resulted in the isolation of six compounds which are presented in order of their elution. **2,5-Difluorobenzophenone (1)**, after distillation at reduced pressure, was isolated as a clear, colorless oil: 5.1 g (39% recovery); bp 120–125 °C (0.35 mm) [lit.[13] bp 120–123 °C (0.35 mm)]. **5-Fluoro-2-methoxybenzophenone (8)**, after crystallization from hexane, was isolated as beige prisms: 0.38 g (3%); mp 78–80 °C (lit.[18] mp 80 °C); $^1$H NMR ($CDCl_3$) $\delta$ 3.63 (s, 3, $CH_3$), 6.8–7.9 (m, 8, Ar); EIMS, $m/z$ (relative intensity) 230 (34, $M^+$). **2,5-Difluorobenzophenone 2,4-dimethylthiosemicarbazone (6)** was flash chromatographed a second time using 10% EtOAc/hexane affording **6** as a yellow foam:[26] 0.96 g (5%); IR ($CHCl_3$) 1550 (C=N) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.16 (d, 3, $CH_3$, $J_{HH}$ = 5 Hz), 3.27 (s, 3, $CH_3$), 6.7–7.8 (m, 9, Ar, NH); $^{13}$C NMR ($CDCl_3$) 32.1 ($CH_3$), 40.9 ($CH_3$), 115–120 (overlapping m), 127.6, 128.2, 130.6, 136.3, 152.3 (C=N), 155.1 (d, $J_{CF}$ = 248.3 Hz), 158.2 (d, $J_{CF}$ = 247.7 Hz), 182.1 (C=S); EIMS, $m/z$ (relative intensity) 319 (50, $M^+$). **5-(2,5-Difluorophenyl)-2,4-dimethyl-5-phenyl-1,2,4-triazolidine-3-thione (7)**, after crystallization from $CCl_4$, was isolated as yellow prisms: 2.94 g (15%); mp 166–168 °C; IR (KBr) 3180 (NH) cm$^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 3.07 (d, 3, 4-$CH_3$, $J_{HF}$ = 4 hz), 3.37 (s, 3, 2-$CH_3$), 4.46 (s, 1, NH), 6.9–7.6 (m, 8, Ar); $^{13}$C NMR 31.9 (d, 4-$CH_3$, $J_{CF}$ = 7.4 Hz), 35.4 (2-$CH_3$), 84.1 ($C_5$), 115–119 (overlapping m), 126.4, 128.8, 129.4, 137.1, 155.0 (d, $J_{CF}$ = 244.2 Hz), 158.7 (d, $J_{CF}$ = 243.7 Hz), 179.4 (C=S); EIMS, $m/z$ (relative intensity) 319 (100, $M^+$). Anal. Calcd for $C_{16}H_{15}F_2N_3S$: C, 60.17; H, 4.73; N, 13.16. Found: C, 59.92; H, 4.70; N, 13.20. **2,4-Dimethyl-5-phenyl-3*H*-1,2,4-triazole-3-thione (3)**, after crystallization from *i*-$C_3H_7OH$, was isolated as colorless plates: 3.3 g (27%); mp 133–135 °C; identical with an authentic sample.[15] **2,4-Dimethylthiosemicarbazide (2)**, after crystallization from *i*-$C_3H_7OH$, was isolated as colorless needles: 2.2 g (31% recovery); mp 135–137 °C (lit.[14] mp 137–138 °C).

**Reaction of 6 and $K_2CO_3$.** Thiosemicarbazone **6** (0.37 g, 1.2 mmol) and $K_2CO_3$ (0.16 g, 1.2 mmol) were refluxed in $CH_3OH$ (5.5 mL) for 17 h. The reaction was then worked up as previously described affording a pale yellow solid. Purification by preparative-layer chromatography using 20% EtOAc/hexane and crystallization from *i*-$C_3H_7OH$ gave **3** as colorless plates: 0.18 g (75%); mp 133–135 °C; identical with an authentic sample.[15]

**Reaction of 7 and $K_2CO_3$.** Triazolidine **7** (2.00 g, 6.26 mmol) and $K_2CO_3$ (0.87 g, 6.3 mmol) were refluxed in $CH_3OH$ (30 mL) for 24 h. The reaction was then worked up as previously described giving a pale yellow solid. Purification by flash chromatography using 2% EtOAc/$CH_2Cl_2$ and crystallization from *i*-$C_3H_7OH$ afforded **3** as colorless plates: 0.92 g (72%); mp 133–135 °C; identical with an authentic sample.[15]

**Registry No.** 1, 85068-36-6; 2, 79-19-6; 3, 7112-00-7; 4, 7112-01-8; 6, 100994-58-9; 7, 100994-59-0; 8, 342-59-6.

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[26] A satisfactory elemental analysis could not be obtained for 6.

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# Delocalized Carbanions: 3,3',5,5'-Tetramethylenebiphenyl Tetraanion, a New Tetraanion

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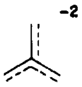
There have been many studies on delocalized carbanions in the past several years.[1-5] Indeed, carbanions can be very useful synthetically in a number of ways. Presently, we are studying new routes to anionic initiators to prepare linear and star polymers from delocalized carbanions where one arm of the star forms for each charge on the carbanion. In a previous paper we reported the use of the allyl anion (**1**), 2-methylenepropylenyl dianion (**2**), and the cycloheptatrienyl trianion (**3**) as anionic initiators.[5]

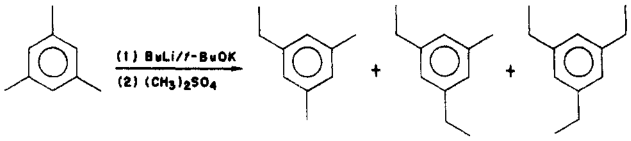
1



2

3

**Table I. Quench Products of the Mesitylene Anions**



4 5a 5b 5c

| metalating system[a] | solvent/reactn temp (°C) | av[b] charge | prod. ratios **4:5a:5b:5c** |
|---|---|---|---|
| 6 | pentane/25 | 1.3 | 3:46:16:1 |
| 3.3 | pentane/25 | 2.0 | 1:7:20:7 |
| 3.3 | cyclohexane/78 | 2.4 | 1:1:2.7:3 |
| 4 | hexane/69 | 2.7 | 1:1.5:7.5:37 |
| 6 | hexane/69 | 2.6 | 1:1:5:14.5 |
| 4 | heptane/90 | 1.9 | 1:1:3:9 |

[a] Equivalents of both *n*-BuLi and *t*-BuOK; all reactions were carried out for 24 h except for the first which was 2.5 h. [b] Determined from quench products by GC.

The progression of mono-, di-, and trianion would naturally lead to a tetraanion. In the quest for precursors for a tetraanion, both benzylic and allylic precursors were initially investigated. Under the more rigorous conditions used, the benzylic precursors were shown not to undergo butyl addition side reactions. We report the preparation of 3,3',5,5'-tetramethylenebiphenyl tetraanion (**9**) prepared from 3,3',5,5'-tetramethylbiphenyl (TMBP) (**8**). A thallium(I) bromide/Grignard coupling procedure was utilized to couple two molecules of 5-bromomagnesio-*m*-xylene (**7**) (the Grignard of 5-bromo-*m*-xylene (**6**)) to prepare **8**.[6]

In the past, researchers have used *n*-butyllithium/tetramethylethylenediamine as a metalating reagent.[7,8] Lochmanns' base, *n*-butyllithium/potassium *tert*-butoxide, has been found to be a faster, less nucleophilic, metalating reagent for the preparation of delocalized carbanions.[4] For these reasons, Lochmann' base was used as the metalating reagent for **8**.

Mesitylene was used as a model system to obtain optimum metalating conditions. The amount of base, the solvent, and the reaction temperature were all varied. The carbanions prepared were quenched with dimethyl sulfate and characterized via $^1$H NMR and GC. The results of several reactions are summarized in Table I.

The increase of reaction temperature from room temperature to that of refluxing solvent has a remarkable effect on the metalating power of the base (from an average charge of 1.3 at room temperature to 2.7 at reflux). Metalation of allylic moieties at elevated temperatures produce side reactions from butyl addition which are not

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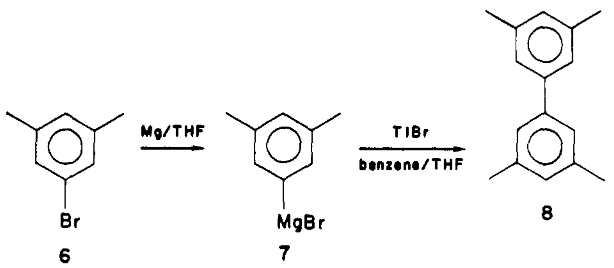
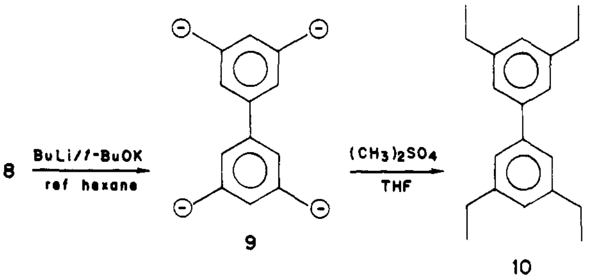
0022-3263/86/1951-1618$01.50/0

observed in the benzylic metalations.[9] The best overall reaction conditions was found to be a 33% excess of base in refluxing hexane. Bates has reported similar results under the same conditions.[2]

Compound **8** was prepared from the Grignard reagent of 5-bromo-*m*-xylene (**6**) followed by coupling via a thallium bromide coupling reaction as reported by McKillop.[6] The product was recovered in high yield and was characterized by $^{1}$H NMR and MS.



The reaction of **8** with Lochmanns' base in pentane at room temperature only metalates approximately one-half of the benzylic positions as shown by $^{1}$H NMR. It is unknown whether or not these products are due to a mixture of mono-, di-, tri-, and tetraanions or if there is a major product due to just one dianion. The more probable product would be the dianion resulting from a single benzylic metalation occurring on each ring. Metalation in refluxing hexane using a 33% excess of base, as suggested by the results from mesitylene, and then subsequent methylation using dimethyl sulfate produced >90% tetraethylbiphenyl (**10**) as determined by $^{1}$H NMR.



## Experimental Section

$^{1}$H nuclear magnetic resonance (NMR) spectra were recorded on a Varian EM-360 spectrometer. Chemical shifts are reported downfield from tetramethylsilane (Me$_4$Si). Melting points were taken on a National Instrument Co., Inc., melting point apparatus and are uncorrected. Gas chromatography was performed on a Varian Aerograph Series 1800 GC using a 6 ft × $^{1}/_{4}$ in. column loaded with 10% Carbowax 20M on 80/100 Supelcoport. Mass spectroscopy was performed on a Kratos MS 9/50. Elemental analyses were performed by Galbraith Laboratories. Potassium *tert*-butoxide, 2.5 M *n*-butyllithium (concentration checked by titration),[10] magnesium, thallium bromide, 5-bromo-*m*-xylene, and dimethyl sulfate were all obtained from aldrich Chemical Co. and used without purification. Pentane, hexane, heptane, cyclohexane, and benzene were purified by first washing with concentrated sulfuric acid, distilled water, saturated sodium bicarbonate solution, and then distilled water. Each was dried over magnesium sulfate for 24 h, filtered, and distilled onto 4-Å molecular sieves. Mesitylene was purified in the same manner except cold concentrated sulfuric acid was used. Tetrahydrofuran (THF) was distilled from benzophenone/potassium metal. All reactions were performed under either nitrogen or argon.

**Metalation of Mesitylene (4) at Room Temperature.** To a suspension of 4.0 g of *t*-BuOH (35 mmol) in 40 mL of pentane was added 13 mL of 2.5 M *n*-BuLi (33 mmol). The resulting beige suspension was allowed to stand for 10 min after which 1.4 mL of mesitylene (10 mmol) in 10 mL of pentane was slowly added. After 90 min of stirring, the bright yellow precipitate was allowed to settle, and the pentane layer was drawn off. The precipitate was blown dry with dry nitrogen and then dissolved in 30 mL of THF. A second flask was prepared with 60 mL of THF and 3.3 mL of dimethyl sulfate (35 mmol). The anion/THF solution was then slowly added to the second flask with intense stirring. The orange solution was allowed to react for 60 min after which 80 mL 10 g of KOH, 10 g of H$_2$O, and 80 g of EtOH was added and refluxed for 4 h to hydrolyze the excess dimethyl sulfate. Workup was completed by extraction of the cooled solution with saturated aqueous NaCl. Pentane was added to the organic layer which forced out a second aqueous layer. This was mixed with the first aqueous layer and all was back-extracted with pentane. The organic layers were combined, dried over magnesium sulfate, and filtered, and the pentane was removed by rotary evaporation. The crude mixture was distilled in a Kugelrohr apparatus under nitrogen.

**At Elevated Temperature.** The mesitylene anions were prepared as above by using 3.3–6 equiv of *t*-BuOK and *n*-BuLi. The reaction was carried out in either hexane, cyclohexane, or heptane at reflux temperature. The base mixture was refluxed before addition of the mesitylene, and the reaction was carried out for 24 h. The anion salt suspension was cooled and centrifuged to separate the salt from the solvent. Quenching and workup were performed as in the room temperature procedure. The products were separated by GC (85 °C; 6 ft, 10% Carbowax 20M column). The retention times were the following: **4** $t_R$ 5.0 min, **5a** $t_R$ 7.0 min, **5b** $t_R$ 9.5 min, and **5c** $t_R$ 13.6 min.

**Preparation of 3,3′,5,5′-Tetramethylbiphenyl (8).** In a round-bottomed flask equipped for stirring and reflux was placed 1.4 g of Mg powder (57 mmol) in 30 mL THF. To this was added 9.6 g of 5-bromo-*m*-xylene (52 mmol) in 20 mL of THF in 5-mL portions, and the solution was gently heated until reflux was achieved. The heat was then removed while reflux was maintained. After the solution had been cooled, 50 mL of benzene was added to the flask. TlBr (26.6 g, 94 mmol) was then added, and the solution was refluxed for 4 h. When cool, the solution was acidified with 10% HCl and filtered, the filtrate was washed with benzene, and the benzene water solution was separated. The benzene layer was collected, dried over magnesium sulfate for 24 h, and filtered, and the solvent was removed by rotary evaporation. The crude product was vacuum distilled in a Kugelrohr apparatus and then sublimed. The uncorrected mp was found to be 48–48.5 °C; the reported mp is 48.6–49 °C:[11] $^{1}$H NMR (CDCl$_3$) $\delta$ 2.30 (s, 12 H), 6.85 (s, 2 H), 7.15 (s, 4 H); MS, (relative intensity) M + 2, 212 (1.45), M + 1, 211 (17.36), M, 210 (100).

**Metalation of 3,3′,5,5′-Tetramethylbiphenyl (8). At Room Temperature.** The same general procedure was followed for the metalation of **8** as described above, with 0.47 of g *t*-BuOK (4.2 mmol) and 1.7 mL of 2.5 M *n*-BuLi (4.2 mmol). Compound **8** (0.17 g, 0.8 mmol) was dissolved in pentane and added to the base.

**At Elevated Temperature.** The anions of **8** were prepared as described above with 5.86 of *t*-BuOK (52 mmol) and 21 mL of 2.5 M *n*-BuLi (52 mmol) in 60 mL of hexane. In 20 mL of pentane was dissolved 2.31 g of **8** (11 mmol) which was added slowly to the refluxing base solution.

**Preparation of 3,3′,5,5′-Tetraethylbiphenyl (10).** The precipitated tetraanion **9** from the above elevated temperature reaction was centrifuged, and the hexane layer was drawn off. The precipitate was blown dry with dry nitrogen and then dissolved in 30 mL of THF. A second flask was prepared with 100 mL of THF and 6 mL of dimethyl sulfate (60 mmol). The anion/THF solution was then slowly syringed into the second flask with intense stirring. The orange solution was allowed to react for 60 min after which 80 mL of 10 g of KOH, 10 g of H$_2$O, and 80 g of EtOH was added. This solution was refluxed for 4 h to hydrolyze any excess dimethyl sulfate. Workup was completed by extraction of the cooled solution with saturated aqueous NaCl. Pentane was added to the organic layer which forced out a second aqueous layer. The organic layers were combined, dried over magnesium sulfate, and filtered, and the pentane layer was removed by rotary evaporation.

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A viscous oil was obtained, 2.68 g, and the crude yield was determined via $^1$H NMR (with an internal standard) to be >90%. The crude mixture was distilled in a Kugelrohr apparatus under vaccum: $^1$H NMR ($CDCl_3$) $\delta$ 7.2 (s, 2 H), 6.95 (s, 1 H), 2.65 (q, 4 H), 1.28 (t, 6 H); MS (relative intensity) **M** + 2, 268 (2.32), M + 1, 267 (22.74), M, 266 (100). Anal. Calcd for $C_{20}H_{26}$: C, 90.16; H, 9.84. Found: C, 90.34; H, 9.73.

**Acknowledgment.** We acknowledge financial support from the National Science Foundation, Polymer Program (Grant DMR 8214211). We also thank Craig Ogle and Robert Bates for their private discussions.

**Registry No.** 4, 108-67-8; **5a**, 934-74-7; **5b**, 2050-24-0; **5c**, 102-25-0; **6**, 556-96-7; **8**, 25570-02-9; **9**, 84980-70-1; **10**, 36919-84-3.

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## Selective O-Demethylation of 7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine

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*Received October 21, 1985*

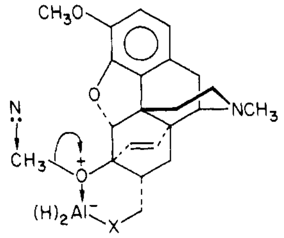
The remarkable opioid agonist/antagonist properties of several 7α-(1-hydroxy-1-methylalkyl)-6,14-*endo*-ethenotetrahydrooripavines[1] prompted us to synthesize 7α-(aminomethyl)-6,14-*endo*-ethenotetrahydrooripavine (**6**). This key intermediate can be converted to a new series of potential analgesics by acylation of the 7α-aminomethyl function, can be used to prepare potential selective irreversible labels of opioid receptors,[2] and can be attached to an appropriate support to form an affinity chromatography matrix for opioid receptor purification.[3]

7α-(Aminomethyl)-6,14-*endo*-ethenotetrahydrothebaine (**4**) was synthesized from thebaine (**1**) as shown in Scheme I. The Diels–Alder addition of acrolein in refluxing benzene gave the previously reported 7α-formyl derivative (**2**).[4] Reaction of **2** with hydroxylamine hydrochloride gave the aldoxime **3** that was treated with LAH in THF to yield the 7α-aminomethyl product (**4**). A previous attempt to prepared **4** by reduction of the corresponding 7α-carboxamide with LAH gave only rearrangement products.[5] The conversion of **4** to **6** by selective O-demethylation at the 3-position had been accomplished in 7α-tertiary alcohol analogues by reaction with potassium hydroxide in diethylene glycol at 200–210 °C.[1] Instead of these harsh conditions, we wished to find a more facile selective 3-O-demethylation procedure.

Treatment of codeine with boron tribromide in chloroform has been found to selectively demethylate the phenolic ether to give morphine in high yield.[6] This established the stability of the oxide bridge toward brief exposure to strongly acidic conditions but did not show what effect this treatment would have on the 6-methoxy group. Brief treatment of **4** with $BBr_3$ in chloroform at room temperature afforded **6** by selective 3-O-demethylation as shown by the loss of the NMR singlet at $\delta$ 3.83 that had been previously assigned to this group.[7] Recently, Jacobson and co-workers have reported the analogous selective 3-O-demethylation of 7α-amino-4,16-*endo*-ethenotetrahydrothebaine with boron tribromide in $CHCl_3$.[8] In order to determine whether a nitrogen atom in the 7α-function plays a vital role in these selective 3-O-demethylations, 7α-methyl-6,14-*endo*-ethenotetrahydrothebaine (**11**) was synthesized from **8** via the tosylate **10** as outlined in Scheme I. Treatment of **11** with boron tribromide gave multiple products. Thus, an amino group in the 7α-position of these compounds appears necessary for selective 3-O-demethylation. This suggests that the formation of a boron complex with the appropriate 7α-substituent blocks reaction at the 6-position.

Occasionally, the NMR spectrum of the crude 7α-aminomethyl product **4** formed by the LAH/THF reduction of **3** showed a loss in the intensity of the singlet ($\delta$ 3.56) that had been assigned to the 6-methoxy function.[7] This totally unexpected selective 6-O-demethylation was traced to the presence of residual chloroform that had not been removed during the workup of **3**. The addition of $CCl_4$, $CHCl_3$, or $CH_2Cl_2$ to a THF solution of **3** prior to reduction with LAH afforded **5** in good yields. Furthermore, **4** was 6-*O*-demethylated to **5** by treatment with LAH/THF/chlorinated methane. Therefore, the aldoxime appears to be reduced to an amine/aluminum complex before demethylation occurs.

In order to ascertain whether this surprising demethylation was unique to compounds containing a 7α-aminomethyl function, 7α-formyl-6,14-*endo*-ethenotetrahydrothebaine (**2**) was subjected to the same conditions. The aldehyde was reduced cleanly to the 7α-hydroxymethyl compound **8** in the absence of chlorinated methane, while the addition of chlorinated methane gave the diol **9**. Additionally, **8** was converted to **9** by inclusion of a chlorinated methane in the reduction medium. This suggests initial reduction of the aldehyde to the primary alcohol followed by 6-O-demethylation of the 7α-(hydroxymethyl)/aluminum complex. To prove that an electron-rich atom associated with the 7α-substitutent is required for demethylation, the 7α-methyl compound **11** was treated with LAH/THF/chlorinated methane. This reaction gave only starting material. Thus, a six-membered ring aluminum complex as shown below, or a variation of it, undoubtedly plays a major role is this unusual demethylation, but the role of the chlorinated methane is less clear. It may be necessary for the generation of the nucleophile required by a $S_N2$ demethylation process. No solid evidence concerning the fate of the 6-methyl group has been obtained.



X = O, NH

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