122–124 °C; NMR (Me_2SO-d_6) δ 6.62 (dd, J = 1.8, 3.9 Hz, 1 H, thiophene 3-H), 6.88 (dd, J = 3.9, 6.0 Hz, 1 H, thiophene 4-H), 7.07 (dd, J = 1.8, 6.0 Hz, 1 H, thiophene 5-H), 7.18 (dd, J = 1.2, 8.1 Hz, 1 H, Ar 6-H), 7.28 (dt, J = 1.2, 7.2 Hz, 1 H, Ar 4-H), 7.58 (dt, J = 1.8, 7.2 Hz, 1 H, Ar 5-H), 7.90 (dd, J = 1.8, 7.8 Hz, 1 H, Ar 3-H). Anal. Calcd for $C_{11}H_8O_3S$: C, 59.98; H, 3.66. Found: C, 60.00; H, 3.69.

Acknowledgment. We thank Dr. H. B. Renfroe for valuable discussions and for his encouragement and support of this work and Dr. H. W. Gschwend for advice concerning the preparation of the manuscript. We also express our gratitude to Dr. R. K. Rodebaugh for discussions concerning the interpretation of the NMR data and for providing spectra (XL-100 spectrometer). We thank Mrs. L. Raabis for providing IR and NMR spectra (A-60A and EM-390 spectrometers), Mr. C. Shimanskas for the mass spectra, Mr. G. Robertson and his staff for microanalytical data, and Mrs. D. Vivian and Mrs. R. Prieston for preparing the typescript.

Registry No. 1, 54449-13-7; 3, 42057-01-2; 4, 81028-66-2; 5, 81028-67-3; 6, 81028-68-4; 7, 81028-69-5; 8, 81028-70-8; 9, 81028-71-9; 10, 81028-72-0; 10 2'-CO_2H derivative, 81028-73-1; 11, 81028-74-2; 12, 81028-75-3; 13, 81028-76-4; 14, 81028-77-5; 15, 81028-78-6; 16, 42057-02-3; 19, 81028-79-7; 20, 81028-80-0; 21, 81028-81-1; 22, 58580-05-5; I (X = O; R = H), 63285-84-7; I (X = O; R = 2,4-Me_2), 81028-82-2; I (X = O; R = 2-CO_2Et, 4-Cl), 81028-83-3; I (X = O; R = 2-CO_2Et, 4-OMe), 81028-84-4; I (X = S; R = H), 16718-11-9; III (X = O; R^1 = H; R^3 = CO_2Et), 81028-85-5; III (X = O; R^1 = Me; R^3 = Me), 81028-86-6; III (X = S; R^1 = H; R^3 = Me), 72899-39-9; 3-(2-carboxy-4-methoxyphenoxy)thiophene, 81028-87-7; 3-(2-carboxy-4-chlorophenoxy)thiophene, 81028-88-8; 2-(2-carboxyphenoxy)-thiophene, 81028-89-9; *p*-cresol, 106-44-5; 3-bromothiophene, 872-31-1; thiophenol, 108-98-5.

Notes

Free-Radical Diazo Coupling. A New General Reaction of Diazonium Salts

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The reaction of nucleophiles at the β-nitrogen of arenediazonium salts and the importance of the electrophilic aromatic diazo coupling are well-known.[1] We have in recent years shown[2] the very important role played by polar effects in the reactions of nucleophilic alkyl radicals with electron-deficient aromatic compounds; diazonium salts, owing to their positive charge and the high electron-affinity,[3] are particularly interesting in this connection.

We now describe new general synthesis of alkylaryldiazenes on the basis of the reactions of Scheme I: addition

Scheme I

$$R\cdot + N{\equiv}N^+\text{-}Ar \rightarrow RN{=}\dot{N}^+\text{-}Ar \quad (1)$$

$$RN{=}\dot{N}^+\text{-}Ar + M^{n+} \rightarrow RN{=}NAr + M^{(n+1)+} \quad (2)$$

of alkyl radicals to arenediazonium cations (eq 1) and reduction of the intermediate azo radical cation adducts by metal salts (M^{n+}, eq 2). Equation 1 has been recently postulated in pulse radiolisis studies of arenediazonium salts.[4]

Several sources of alkyl radicals R· were found suitable for this reaction. For example, alkyl iodides (RI; R = methyl, primary, secondary, or tertiary alkyl, or benzyl)

Scheme II

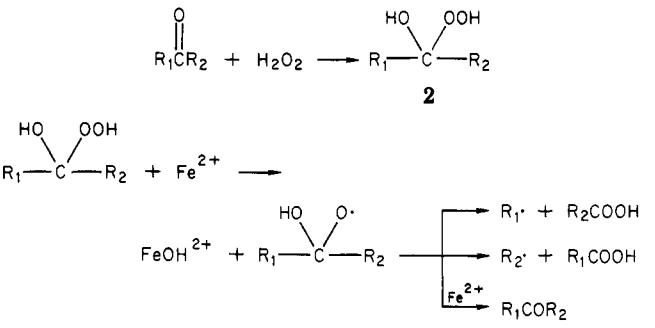
$$ArN_2^+ + Ti(III) \rightarrow Ar\cdot + N_2 + Ti(IV)$$

$$Ar\cdot + RI \rightarrow ArI + R\cdot$$

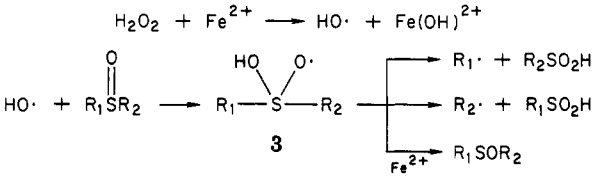
$$R\cdot + N{\equiv}N^+\text{-}Ar \rightleftarrows RN{=}\dot{N}^+\text{-}Ar$$

$$RN{=}\dot{N}^+\text{-}Ar + Fe^{2+}(Ti^{3+}) \rightarrow RN{=}NAr + Fe^{3+}(Ti^{4+})$$

Scheme III



Scheme IV



give rise cleanly in the presence of arenediazonium salts and reducing metal salts (M^{n+} = Ti^{3+} or Fe^{2+}) to the arylalkyldiazenes (1) according to the stoichiometry of eq 3. The results obtained with some iodides are reported

$$2ArN_2^+ + RI + 2M^{n+} \rightarrow ArN{=}\underset{\mathbf{1}}{NR} + ArI + 2M^{(n+1)+} + N_2 \quad (3)$$

in Table I (for a useful comparison only, the results for 4-chlorobenzenediazonium sulfate are reported; other substituents compatible with the reducing medium used give similar results).

The reaction can be explained by the mechanism of Scheme II. The aryl radical coming from the decompo-

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0022-3263/82/1947-1759$01.25/0

Table I. Free-Radical Diazo Coupling by Decomposition of 4-Chlorobenzenediazonium Sulfate Induced by Titanium(III) Chloride in the Presence of Alkyl Iodides and Iron(II) Sulfate [a]

entry	R	% yield for 1 mol of ArI/mol of ArN_2^+ 1 [b]
1	CH_3	28
2	CH_3 [c]	12
3	C_2H_5	38
4	cyclohexyl	70
5	cyclohexyl [c]	60
6	t-C_4H_9	86
7	CH_2Ph [d]	40

[a] In 1:1 water/acetone at 0 °C. [b] Yield based on the stoichiometry of reaction 3. [c] The arenediazonium sulfate (0.46 M, 17 mL) was dropped into a mixture of RI (20 mmol) and $TiCl_3$ (15% water solution, 1.05 M, 18.5 mL) in H_2O/CH_3OH (1:3, 40 mL) at 0 °C. [d] 15% of 1,2-diphenylethane was detected by GLC on a column (2 m × 1/8 in.) packed with 3% FFAP on Chromosorb W-DMCS (80–100 mesh). This column was used also for the yield determination of ArI.

sition of the arenediazonium salt induced by the titanous salt[5] generates, by selective iodine transfer,[6] alkyl radicals which undergo free-radical diazo coupling. Another example of a simple and convenient source of alkyl radicals is offered by the reaction of ketone–hydrogen peroxide mixtures with Fe(II) salts[7] (Scheme III). Various peroxides are present in these mixtures, depending on the experimental conditions,[7] but, owing to their similar behavior with regard to the generation of alkyl radicals,[7] only structure **2** can be indicated. Some results for different ketones are reported in Table II. With unsymmetrical ketones the formation of the most stable alkyl radical is favored. Very similar behavior was observed with alkyl sulfoxide and Fenton reagent (hydrogen peroxide and ferrous ion) where alkyl radicals were generated by fragmentation of the intermediate oxygen radical **3**[8] (Scheme IV). Alkyl radical adducts arising from the addition of aryl radicals to olefins also proved to be suitable for this reaction.[9]

Preliminary qualitative experiments indicate that a variety of other alkyl radical adducts, arising from free-radical addition to olefins, are suitable for diazo coupling and that alkyl radicals from other well-known sources such as hydroperoxides (through β scission, inter- and intramolecular addition, or hydrogen abstraction of alkoxy radicals), acyl peroxides, peresters, oxiranes, and N-chloro amines are effectively trapped by diazonium salts, giving the corresponding diazenes.

Thus this new reaction appears to be a very general, simple, and convenient one-step procedure for the synthesis of arylalkyldiazenes particularly for tertiary derivatives for which the other general alternative synthetic routes are less convenient.[10]

It appears that the reaction also has features of reversibility, since good results are obtained only in the presence of relatively high concentration of metal salts, which reduce the intermediate radical adduct, shifting the equilibrium toward the azo compound. The formation of bibenzyl in experiments 7 and 13 could also support the reversibility of the addition.

The results of Table I suggest a high rate constant for alkyl radical addition to diazonium ions; this is supported by experiments 2 and 5, in which the stationary concentration of diazonium salt is always very low, due to the fast decomposition reaction by Ti(III) salt. Preliminary kinetic results (still in progress) indicate that polar effects, arising from strong SOMO–LUMO orbital interactions,[11] play an important role in determining the high reaction rate with a transition state characterized by a considerable charge transfer (eq 4). Thus, tertiary radicals ($k_1 \geq 10^8$ M^{-1} s^{-1} at 0 °C) are considerably more reactive than primary alkyl radicals ($k_1 \simeq 10^6$ M^{-1} s^{-1} at 0 °C) owing to their higher nucleophilic character and in spite of the unfavorable enthalpic and steric aspects, thus explaining the increasing yield from methyl to primary, secondary, and tertiary alkyl radicals as reported in Tables I and II. The limiting case off this transition state is a complete electron transfer (eq 5) when the diazonium salt is reduced to diazenyl radical,

$$[R\cdot\ N\equiv\overset{+}{N}-Ar] \leftrightarrow [R^+ \cdot N{=}N-Ar] \qquad (4)$$

$$R\cdot + N\equiv\overset{+}{N}-Ar \longrightarrow R^+ + Ar-N{=}N\cdot \longrightarrow Ar\cdot + N_2 \qquad (5)$$

which decomposes quickly to an aryl radical.[12] This actually occurs when the nucleophilic character (or the reducing property) of the alkyl radical is increased by heteroatoms (mainly O and N; i.e., RĊH–OH, RĊH–OR, RCO·, $R_2NCO\cdot$, RĊH–NR_2, etc.).[13]

The reaction offers further evidence of the importance of polar effects: aryl radicals or alkyl radicals, in which the carbon-centered radical is bonded to an electron-withdrawing group (i.e., COOR, COR, $CONR_2$, CN, SO_2R, etc.), do not add to diazonium salts or give only poor results.[9]

Experimental Section

Reaction of Alkyl Iodides with 4-Chlorobenzenediazonium Salt. A typical experimental procedure was as follows. A cold solution of $FeSO_4 \cdot 7H_2O$ (8 g, 31 mmol) in water (15 mL) was added to a solution of 4-chlorobenzenediazonium sulfate made by diazotation at 0 °C of 4-chloroaniline (0.897 g, 7.8 mmol) in 10% H_2SO_4 (15 mL) with a solution of $NaNO_2$ (0.75 g, 8 mmol) in water (2 mL). Cyclohexyl iodide (3 mL, 23 mmol) in methanol (40 mL) was added to the resulting solution, and the heterogeneous mixture was stirred vigorously. A 15% $TiCl_3$ solution (1.05 M, 7.6 mL) was added at 0 °C in 25 min. Nitrogen was evolved. The reaction was stirred for additional 15 min at 0 °C and extracted with pentane (5 × 10 mL). The pentane was washed with water and concentrated, and the residue was chromatographed on silica gel with pentane and pentane–diethyl ether the eluents. A yellow

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Table II. Free-Radical Diazo Coupling by Ketones, Peroxides,[a] and *p*-Chlorobenzendiazonium Sulfate[b]

$$R_1COR_2 + H_2O_2 + p\text{-}ClArN_2^+ \xrightarrow{M^{n+}} R_1N{=}NAr\text{-}p\text{-}Cl + R_2N{=}NAr\text{-}p\text{-}Cl$$

entry	R_1	R_2	[peroxide],[c] M	ratio peroxide/ diazonium salt	% yield[d] $R_1N{=}NAr$	% yield[d] $R_2N{=}NAr$
8	CH_3	CH_3	*e*	1:1	15	
				2:1	26	
9	C_2H_5	C_2H_5	6.0	1:1	36	
				2:1	60	
10	i-C_3H_7	CH_3	6.1	1:1	56	1.8
				2:1	87	3.0
11	i-C_3H_7	i-C_3H_7	4.0	1:1	50	
12	t-C_4H_7	CH_3	2.3	1:1	67	0.4
				2:1	90	0.7
13[f]	CH_2Ph	CH_3	4.1	1:1	38	0.5

[a] The peroxide solutions were prepared by addition of 36% H_2O_2 to ketone (1:1 molar ratio) and a few drops of 50% H_2SO_4; the organic phase was washed with H_2O and dried on Na_2SO_4. In experiment 12 the peroxide was prepared as previously but at an initial temperature of 50 °C. [b] All the reactions were carried out as follows. The peroxide solution (7.8 mmol) was added in 15 min to a mixture of *p*-chlorobenzendiazonium sulfate (7.8 mmol, 17 mL) and $FeSO_4 \cdot 7H_2O$ (32 mmol) in water (40 mL) and acetic acid (30 mL) at −5 °C. Pentane (3 × 30 mL) extracts after 15 min give the azo derivatives which were isolated and quantitatively analyzed by GLC. [c] Peroxide molarity was determined by iodometric titration. [d] Yields are based on the diazonium salt. [e] The peroxide was prepared by addition of 59% H_2O_2 (0.45 and 0.9 mL, respectively, for the 1:1 and 2:1 experiments) to acetone (7 mL) over Na_2SO_4 (3 g) for 0.5 h. [f] Bibenzyl (12%) was also detected.

liquid was isolated and was an analytically pure sample of 1 (R = cyclohexyl): 0.606 g (70% yield based on reaction 3); bp 90–91 °C (0.5 mmHg); n^{20}_D 1.5134; UV (EtOH) λ_{max} 403 (log ϵ 2.28), 268 (4.19); NMR ($CDCl_3$) δ 3.62 (m, 1 H, CH), 1.2–2.0 (m, 10 H), 7.0–7.4 (A_2B_2 system, 4 H); mass spectrum, *m/e* 222 ($M^{+\cdot}$), 139, *111*, 83, 55.

The results reported in Table I were obtained under the same conditions with the exception of the entries 2 and 5; spectral (UV, NMR, and mass spectra) and analytical data are in good agreement with all the diazene structures of the products obtained by purification of the reaction mixtures as mentioned above.

Reactions of Ketone Peroxides with 4-Chlorobenzenediazonium Salt. A typical experimental procedure was as follows. H_2O_2 (36%, 18. mL, 0.2 mol) was added to 3-methyl-2-butanone (17.2 g, 0.2 mol) under stirring at 20 °C. H_2SO_4 (50%, 0.5 mL) was added, and the temperature increased to 50 °C. The mixture was stirred for 30 min, the organic phase was washed with saturated NaCl solution, and the peroxide was determined by iodometric titration (70% conversion of the ketone to peroxides). The crude peroxide (15.6 mmol) was added under stirring at −5 to 0 °C within 15 min to a mixture of 4-chlorobenzenediazonium sulfate (15.6 mmol, prepared as above) and $FeSO_4 \cdot 7H_2O$ (16 g, 62 mmol) in water (80 mL) and acetic acid (60 mL). After being stirred 15 min, the mixture was extracted with pentane, and the solution was washed with water and concentrated. The residue was purified by column chromatography on silica gel with pentane as the eluent. (4-Chlorophenyl)isopropyldiazene [n^{20}_D 1.5017; UV (EtOH) λ_{max} 402 nm (log ϵ 2.26), 266 (4.10); NMR ($CDCl_3$) δ 3.91 (septet, 1 H, CH), 1.31 (d, 6 H), 7.0–7.4 (A_2B_2 system, 4 H, Ar); mass spectrum, *m/e* 182, 139, *111*, 43] was isolated in 87% yield as the diazonium salt. (4-Chlorophenyl)methyldiazene was also isolated in 1.8% yield.

The results reported in Table II were obtained under the same experimental conditions with the appropriate ketone.

Reaction of Di-*n*-propyl Sulfoxide with Hydrogen Peroxide and 4-Chlorobenzenediazonium Salt. H_2O_2 (36%, 0.002 mol) was dropped at 0 °C under stirring to a mixture of 0.006 mol of di-*n*-propyl sulfoxide (from EGA), 4-chlorobenzenediazonium tetrafluoborate (0.001 mol) and $FeSO_4 \cdot 7H_2O$ (0.002 mol) in 50 mL of water. After stirring 10 min, the mixture was extracted with pentane (5 × 10 mL), the solution was washed with water and concentrated. The residue was purified by column chromatography as above. (4-Chlorophenyl)-*n*-propyldiazene was isolated as the first component in 31% yield based on the diazonium salt: bp 58–59 °C (1mmHg), n^{20}_D 1.5211; UV (EtOH) λ_{max} 4.05 nm (log ϵ (2.11), 261 (4.18); NMR ($CDCl_3$) δ 3.85 (t, 2 H, CH_2N=), 1.2–2.0 (m, 4 H), 0.8 (t, 3 H, CH_3), 7.0–7.4 (A_2B_2 system, 4 H, Ar); mass spectrum, *m/e*: 182 ($M^{+\cdot}$), 181, 165, 139, 111, 76, 43.

Registry No. 1 (R = CH_3), 80227-98-1; 1 (R = C_2H_5), 80227-99-2; 1 (R = cyclohexyl), 80228-00-8; 1 (R = t-C_4H_9), 80228-01-9; 1 (R = CH_2Ph), 80228-02-0; 1 (R = i-C_3H_7), 80228-03-1; 1 (R = n-C_3H_7), 80228-04-2; methyl iodide, 74-88-4; ethyl iodide, 75-03-6; cyclohexyl iodide, 626-62-0; *tert*-butyl iodide, 513-38-2; benzyl iodide, 620-05-3; 2-propanone, 67-64-1; 3-pentanone, 96-22-0; 3-methyl-2-butanone, 563-80-4; 2,4-dimetyl-3-pentanone, 565-80-0; 3,3-dimethyl-2-butanone, 75-97-8; 1-phenyl-2-propanone, 103-79-7; di-*n*-propyl sulfoxide, 4253-91-2; 4-chlorobenzenediazonium tetrafluoborate, 673-41-6; 4-chlorobenzenediazonium sulfate, 53486-30-9.

Resolution of Dextro- and Levomethorphan via Their Quaternary Ammonium Salts. 1. Stereoselectivity of the Quaternization[1]

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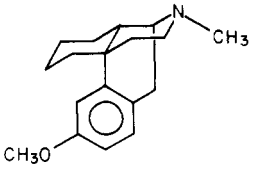
Dextromethorphan (1) and levomethorphan constitute an example of an enantiomorphic pair with drastically different pharmacological actions—the former is a widely used nonprescription antitussive, whereas the latter is a potent narcotic. This difference creates the need to



monitor and control the level of the levo isomer in pharmaceutical products containing 1. No official method of analysis for dextromethorphan is included in the U.S.

(1) Presented in part at the 179th National Meeting of the American Chemical Society, Houston, TX, Mar 1980; Abstract No. ORGN 015.