14161-72-9; *trans*-**5**, 1416173-0; acetophenone, 98-86-2; *N*-benzylmethylphenylketimine, 14428-98-9; hychoxylamine-*O*-sulfonic acid, 2950-43-8.

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Aromatic Electrophilic Substitution by Pummerer Rearrangement Intermediates

D. K. Bates

Department of Chemistry and Chemical Engineering, Michigan Technological University, Houghton, Michigan 49931

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Sulfoxides have been developed extensively as synthetic reagents. The most common reactions are β elimination for the introduction of double bonds[1] and [2,3] sigmatropic rearrangement for allylic transposition of alcohols.[2] Sulfoxides have also been ingeniously used for benzo[*b*]thiophene synthesis, i.e., the Thyagarajan rearrangement.[3] Replacement of the sulfoxide moiety with an *N*-oxide resulted in a new general synthesis of indoles.[4]

The present study was initiated in the hope that replacement of the acetylenic moiety with a cyano group might result in a general 4,5-benzoisothiazole synthesis via a pathway analogous to the Thyagarajan process. In the event, however, a very different sequence intervened leading to a novel electrophilic aromatic substitution reaction, the first example of intermolecular attack of Pummerer rearrangement intermediates on an aromatic ring.

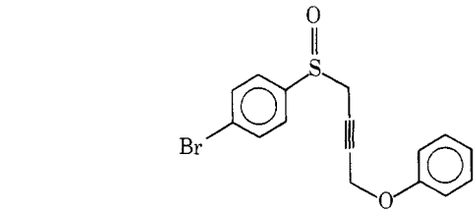
Compound **1** was found to be inert under conditions which converted **2** into the benzo[*b*]thiophene skeleton[3] (refluxing chloroform). Indeed, **1** proved to be quite thermally stable, being recovered unchanged after prolonged reflux in benzene, carbon tetrachloride, ethanol, 1-butanol, and toluene. However, **1** in refluxing xylene formed two products, *p*-bromophenyl disulfide and a crystalline solid, α-(4-bromophenylthio)-2,5-xylylacetonitrile (**3**), corresponding to a condensation of **1** with *p*-xylene and loss of a water molecule. This structure was deduced from spectral data. The IR showed a nitrile absorption and lacked a sulfoxide band. The NMR showed two nonidentical methyl groups (δ 2.32 and 2.42), a methine singlet (δ 4.97), and seven aromatic hydrogens, and the mass spectrum showed a molecular ion at *m/e* 333/331.

A similar reaction took place when **1** was refluxed in anisole, yielding *p*-bromophenyl disulfide, the ortho and para condensation products **5** and **6**, and bis(4-methoxyphenyl)acetonitrile (**4**).[12]

In view of the unexpected nature of the reaction of **1**, several analogous compounds (**7–10**) were synthesized and refluxed in anisole to delineate the scope and mechanism of this transformation.

Compound **7** gave the corresponding condensation product **11**, and **8** led to **12**. Compounds **9** and **10** do not provide condensation products in refluxing anisole or xylene.[5]

The reactions are reminiscent of the Pummerer rearrangement,[6] an acid-catalyzed reaction of sulfoxides in which sulfur becomes reduced with concomitant functionalization of the α-carbon. The catalysts normally used are HCl or *p*-toluenesulfonic acid. The present examples are rare cases of "uncatalyzed"[7] Pummerer rearrangements and are the first examples of reaction with such weakly nucleophilic species as xylene and anisole.[8]



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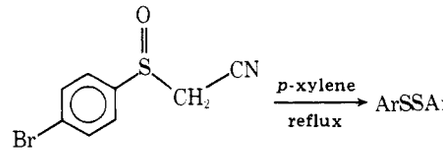

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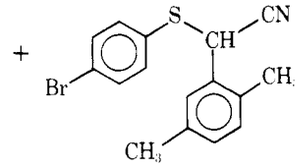

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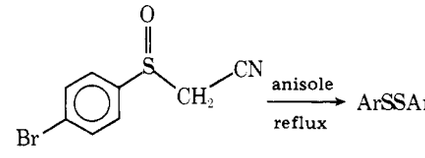

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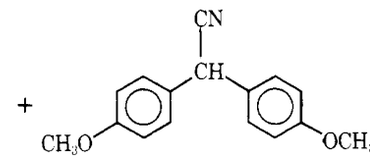

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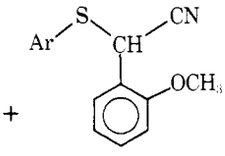

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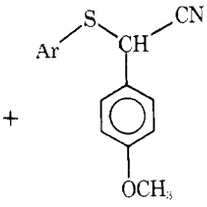

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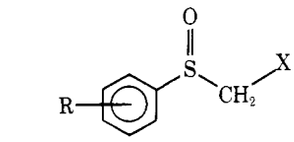
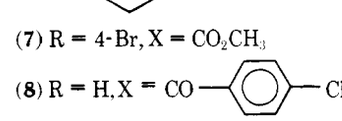


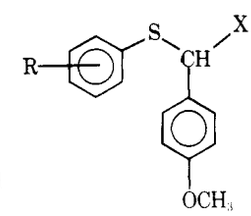
(7) R = 4-Br, X = CO_2CH_3



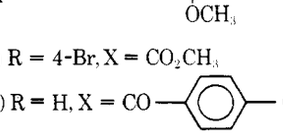
(8) R = H, X = CO—Cl

(9) R = 2-CN, X = Ph

(10) R = H, X = Ph

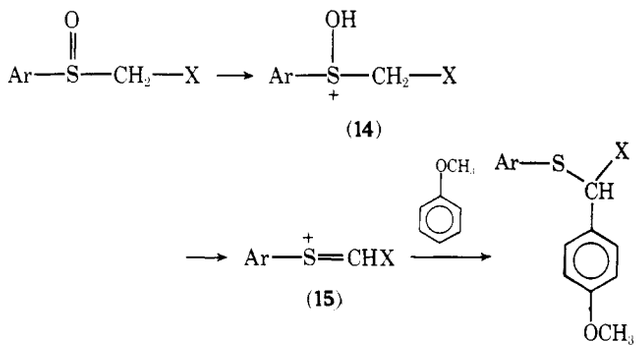


(11) R = 4-Br, X = CO_2CH_3



(12) R = H, X = CO—Cl

Scheme I



The present result is presumed to be due to the very acidic nature of the methylene hydrogens in **1**, **7**, and **8**. These acid hydrogens apparently act as the proton source for initiation of the rearrangement (Scheme I). This hypothesis is supported by the lack of reactivity of **9** and **10** in the thermal Pummerer process. However, heat plays an important role in these "uncatalyzed" reactions as the sulfoxides were inert below 140 °C when heated with xylene or anisole. When refluxed in toluene or benzene, all sulfoxides were recovered unchanged. Additionally, benzene and toluene solutions of **7** in sealed tubes at 150–160 °C underwent no reaction (although in some instances decomposition to 4-bromophenyl disulfide and methyl 4-bromophenylthioacetate occurred). On no occasion was reaction with toluene or benzene observed.

The addition of *p*-toluenesulfonic acid to solutions of **8** in acetonitrile, benzene, and toluene at their respective boiling points gave *p*-chlorobenzoic acid[13] and diphenyl disulfide as the only isolable products. It thus appears that, although intermediate **15** of Scheme I may form, benzene and toluene are not sufficiently nucleophilic to capture it and another reaction mode intervenes.

Application of this process to oxindole and benzofuran-2(3*H*)-one synthesis is currently under investigation.

Experimental Section

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Spectal data was collected as follows: ir, crystallized melts unless otherwise specified, Perkin Elmer 621 or 435B; NMR, $CDCl_3$, Me_4Si reference (δ 0.00), Varian T-60; mass spectra, Hitachi-Perkin Elmer RMU-6E. Microanalyses were performed by Mr. Mike Gilles in the Michigan Technological University microanalytical laboratory. The sulfoxides utilized in this study were prepared by oxidation of the corresponding sulfides with *m*-chloroperbenzoic acid (vide post). The sulfides were prepared by halide displacement from the corresponding alkyl halide with the appropriate thiol in ethanolic KOH. The following data was collected for the sulfoxides.

4-Bromophenylsulfinylacetonitrile (1): mp 105.5–106.5 °C (from ethylene dichloride/hexane; MS (70 eV) $M^{+\cdot}$ 243, 203 (100%); NMR δ 7.90–7.45 (4 H, m), 3.86 (1 H, d, J = 14.5 Hz), 3.54 (1 H, d, J = 14.5 Hz). Anal. Calcd for C_8H_6BrNOS: C, 39.3; H, 2.5. Found: C, 39.0; H, 2.5.

Methyl 4-Bromophenylsulfinylacetate (7): mp 84.5–85 °C (from benzene); NMR δ 7.80–7.40 (4 H, m), 3.90 (2 H, d, J = 13 Hz), 3.64 (2 H, d, J = 13 Hz), 3.73 (3 H, s); MS (70 eV) *m/e* 276 ($M^{+\cdot}$), 203 (100%). Anal. Calcd for $C_9H_9BrO_3S$: C, 39.0; H, 3.3. Found: C, 39.3; H, 3.3.

ω-Phenylsulfinyl-4-chloroacetophenone (8): mp 124–125 °C (from cyclohexane/chloroform); NMR δ 8.00–7.75 (2 H, d, J = 8 Hz), 7.70–7.30 (7 H, m), 4.61 (2 H, d, J = 14 Hz), 4.19 (2 H, d, J = 14 Hz); IR 1665, 1090, 1050 cm^{-1}; MS (70 eV): *m/e* 278 ($M^{+\cdot}$), 125 (100%). Anal. Calcd for $C_{14}H_{11}ClO_2S$: C, 60.3; H, 4.0. Found: C, 60.4; H, 3.9.

Preparation of 2-Cyanophenyl Benzyl Sulfide. The corresponding amide[9] (mp 150.5–152 °C, lit. 150–151 °C; 5.9 g, 0.024 mol) was refluxed 5 h with thionyl chloride (5 mL, d = 1.66 g/ml, 0.070 mol) in dry benzene (4 mL). Evaporation of volatiles in vacuo followed by filtration through neutral alumina gave 2-cyanophenyl benzyl sulfide (4.0 g, 74%): mp 57–58 °C (C_2H_5OH); IR (KBr) 2210 cm^{-1}; NMR δ 7.67–7.03 (9 H, m), 4.18 (2 H, s); MS (70 eV) *m/e* 225 ($M^{+\cdot}$), 91 (100%). Anal. Calcd for $C_{14}H_{11}NS$: C, 74.6; H, 4.9; N, 6.2. Found: C, 74.6; H, 4.9; N, 6.0.

Preparation of 2-Cyanophenyl Benzyl Sulfoxide (9). The sulfide (2.25 g, 0.01 mol) in methylene chloride (50 mL) was cooled to 0 °C in an ice bath and *m*-chloroperbenzoic acid (85%, 2.02 g, 0.01 mol) in methylene chloride (50 mL) was added dropwise. The cold solution was stored overnight at 0 °C. The mixture was then filtered and the filtrate washed with K_2CO_3 solution (5%, 100 mL). Drying ($MgSO_4$) and solvent evaporation in vacuo gave the sulfoxide (2.21 g, 92%): mp 114–116 °C (C_2H_5OH); IR 2250, 1085 cm^{-1}; NMR δ 7.63–7.43 (4 H, m), 7.33–6.83 (5 H, m), 4.34 (2 H, d, J = 14 Hz), 4.08 (2 H, d, J = 14 Hz); MS (70 eV) *m/e* 241 ($M^{+\cdot}$), 91 (100%). Anal. Calcd for $C_{14}H_{11}NOS$: C, 69.7; H, 4.6; N, 5.8. Found: C, 69.7; H, 4.5; N, 5.7.

Thermolysis of 4-Bromophenylsulfinylacetonitrile (1) in *p*-Xylene. The title compound (1.5 g) in *p*-xylene (50 mL) was refluxed 15 h at which time the solvent was evaporated in vacuo. The resultant oil was chromatographed on silica gel (hexane slurry, 2.5 × 26 cm) The column was eluted with gradually increasing amounts of ether in hexane (4–50%), 125-mL fractions being collected. Data for these fractions are summarized in Table I.

Thermolysis of 1 in Anisole. The title compound (3.0 g) in anisole (75 mL) was refluxed 12.5 h under nitrogen at which time the anisole was evaporated in vacuo. The residue was chromatographed on silica gel (hexane slurry, 5 × 30 cm) as described above. Data for these fractions are summarized in Table I.

Thermolysis of Methyl 4-Bromophenylsulfinylacetate (7) in Anisole. The sulfoxide (2.02 g) in anisole (20 mL) was refluxed 18 h at which time the solvent was evaporated in vacuo. Chromatography of the residue on silica gel [5 × 40 cm column eluted with hexane (1.6 L) and 10% CH_2Cl_2 in hexane (4 L), 250-mL fractions being collected] gave *p*-bromophenyl disulfide (fractions 3–12, 0.25 g, identical with an authentic sample prepared by Me_2SO oxidation of *p*-bromophenylthiophenol[10]) and 1.3 g of an oil (fractions 15–18) from which 0.7 g of pure **11** could be obtained by crystallization from hexane: mp 85–88 °C (constant melting point); IR 1740 cm^{-1}; NMR δ 7.60–7.20 (6 H, m), 7.10–6.80 (2 H, d, J = 9 Hz), 4.93 (1 H, s), 3.83 (3 H, s), 3.73 (3 H, s); MS (70 eV) *m/e* 366 ($M^{+\cdot}$), *m/e* 179 (100%), Anal. Calcd for $C_{16}H_{15}BrO_3S$: C, 52.3; H, 4.1. Found: C, 52.2; H, 4.0.

The mother liquor could not be crystallized nor could the components be separated chromatographically. The NMR indicated the presence of **11** and another substance, presumably the ortho isomer [NMR δ 5.23 (s)] of **11**. The integral ratio of the δ 4.93 peak of the methine hydrogen in **11** and the δ 5.23 peak was 1/1 in the mother liquor.

Thermolysis of 7 in Toluene. Compound **7** (0.50 g) was dissolved in toluene (10 mL) and the resulting solution was sealed at atmospheric pressure in a soft glass tube (1.6 × 8 cm). The sealed tube was heated at 160 °C (oven temperature) for 24 h. Solvent evaporation and preparative layer chromatography (SiO_2, benzene) gave 4-bro-

Table I

Chrom fraction	% yield	Composition
1 in *p*-xylene:		
1–2	17	4-Bromophenyl disulfide[a]
5–6	32	(**3**)[b]
1 in anisole:		
2–3	14	4-Bromophenyl disulfide[a]
8–9	17	(**5**)[c]
10–12	39	(**6**)[d]
14–17	11	(**4**)[e]

[a] Identical with an authentic sample. [b] mp 101–102 °C (hexane); NMR δ 7.66–6.78 (7 H, m), 4.97 (1 H, s), 2.42 (3 H, s), 2.32 (3 H, s); IR 2245 cm^{-1}; MS (20 eV) *m/e* 331 ($M^{+\cdot}$), *m/e* 144 (100%). Anal. Calcd for $C_{16}H_{14}BrNS$: C, 57.8; H, 4.2. Found: C, 57.9; H, 4.2. [c] mp 58–59 °C (hexane); NMR δ 7.60 (8 H, m), 5.33 (1 H, s), 3.80 (3 H, s); IR 2250 cm^{-1}; MS (70 eV) *m/e* 333 ($M^{+\cdot}$), 146 (100%). Anal. Calcd for $C_{15}H_{12}BrNOS$: C, 53.9; H, 3.6, N, 4.2. Found: C, 54.1; H, 3.6, N, 4.0. [d] mp 121.5–122 °C (hexane); NMR δ 7.63–6.73 (8 H, m), 4.90 (1 H, s), 3.75 (3 H, s); IR 2255 cm^{-1}; MS (70 eV) *m/e* 333 ($M^{+\cdot}$) *m/e* 146 (100%). Anal. Calcd for $C_{15}H_{12}BrNOS$: C, 53.9; H, 3.6; N, 4.2. Found: C, 54.1; H, 3.6; N, 4.2. [e] mp 155 °C (petroleum ether) [lit.[11] mp 154–155 °C]; NMR δ 7.42–6.78 (8 H, m), 5.03 (1 H, s), 3.75 (6 H, s); MS (70 eV) *m/e* 253 ($M^{+\cdot}$).

mophenyl disulfide (147 mg), methyl 4-bromophenylthioacetate (95 mg), and recovered starting material (90 mg). No evidence of reaction with toluene was found even in the NMR of the crude product.

Thermolysis of 8 in Anisole. A solution of **8** (1 g, 0.0038 mol) in anisole (20 mL) was refluxed for 4 h. The residue remaining after evaporation of excess anisole in vacuo was chromatographed on SiO_2 (3 × 18 cm) and eluted with hexane (3 L), and then with 5% $CHCl_3$ in hexane (10 L). Collection of 250-mL fractions gave diphenyl disulfide (0.2 g, fractions 3–29) and **13** (0.4 g, 28%, fractions 40–45): mp 71.5–72.5 °C (C_2H_5OH); IR 1680 1585, 1260 cm^{-1}; NMR δ 8.00–7.75 (2 H, d, J = 8 Hz), 7.45–7.15 (9 H, m), 6.95–6.70 (2 H, d, J = 8 Hz), 5.75 (1 H, s), 3.72 (3 H, s); MS (70 eV), m/e 368 ($M^{+\cdot}$), 229 (100%). Anal. Calcd for $C_{21}H_{17}ClO_2S$: C, 68.4; H, 4.7. Found: C, 68.8; H, 4.5.

Acknowledgments. The author thanks Sigma Xi for partial support of this work and Dr. V. Sandel for reviewing the manuscript.

Registry No.—**1**, 63215-96-3; **3**, 63215-97-4; **4**, 6275-26-9; **5**, 63215-98-5; **6**, 63215-99-6; **7**, 63216-00-2; **8**, 58936-71-3; **9**, 63216-01-3; **11**, 63216-02-4; **12**, 63216-03-5; 4-bromophenylthioacetonitrile, 50837-23-5; methyl 4-bromophenylthioacetate, 50397-69-8; ω-phenylthio-4-chloroacetophenone, 33192-00-6; 2-carboxamidophenyl benzyl sulfide, 54705-18-9; 2-cyanophenyl benzyl sulfide, 63216-04-6; **11** ortho isomer, 63216-05-7; 4-bromophenyl disulfide, 5335-84-2; 4-bromobenzenethiol, 106-53-6; benzenethiol, 108-98-5.

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(4) B. S. Thyagarajan, J. B. Hilliard, K. V. Reddy, and K. C. Majumdar, *Tetrahedran Lett.*, **23**, 1999 (1974).

(5) Compound **10** is recovered unchanged; **9** decomposes in anisole to give at least four products, none of which contain anisole. The reaction of **9** is under further investigation.

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(8) Recently, the *p*-toluenesulfonic acid catalyzed *intramolecular* counterpart of this reaction was reported: Y. Oikawa and O. Yonemitsu, *J. Org. Chem.*, **41**, 1118 (1976).

(9) S. Oae and T. Numata, *Tetrahedron*, **30**, 2641 (1974).

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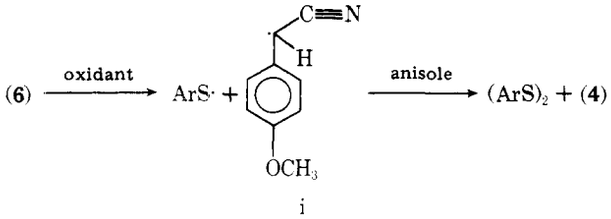
(12) Compounds **5** and **6** are quantitatively recovered after prolonged (24 h) reflux in anisole alone or anisole containing a molar excess of *p*-toluenesulfonic acid. The formation of **4** via a sequence of sulfur protonation in **6** followed by loss of *p*-bromobenzenethiol and electrophilic attack on anisole by the resultant carbocation is therefore untenable. An alternative process involves conversion of **6** into **i** followed by free radical attack on anisole. Due to the scale of the reaction, other isomers of **4**, though



i

probably formed, were present in quantities too small to detect. The oxidant in this reaction would be unreacted **1**; sulfoxides are known oxidants (ref 10). Using *m*-chloroperbenzoic acid (CH_2Cl_2) as the oxidant, the sulfoxide of **6** and 2,3-di(4-methoxyphenyl)succinonitrile, the coupling product of **i**, were isolated. Formation of **i** appears to be quite facile; in the presence of anisole **4** forms, but in the absence of a reactive solvent **i** dimerizes.

(13) The mode of formation of *p*-chlorobenzoic acid is unknown. In the presence of moisture a retro-Claisen condensation could convert **8** into *p*-chlorobenzoic acid and methyl phenyl sulfoxide. The latter product was not observed however. One could speculate that *p*-chlorobenzoic acid arises from decomposition of the hemihydrate of *p*-chlorophenylglyoxal, the expected Pummerer rearrangement product from **8** in acid solution in the presence of fortuitous water (ref 14).

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Determination of the Rate of Reduction of Benzophenone-*1*-^{14}C by Lithium Benzhydrolate

Georg Wittig

Organisch-Chemisches Institut der Universität, Heidelberg, West Germany

R. D. Hamilton*[1]

Department of Chemistry, Fort Lewis College, Durango, Colorado, 81301

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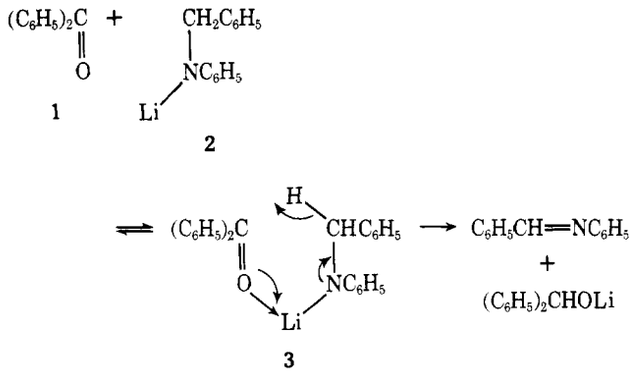
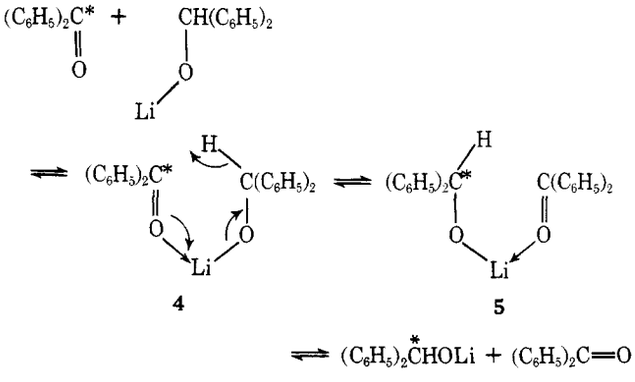
In previous work concerning the properties of N-metalated secondary amines as hydride donors, Wittig and co-workers[2,3] found that lithium *N*-benzylanilide (**2**) effected a reduction of ketones [e.g., benzophenone (**1**)] to yield corresponding lithium alcoholates and Schiff bases. On the basis of kinetic studies, the authors proposed that a rapid equilibrium was established between starting materials and a 1:1 "ate complex"[4] (**3**), and that hydride transfer occurred in a subsequent



irreversible rate-determining step. The reaction was found to be second order, being first order with respect to each reactant.

In view of these results, it was of interest to investigate the nature of the reduction between an analogous O-metalated alcohol, benzhydrol, and benzophenone. Of special interest was the determination of the rate of the carbinol–carbonyl equilibrium for comparison to that of the N-metalated amine/benzophenone system. It was thought that the reaction would proceed via rapid formation of an ate complex (**4**), slow transfer of hydride to form a new ate complex (**5**), and, finally, rapid equilibration to form products. Similar mechanisms involving cyclic intermediates such as **4** and **5** have been



$\rightleftharpoons (C_6H_5)_2\overset{*}{C}HOLi + (C_6H_5)_2C{=}O$

generally adopted for both Grignard[5] and Meerwein–Ponndorf–Verley (MPV)[6] reductions. Further, it has been established that hydrogen transfer takes place directly from metalated component to ketone in these reactions.[5,7]

In this study, radioactive benzophenone-*1*-^{14}C was allowed to react with inactive benzhydrol in tetrahydrofuran (THF) at 90 °C. At various time intervals, the reaction was quenched