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A BRIDGEHEAD α-AMINO CARBANION: FACILE PREPARATION OF C5(BRIDGEHEAD)-SUBSTITUTED ANALOGUES OF (±)-5H-DIBENZO[a,d]CYCLOHEPTEN-5,10-IMINE INCLUDING A STABLE α-IODO SECONDARY AMINE

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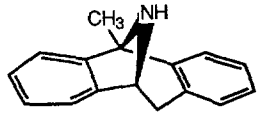
Abstract: The preparation of C5(bridgehead)-substituted analogues of (±)-5*H*-dibenzo[a,d]cyclohepten-5,10-imine via α-lithiation of a *tert*-butylformamidine precursor is presented.

MK-801 [(+)-5-methyl-5*H*-dibenzo[a,d]cyclohepten-5,10-imine] is a potent and selective ligand for brain phencyclidine (PCP) receptors[2] which possesses both anticonvulsant[3] and neuroprotective[4,5] properties *in vivo*. In conjunction with ongoing studies in our laboratory directed toward further elucidating the structure and function of PCP receptors, we required a short, highly divergent synthetic route to C5-substituted analogues of (±)-*des*-methyl MK-801 (**1a**).



MK-801

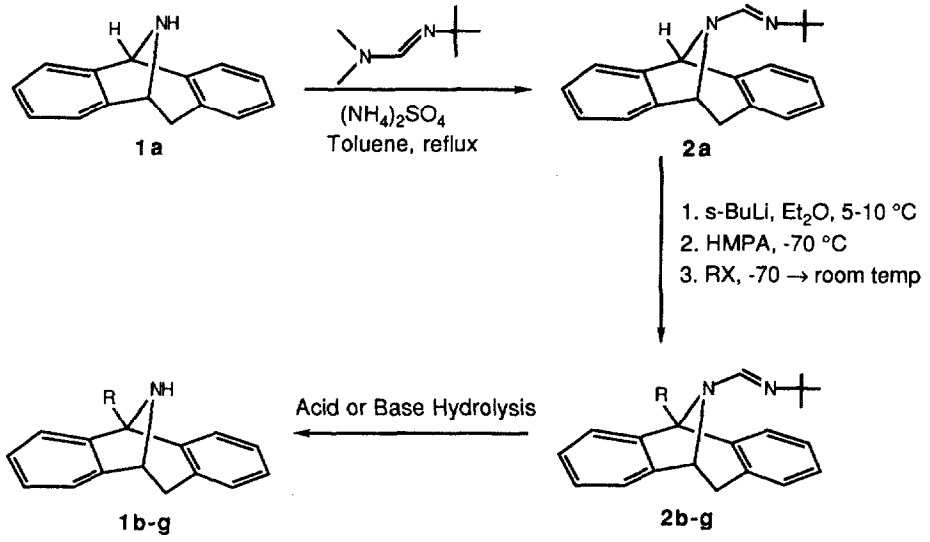
We envisioned that C5-substituted analogues of **1a** could be obtained by the alkylation (or acylation) of the α-amino carbanion from *tert*-butylformamidine **2a**. Although the alkylation of carbanions generated adjacent to amine derivatives (including *tert*-butylformamidines) is now a well-known process,[6-10] there have been no examples reported in which the α-amino carbanion is generated at a bridgehead position. We now report our preliminary observations relating to the lithiation of the doubly benzylic bridgehead position of **2a**, and subsequent reaction of this carbanion with electrophiles.

The preparation of **1a** was accomplished as previously described.[11] Condensation of **1a** (Scheme 1) with N'-*tert*-butyl-N,N-dimethylformamidine in the presence of catalytic $(NH_4)_2SO_4$ afforded, after column chromatography (silica gel 60, 7% Et_3N in hexanes eluent), excellent yields of **2a** (94-99%, 10 - 100 mmol scale).[12] Treatment of **2a** (1 - 2 mmol) in anhydrous ether (10 - 20 mL) with *sec*-butyllithium (1.2 eq) at 5 - 10°C generated an orange-red colored solution of the C5 anion. This species is remarkably stable even at room temperature, as evidenced by no observable loss of material upon H_2O quench after 1h at 24°C. Addition of iodomethane (entry 1) to the C5 anion at 5 - 10°C immediately discharged the orange-red color and produced a pale yellow solution. Purification of the major product (silica gel 60, 2% Et_3N in hexanes eluent) afforded the C5-methyl formamidine **2b** (74%). Alkaline hydrolysis of **2b** (KOH, ethylene glycol, 150°C, 15

min) then gave a nearly quantitative yield (97%) of the desired product, (±)-MK-801 (**1b**, 72% overall) which was chromatographically and spectroscopically identical to a sample prepared by the literature method.[11] In a similar manner, the C5 anion was quenched with C2 - C10 straight chain alkyl iodides (entries 2-5). In these examples, however, it was necessary to add HMPA prior to the electrophile.[10] Thus, while addition of ethyl iodide to the C5 anion in the absence of HMPA (entry 2a) resulted in only 34% conversion to the desired product **2c** after 1.5 h at 24°C (60% unchanged **2a**), the same reaction in the presence of 1.5 eq HMPA required only 10 min to effect nearly quantitative (97%) conversion to the 5-ethyl derivative **1c** (entry 2b).[12]

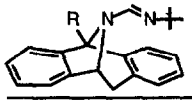
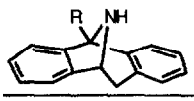
The ability to introduce an ester functionality at the C5 position was of particular interest to us, as a wide range of substituents might then become readily accessible through classical synthetic methodology. As expected, addition of ethyl chloroformate to the C5 anion proceeded smoothly in the absence of HMPA (entry 6), and subsequent solvolysis of the formamidine moiety (EtOH, H_2SO_4 (0.5 eq), reflux)[13] afforded the amino ester **1g** in 72% overall yield.[12]

Scheme 1



Finally, we attempted the addition of 2,2,2-trifluoroethyl iodide to the C5 anion in the presence of 1.5 eq HMPA (entry 7). Surprisingly, the only product of this reaction (72% GC yield, 67% isolated) was identified as the 5-*iodo* formamidine derivative **2h.**[12] When this reaction was repeated in the presence of 5 eq HMPA, the yield of **2h** was slightly improved (81% GC yield), and no free iodine was detected (negative starch-iodide test), suggesting that the conversion of **2a** to **2h** is proceeding by way of a direct metal-halogen exchange reaction. This appears to be strictly analogous to the observed rapid transmetallation of methyllithium in the presence of pentafluoroethyl iodide.[14,15] Solvolysis of the formamidine group of **2h** under acidic conditions (EtOH: 1N H_2SO_4 1:1, reflux) then provided (after silica gel chromatography) the α-iodo secondary amine **1h** (53% from **2a**).[12] Compound **1h** (oxalate salt) is stable to the atmosphere and in

aqueous solution ($t_{1/2}$ > 3 days in 5 mM Tris HCl (pH 7.4) buffer), but is unstable to UV irradiation (λ = 254 nm). Thus, after developing the thin layer chromatograms of **1h** and **2h**, irradiation of these products at λ = 254 nm rapidly (within seconds) causes a visible darkening of the bands which is apparently the result of the evolution of free iodine (as evidenced by scent and a positive starch-iodide test). Further studies directed toward elucidating the photochemical properties of **1h** are currently in progress.

entry	electrophile	alkylation method[a]	 (%)[b]	hydrolysis method[c]	 (%)[d]
1	CH_3I	A	**2b**, R=CH_3 (74)	A	**1b**, R=CH_3 (72)
2a	C_2H_5I	A	**2c**, R=C_2H_5 (34)	- -	------- --
2b	C_2H_5I	B	**2c**, R=C_2H_5 (97)	A	**1c**, R=C_2H_5 (56)
3	C_3H_7I	B	**2d**, R=C_3H_7 (79)	A	**1d**, R=C_3H_7 (60)
4	$C_6H_{13}I$	B	**2e**, R=C_6H_{13} (80)	A	**1e**, R=C_6H_{13} (58)
5	$C_{10}H_{21}I$	B	**2f**, R=$C_{10}H_{21}$ (76)	A	**1f**, R=$C_{10}H_{21}$ (63)
6	$ClCO_2C_2H_5$	A	**2g**, R=$CO_2C_2H_5$ (87)	B	**1g**, R=$CO_2C_2H_5$ (72)
7	CF_3CH_2I	B	**2h**, R=I (81)	B	**1h**, R=I (53)

[a] Method A: addition of 1.1 eq. s-BuLi to **2a** in Et_2O at 5-10°C followed, after 30 min, by addition of the appropriate electrophile and slow warming to room temp. Method B: generation of the anion as above followed by cooling to -70°C, addition of 1-3 equivalents of HMPA and, after 20 min, addition of the appropriate electrophile with subsequent slow warming to room temp. [b] Uncorrected capillary GC yield. [c] Method A: KOH, ethylene glycol, 150°C. Method B: EtOH, H_2SO_4 (0.5 eq), reflux. [d] Isolated yield from **2a**.

In summary, we have developed a divergent synthetic route to C5-(bridgehead) substituted analogues of (±)-MK-801 including a novel and remarkably stable α-iodo secondary amine. Further derivatization of the C5-position utilizing this methodology, biochemical evaluation of new analogues as phencyclidine receptor ligands and the preparation of (±)-5-[^{11}C]methyl MK-801 will be described in detail elsewhere.

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References and Footnotes

(1) NIAMS National Reasearch Service Award Fellow

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(12) Physical properties of representative examples: **2a:** mp = 63-64°C; CIMS (NH_3) 291 (M^++1), 275, 208, 191; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.08 (s, 9H; $C(CH_3)_3$), 2.55 (d, 1H, *J* = 17 Hz; H_{11ax}), 3.66 (dd, 1H, *J* = 17 and 5 Hz; H_{11eq}), 5.34 (d, 1H, *J* = 5 Hz; H_{10}), 5.42 (s, 1H; H_5), 6.89 -7.52 (m, 8H; H_{ar}); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 30.22, 30.70, 53.62, 58.59, 63.77, 119.85, 121.72, 123.89, 125.56, 126.83, 127.31, 130.26, 132.55, 140.54, 141.85, 146.88, 147.35. Anal. calcd. for $C_{20}H_{22}N_2$: C, 82.72; H, 7.64; N, 9.64. Found: C, 82.79; H, 7.64; N, 9.55. **2h:** EIMS (416, M^+; 289, M-127); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 1.20 (s, 9H; $C(CH_3)_3$), 2.30 (d, 1H, *J* = 17 Hz; H_{11ax}), 4.05 (dd, 1H, *J* = 17 and 5 Hz; H_{11eq}), 5.45 (d, 1H, *J* = 5 Hz; H_{10}), 6.75 - 7.55 (m, 8H; H_{ar}), 8.00 (N=CHN). **1c**: mp (oxalate salt) = 234-235°C; IR (film) 3220 cm^{-1} (NH); ^{1}H-NMR (220 MHz, $CDCl_3$) δ 1.00 (t, 3H, *J* = 7 Hz; CH_2CH_3), 2.07 - 2.50 (m, 3H; NH, CH_2CH_3), 2.58 (d, 1H, *J* = 17 Hz; H_{11ax}), 3.30 (dd, 1H, *J* = 17 and 5 Hz; H_{11eq}), 4.56 (d, 1H, *J* = 5 Hz; H_{10}), 6.77 - 7.20 (m, 8H; H_{ar}); EIMS m/z (relative intensity) 235 (M^+, 80), 220 (100), 206 (15); Anal. calcd. for $C_{17}H_{17}N$ $C_2H_2O_4$: C, 70.14; H, 5.89; N, 4.30. Found: C, 70.03; H, 5.91; N, 4.31. **1g**: mp (HCl salt) = 229-230°C; IR (film) 3260 (NH), 1745 (C=O) cm^{-1}; EIMS m/z (relative intensity) 279 (M^+, 50), 250 (15), 233 (12), 206 (60), 205 (100), 178 (30); ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J* = 7 Hz; OCH_2CH_3), 2.60 (brs, 1H; NH), 2.71 (d, 1H, *J* = 17 Hz; H_{11ax}), 3.44 (dd, 1H, *J* = 17 and 5 Hz; H_{11eq}), 4.42 (q, 2H, *J* = 7 Hz; OCH_2CH_3), 4.77 (d, 1H, *J* = 5 Hz; H_{10}), 6.90 - 7.66 (m, 8H; H_{ar}); Anal. calcd. for $C_{18}H_{17}NO_2$·HCl: C, 68.46; H, 5.74; N, 4.44. Found: C, 68.52; H, 5.79; N, 4.41. **1h:** mp (oxalate salt) = 207-209°C; IR 3300 cm^{-1} (NH); EIMS m/z (relative intensity) 333 (M^+, 2), 206 (M-127, 100), 179 (20), 178 (18); ^{1}H-NMR (300 MHz, Acetone-d6) δ 2.63 (d, 1H, *J* = 17 Hz; H_{11ax}), 3.56 (dd, 1H, *J* = 17 and 5 Hz; H_{11eq}), 4.82 (d, 1H, *J* = 5 Hz; H_{10}), 6.00 (brs, 3H; NH·oxalate), 6.85 - 7.60 (m, 8H; H_{ar}); Anal. calcd. for $C_{15}H_{12}IN$·$C_2H_2O_4$: C, 48.25; H, 3.33; N, 3.31. Found: C, 48.32; H, 3.35; N, 3.27.

(13) The stoichiometric ratio of acid to formamidine is crucial. Use of excess H_2SO_4 results in less than 5% conversion of **2g** to **1g** after 4 days in refluxing EtOH. This represents a novel method for removal of the formamidine auxilliary. Previously described methods include alkaline hydrolysis (KOH/EtOH), aminolysis (H_2NNH_2/EtOH) and reductive elimination ($NaBH_4$ or $LiAlH_4$); see ref. 10 for experimental details.

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