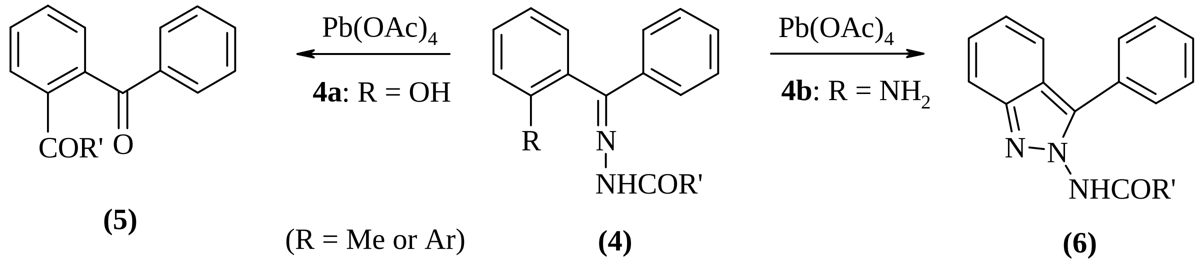
Abstract- *The synthesis of 6-substituted 11H-dibenz[b,e]azepin-11-ones is reported via the lead tetraacetate oxidative cyclization of 2-amino-2-hydroxybenzophenone N-acylhydrazones. A mechanism involving formation of a 2-acyl-2'-aminobenzophenone intermediate is proposed.*

Dibenz[*b,e*]azepines are well established pharmacophores in the pharmaceutical industry demonstrating a variety of CNS activities, as exemplified by the antidepressants mianserin[1] and mirtazapine,[2] antipsychotics perlapine[3] and RMI 81582,[4] and the anticonvulsant ICI 45,337.[5] In the course of our continued investigations on the applicability of a novel reaction of *N*-carbonylhydrazones of *ortho*-substituted aryl ketones with lead tetraacetate (LTA), we now wish to report development of a new expeditious synthesis of this heterocyclic pharmacophore. 6-Aryl- and 6-alkyldibenz[*b,e*]azepin-11-ones (**3**) are obtained in two steps from 2-amino-2'-hydroxybenzophenone (**1**) *via* the LTA treatment of the corresponding *N*-acylhydrazones (**2**) as shown in Scheme 1.



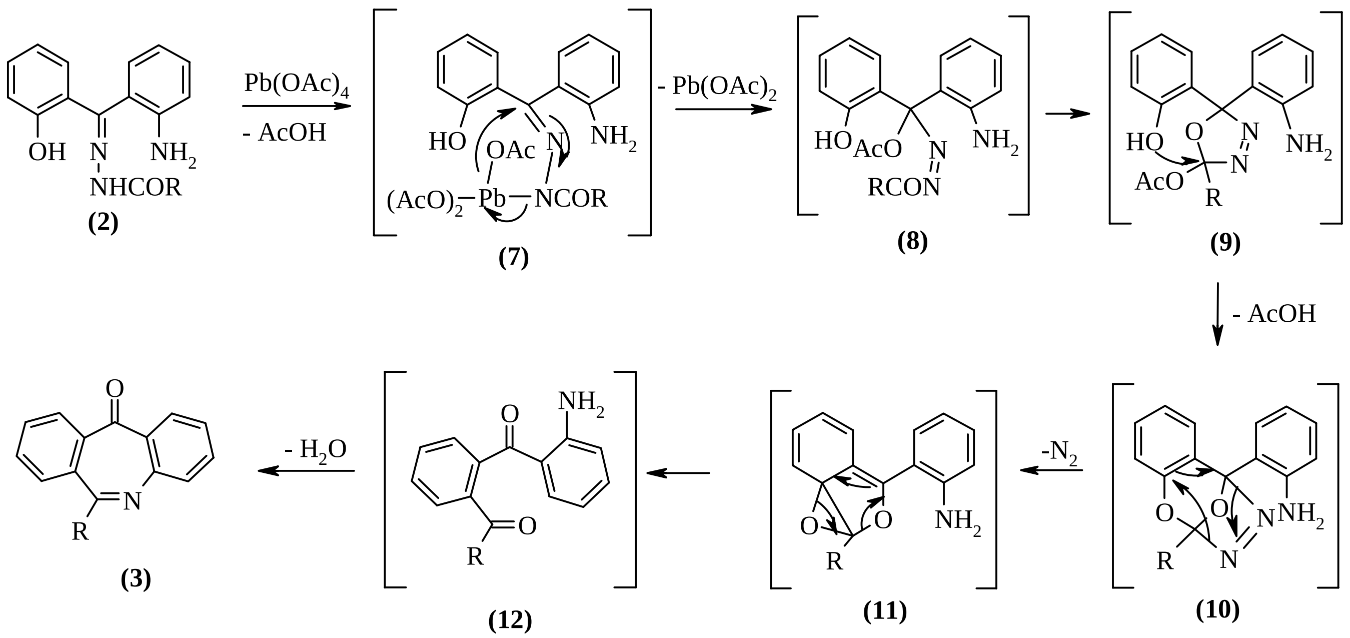
Scheme 1

Earlier work from our laboratories had demonstrated that treatment of *N*-acylhydrazones of 2-hydroxyaryl ketone (**4a**) with LTA results in an unusual replacement of the phenolic hydroxyl with the acyl functionality to give 2-acylbenzophenones (**5**) (Scheme 2).[6] However, when we replaced the *ortho*-hydroxyl with primary amino group, similar LTA treatment of the corresponding 2-aminoaryl ketone *N*-acylhydrazones (**4b**) yielded 2-acylaminoimidaozles (**6**).[7]



Scheme 2

Having shown that either *ortho*-hydroxyl or amino aryl ketones yield novel LTA induced reactions, we examined which pathway would be followed if both functionalities were present and thus prepared a series of *N*-acylhydrazones derived from 2-amino-2'-hydroxybenzophenone. 2-Amino-2'-hydroxybenzophenone (**1**) was obtained by initial addition of *o*-methoxyphenyl Grignard reagent to acetanthranil, followed by acidic amide hydrolysis to give 2-amino-2'-methoxybenzophenone,[8] and subsequent aluminum chloride induced demethylation.[9] Condensation of **1** with *N*-acetyl- and *N*-aroylhydrazides in propan-2-ol routinely yielded the corresponding hydrazones (**2a-e)**. Treatment of **2** with LTA resulted in the hydroxyl replacement to initially give 2-acetyl- and 2-aroyl-2'-aminobenzophenone intermediates, which, without isolation, readily cyclized to the dibenz[*b*,*e*]azepin-11-ones (**3a-e**) in overall satisfactory yields (see Table). In a typical oxidation procedure, LTA is added to a solution of hydrazone (**2)** in THF and the mixture is stirred at room temperature for 2 h. The oily product, obtained after filtration and condensation of the filtrate, was purified by column chromatography. Mechanistically, LTA oxidation of hydrazones derived from aromatic acylhydrazides is known to give reactive azoacetates (**8**), which readily undergo cyclization to 1,3,4-oxadiazolines (**9**).[10] Based on the findings of an earlier mechanistic study,[11] we have proposed that at this stage the *o*-hydroxyl group reacts with the oxadiazoline to give the 1,3-dioxane species (**10**). Elimination of nitrogen and formation of epoxide then leads to intermediate (**11**), which can undergoes electrocyclic rearrangement to form the key 2-acyl-2'-aminobenzophenone (**12**) precursor. Subsequent dehydrative cyclization of **12** yields the observed dibenz[*b*,*e*]azepin-11-one (**3**) (Scheme 3).



Scheme 3

Table

R	Hydrazone	Yield (%)	mp (^{o}C)	Dibenzazepinone[a]	Yield (%)
C_6H_5	**2a**	82	179-180	**3a**	74
o-HO-C_6H_4	**2b**	87	185-186	**3b**	52
o-NO_2-C_6H_4	**2c**	77	184-186	**3c**	47
p-NO_2-C_6H_4	**2d**	88	203-204	**3d**	38
Me	**2e**	80	174-175	**3e**	40

[a] Dibenzazepinones (**3**) are semi-solids.

Hydrazones (**2**) and dibenzazepinones (**3b-e**) are all new compounds and have been identified by their spectroscopic data and elemental analysis. 6-Phenyldibenzazepin-11-one (**3a**) was previously reported obtained as a mixture of products from the photochemical and thermal rearrangement of 10-azido-10-phenyl-9-anthracenone.[12] 2-Amino-2'-hydroxybenzophenone *o*-nitrophenylcarbonylhydrazone (**2c**) was obtained as a mixture of two isomers. In GC-MS analysis, two peaks were observed after 2.47 and 2.81 min and they both gave prominent peaks at m/z 377 corresponding to the molecular ion [M+1]. ^{1}H and ^{13}C NMR spectra indicated a ratio of about 1:2. The mixture of the two isomers was further oxidized by LTA to give the expected product 6-(o-nitrophenyl)dibenzazepin-11-one (**3c**) as one isomer. Interesting, 6-(o-hydroxyphenyl)dibenzazepin-11-one (**3b**) was obtained as a mixture of two isomers. In GC-MS analysis, two peaks were observed after 3.20 and 3.34 min and they both gave prominent peaks at m/z 300 corresponding to the ion [M+1].

In conclusion, a synthesis of 6-substituted dibenz[*b,e*]azepin-11-ones was achieved in an experimentally simple way with satisfactory yields. With a variety of substitutions possible at the 6 position and the bridging carbonyl available for further elaboration, this should prove to be an attractive template for the development of pharmaceutically useful compounds.

EXPERIMENTAL

Melting points were determined on an oil-Buchi apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Unity Plus 300 or 400 MHz in DMSO-d6 unless indicated otherwise. MS were recorded on Micromass Platform II spectrometer. Lead tetraacetate (95%) and acylhydrazides were all purchased from commercial suppliers (Aldrich and Fluka).

A General Procedure for the Preparation of Hydrazones (**2**).

2-Amino-2'-hydroxybenzophenone (**1**) (2.13 g, 10 mmol) and the corresponding hydrazide (10 mmol) were refluxed in propan-2-ol (50 mL) for 24 h. The precipitate was filtered off and washed with propan-2-ol to give the pure hydrazone (**2**) as a pale yellow solid (see Table).

2-Amino-2'-hydroxybenzophenone benzoylhydrazone (**2a**): (propan-2-ol). ^{1}H-NMR δ 5.44 (s, 2H), 6.71-6.84 (m, 2H), 6.97-7.25 (m, 4H), 7.29-7.32 (m, 2H), 7.46-7.50 (m, 2H), 7.54-7.58 (m, 1H), 7.66-7.68 (m, 2H), 10.50 (s, 1H), 12.92 (s, 1H). ^{13}C-NMR δ 115.6, 115.9, 117.2, 118.5, 119.2, 127.3, 128.1, 128.8, 129.1, 129.7, 130.6, 131.2, 132.2, 132.6, 145.4, 157.2, 159.0, 163.2. ES-MS m/z 354 (M+Na), 332 (M+1), 211. Anal. Calcd for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68. Found: C, 72.43; H, 5.19; N, 12.71.

2-Amino-2'-hydroxybenzophenone *o*-hydroxyphenylcarbonylhydrazone (**2b**): (propan-2-ol). ^{1}H-NMR δ 6.72-6.97 (m, 9H), 7.23-7.35 (m, 4H), 7.95-7.97 (s, 1H), 11.00 (br, 1H), 12.92 (s, 1H), 13.20 (s, 1H). ^{13}C-NMR δ 113.3, 115.1, 115.4, 115.7, 117.0, 117.7, 125.8, 127.2, 128.2, 129.1, 129.2, 129.3, 130.7, 131.1, 143.1, 155.7, 157.6, 161.7. ES-MS m/z 694 (2M), 348 (M+1), 211, 121. Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.09. Found: C, 69.05; H, 4.99; N, 12.11.

2-Amino-2'-hydroxybenzophenone *o*-nitrophenylcarbonylhydrazone (**2c**): (propan-2-ol). ^{1}H-NMR δ 5.10 (s, 2H), 5.80 (s, 2H), 6.30-8.25 (m, 22H), 9.60-9.80 (s, 2H), 10.40 (s, 1H), 10.50 (s, 1H), 13.00 (s, 1H), 13.30 (s, 1H). ^{13}C-NMR δ 114.7, 114.8, 116.6, 117.0, 117.3, 117.9, 119.2, 119.5, 120.0, 124.7, 124.8, 129.9, 130.0, 130.3, 130.5, 131.4, 131.7, 131.8, 132.0, 134.2, 134.5, 134.6, 146.3, 147.1, 149.2, 155.4, 156.7, 157.4, 159.7, 161.0, 163.0, 163.6, 165.5, 168.0, 168.2, 174.0. ES-MS m/z 377 (M+1), 227, 211, 150. Anal. Calcd for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.92; H, 4.26; N, 14.85.

2-Amino-2'-hydroxybenzophenone *p*-nitrophenylcarbonylhydrazone (**2d**): (propan-2-ol). ^{1}H-NMR δ 6.69-6.78 (m, 2H), 6.87-7.29 (m, 4H), 7.23-7.29 (m, 2H), 7.87-7.99 (d, 2H), 8.02-8.29 (d, 2H), 9.75 (s, 1H), 12.92 (s, 1H) (NH_2 peak not observed). ^{13}C-NMR δ 113.2, 115.0, 115.2, 115.8, 117.0, 117.5, 122.1, 127.7, 128.1, 129.2, 129.6, 129.9, 137.2, 144.0, 147.8, 156.3, 157.7, 161.0. ES-MS m/z 377 (M+1), 211, 150. Anal. Calcd for $C_{20}H_{16}N_4O_4$: C, 63.82; H, 4.28; N, 14.89. Found: C, 63.95; H, 4.38; N, 14.98.

2-Amino-2'-hydroxybenzophenone acetylhydrazone (**2e**): (propan-2-ol). ^{1}H-NMR δ 1.80 (s, 3H), 4.98 (s, 2H), 6.40-7.40 (m, 8H), 9.65 (s, 1H), 13.05 (s, 1H). ^{13}C-NMR δ 16.9, 114.3, 115.5, 127.5, 128.3, 129.5, 144.0, 146.7, 151.6, 152.4, 153.0, 157.4, 164.5, 165.0, 166.5. ES-MS m/z 270 (M+1), 211. Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.60. Found: C, 66.80; H, 5.63; N, 15.65.

A General Procedure for the Preparation of Dibenzazepinones (**3**).

Hydrazone (**2**) (5 mmol) was dissolved in tetrahydrofuran (30 mL) and LTA (4.43 g, 10 mmol) was gradually added. The mixture was stirred at rt for 2 h. After evaporation of the solvent the mixture was subjected to column chromatography (silica gel 70-230 mesh, pet. ether/ chloroform 1/ 1) to give the pure dibenzazepinone (**3**) (see Table) as a light yellow semi solid.

6-Phenyl-11*H*-dibenz[*b,e*]azepin-11-one (**3a**): (semi-solid). ^{1}H-NMR δ 7.84-7.96 (m, 2H), 7.27-7.74 (m, 11H). ^{13}C-NMR δ 126.7, 127.3, 127.7, 128.2, 129.0, 130.0, 130.3, 130.5, 131.0, 131.2, 131.7, 132.6, 133.9, 141.6, 143.6, 145.1, 165.0, 194.0. ES-MS m/z 306 (M+Na), 284 (M+1), 255, 206, 178. Anal. Calcd for $C_{20}H_{13}NO$: C, 84.78; H, 4.62; N, 4.94. Found: C, 84.60; H, 4.65; N, 4.91.

6-(*o*-Hydroxyphenyl)-11*H*-dibenz[*b,e*]azepin-11-one (**3b**): (semi-solid). ^{1}H-NMR δ 6.50-6.80 (m, 1H), 7.07-7.26 (m, 3H), 7.40-7.53 (m, 3H), 7.60-7.80 (m, 4H), 7.84-7.87 (m, 1H) (OH peak not observed). ^{13}C-NMR δ 118.08, 118.4, 118.5, 118.7, 120.9, 122.3, 123.2, 124.9, 127.1, 127.5, 128.0, 128.1, 128.4, 128.6, 130.0, 130.5, 130.6, 130.8, 131.3, 131.6, 132.3, 132.7, 133.1, 133.3, 133.4, 134.1, 134.6, 135.2, 136.6, 142.7, 144.3, 161.8, 168.3, 194.0. ES-MS m/z 300 (M+1), 283, 272, 206, 178. Anal. Calcd for $C_{20}H_{13}NO_2$: C, 80.25; H, 4.38; N, 4.68. Found: C, 80.33; H, 4.40; N, 4.66.

6-(*o*-Nitrophenyl)-11*H*-dibenz[*b,e*]azepin-11-one (**3c**): (semi-solid). ^{1}H-NMR δ 7.20-7.80 (m, 10H), 7.85-8.18 (m, 2H). ^{13}C-NMR δ 124.7, 128.2, 128.4, 130.0, 130.2, 130.8, 131.6, 132.0, 132.4, 133.2, 134.2, 136.0, 138.0, 143.8, 144.2, 149.0, 162.8, 194.0. ES-MS m/z 329 (M+1), 298, 282, 254. Anal. Calcd for $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 73.09; H, 3.70; N, 8.56.

6-(*p*-Nitrophenyl)-11*H*-dibenz[*b,e*]azepin-11-one (**3d**): (semi-solid). ^{1}H-NMR δ 6.70-7.20 (m, 2H), 7.45-7.74 (m, 6H), 7.95-8.01 (m, 2H), 7.26-8.37 (m, 2H). ES-MS m/z 329 (M+1), 328 (M), 282, 149. Anal. Calcd for $C_{20}H_{12}N_2O_3$: C, 73.16; H, 3.68; N, 8.53. Found: C, 73.26; H, 3.72; N, 8.55.

6-Methyl-11*H*-dibenz[*b,e*]azepin-11-one (**3e**): (semi-solid). ^{1}H-NMR ($CDCl_3$) δ 1.25 (s, 3H), 6.42-7.80 (m, 8H). ^{13}C-NMR δ 29.9, 118.6, 121.5, 127.5, 127.9, 128.5, 128.9, 130.6, 134.1, 135.7, 137.2, 140.5, 143.0, 147.4, 165.8. ES-MS m/z 222 (M+1), 194, 147. Anal. Calcd for $C_{15}H_{11}NO$: C, 81.42; H, 5.01; N, 6.33. Found: C, 81.34; H, 5.00; N, 6.35.

AKNOWLEDGEMENT

The authors thank Royal Society of Chemistry for financial support of this work.

REFERENCES

1. D. Aizenberg, S. Gur, Z. Zemishlany, M. Granek, P. Jeczmien, and A. Weizman, *Clin. Neuropharmacol.*, 1997, **20**, 210.
2. J. M. Gorman, *J. Clin. Psychiatry,* 1999, **60** (Suppl. 17), 9.
3. G. Stille, A. Sayers, H. Lauener, and E. Eichenberger, *Psychopharmacologia*, 1973, **28**, 325.
4. M. A. Young and H. Y. Meltzer, *Psychopharmacology,* 1980, **67**, 101.
5. W. S. Waring and B. A. Whittle, *J. Pharm. Pharmacol.*, 1969, **21**, 520.
6. A. Kotali and P. G. Tsoungas, *Tetrahedron Lett.*, 1987, **28**, 4321.
7. A. Kotali and P. A. Harris, *Heterocycles*, 1994, **37**, 1541.
8. M. Lamchen and A. J. Wicken, *J. Chem Soc*, 1959, 2779.
9. S. Yamaguchi, Y. Oh-Hira, M. Yamada, H. Michitani, and Y. Kawase, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 952.
10. R. W. Hoffman and H. J. Luthardt, *Chem. Ber.*, 1968, **101**, 3861.
11. A. R. Katritzky, P. A. Harris, and A. Kotali, *J. Org. Chem.*, 1991, **56**, 5049
12. J-P. Le Roux, P-L. Desbene, and M. Seguin, *Tetrahedron Lett.*, 1976, 3141.