Experimental Section

Proton magnetic resonance spectra were taken on a Jeol JNM-C60HL spectrometer, using Me_4Si as the internal standard. Infrared spectra were obtained on a Perkin-Elmer 257 from 2% solutions in CCl_4. VPC analyses were performed on a GI Fractovap (C. Erba). UV spectra and kinetics were recorded with a Beckman DBGT spectrophotometer.

Materials. Ceric ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$ (Schuchardt, 99.9% pure) was dried at 85 °C for 1 h. Acetic acid (C. Erba 99.8% pure) was thoroughly fluxed with pure nitrogen before use. Ammonium nitrate (C. Erba, 99% pure), cerous nitrate $[Ce(NO_3)_3 \cdot 6H_2O]$ (C. Erba, 98% pure), anisole (C. Erba, 99% pure), *m*-methoxyphenol (Merck, 97% pure), and *p*-methoxyphenol (C. Erba, 99% pure) were commercial samples and were used as received. *o*-Methoxyphenol (Farmitalia) was distilled before use.

Methoxyphenyl Acetates. The three acetate isomers were prepared by acetylation of the corresponding phenol with acetic anhydride and acqueous alkali. Complete resolution of a mixture of the three isomers was achieved by VPC on a 1-m column, packed with 10% LAC 728, operating at 110 °C.

The Oxidation of Anisole with CAN. In a typical experiment, anisole (9.2 mmol) in 50 mL of oxygen-free acetic acid was added to a homogeneous solution of CAN (4.6 mmol) in 200 mL of the same solvent. The mixture was kept at 40 °C under nitrogen in a dark place. After 22 h (75% of Ce(IV) consumed) the reaction mixture was poured into cold ethyl ether and washed with water. After removing the solvent, the residue, which showed strong carbonyl absorption at 1770 cm^{-1}, was analyzed by VPC. Comparison of the gas chromatogram with those of authentic samples of the three isomeric acetoxyanisoles showed that *o*- and *p*-acetoxyanisole accounted for more than 95% of the reaction products, as based on peak areas. The two acetoxyanisoles were also isolated from a product mixture by means of preparative VPC on a 2-m column packed with SE 30 10% operating at 100 °C and compared with the authentic samples. No peak attributable to the meta isomer was present in the gas chromatogram thus indicating that this isomer, if present, is less than 0.5%.

Kinetic Measurements. The rates of oxidation of anisole were measured by following the disappearance of cerium(IV) in a thermostated cell compartment of a UV spectrophotometer. The optical densities were determined at 410 nm (ϵ 6.2×10^2 M^{-1} cm^{-1}) and in the presence of NH_4NO_3 at 360 (ϵ 4.1×10^3 M^{-1} cm^{-1}), 390 (ϵ 14.9×10^2 M^{-1} cm^{-1}), and 410 nm (ϵ 7.5×10^2 M^{-1} cm^{-1}) depending on the concentration of CAN.

Acknowledgments. The financial support of C.N.R. is gratefully acknowledged also for the part of this work which has been carried out at the University of Perugia.

Registry No.—CAN, 16774-21-3; anisole, 100-66-3; *o*-acetoxyanisole, 613-70-7; *m*-acetoxyanisole, 5451-83-2; *p*-acetoxyanisole, 1200-06-2; acetic acid, 64-19-7.

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(8) Other than by a salt effect, expected for a reaction involving charged species, NH_4NO_3 might influence the oxidation rate also by affecting the equilibrium $(NH_4)_2Ce(NO_3)_6 + 2AcOH \rightleftharpoons Ce(NO_3)_4(AcOH)_2 + 2NH_4NO_3$.[9]
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A New, Mild Method for the Synthesis of Azo Compounds

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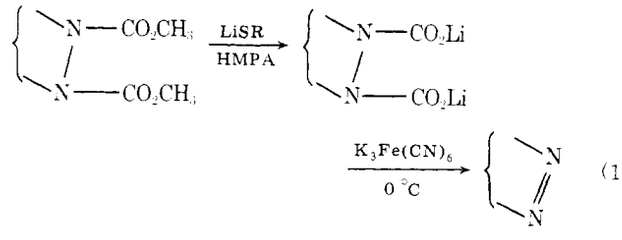
Azo compounds have long played a significant role in the development of mechanistic[1] and synthetic[2] organic chemistry. Often, however, their synthesis is encumbered by the harsh conditions of their genesis. Most methods involve the conversion of a dicarbamate to an hydrazo compound followed by oxidation to afford the desired azo linkage. While alkaline saponification of the dicarbamate at temperatures exceeding 80 °C has frequently been used,[3] in many cases only the most robust compounds survive these harsh conditions. The reductive cleavage of bis(2,2,2-trichloroethyl) esters,[4] the hydrogenolysis of benzyl esters,[5] and the β-elimination of β-tosylethyl esters[6] represent mild alternatives to alkaline saponification. Still, we have uncovered examples where even the conditions of these milder methods have proven to be incompatible with the survival of the desired product.[7]

We now wish to report that we have discovered a mild, one-pot, two-step sequence to effect the conversion of a dicarbamate to an azo linkage.[8] The conversion is effected at or below room temperature and in yields ranging from 60 to 80%; the often-times unstable hydrazo compound which is produced in most methods is bypassed entirely. The low temperatures required to effect the sequence make it possible to isolate even thermally labile azo compounds.

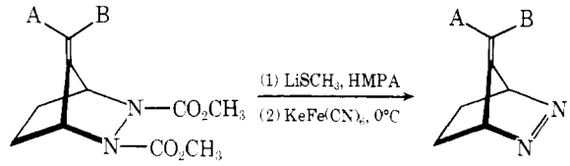
The method, outlined in eq 1, involves the room temperature mercaptide-induced nucleophilic cleavage of a dimethyl dicarbamate to afford a dilithium dicarboxylate. Oxidation with aqueous potassium ferricyanide at 0 °C results in the immediate evolution of gas (CO_2) and the formation of yellow Fe(II) salts.[9,10] Both the lithium salts of *n*-propyl mercaptan and methyl mercaptan have been successfully utilized. These reagents, 0.5–1.3 M in HMPA, are easily prepared and can be stored in the refrigerator for at least 1 month without showing



(1)

0022-3263/78/1943-2921$01.00/0

Table I



1a-e 2a-e

Registry no.	Entry	A	B	Reaction time: Cleavage,[a] h	Reaction time: Oxidation,[b] h	Yield,[c] %	Registry no.
66322-83-6	**1a**	CH_3	CH_3	4	1	65	31689-32-4
66322-84-7	**1b**	$-(CH_2)_5-$		3	1	72	66322-88-1
66322-85-8	**1c**	H	Cl	12	1	62	66322-89-2
66322-86-9	**1d**	Ph	Ph	16	1	82	66322-90-5
66322-87-0	**1e**	C_2H_5	C_2H_5	16	1	75	66322-91-6

[a] Room temperature. [b] 0 °C. [c] Isolated yield.

appreciable deterioration. We prefer to use the lithium salt of methyl mercaptan since the byproduct of the cleavage reaction, dimethyl sulfide, can easily be removed (bp 37 °C).

We have applied this sequence to the synthesis of a variety of bicyclic azo compounds; the results are summarized in Table I.

In a typical procedure, 1.48 mmol of a dicarbamate (**1a–e**) is added to 4.46 mmol of lithium methyl mercaptide (1.2 M in HMPA). After stirring for 3–18 h (note Table I) at room temperature, the reaction mixture is cooled to 0 °C, 4.46 mmol of potassium ferricyanide in 20 mL of water is added, and stirring is continued for another hour. After washing with pH 6 brine, extraction with pentane, and crystallization, the azo compounds **2a–e** are obtained in 60–80% yield.

Because of our interest in the chemistry of bicyclic azo compounds, we have focused attention upon their synthesis. We feel that the method is of sufficient generality to be applicable to a wide range of systems.[11]

Experimental Section

^1H NMR spectra were obtained using a Varian T-60 spectrometer. The spectral data are reported in δ relative to Me_4Si as an internal standard and $CDCl_3$ as solvent. All reactions were performed under a nitrogen atmosphere. Each of the azo compounds synthesized in this study are known compounds; therefore, combustion analyses were not run.

Materials. Methyl mercaptan (Linde) was used directly from a lecture bottle. Hexamethylphosphoramide (Aldrich) was vacuum distilled from barium oxide into a receiver containing 4A molecular sieves (Linde). The distilled solvent was then purged of oxygen by repeated freeze–thaw cycles. The dicarbamates **1a–e** were prepared by known sequences.[3b]

Lithium Methyl Mercaptide. Methyl mercaptan (25 mL, 0.45 mol) was condensed directly into a glass jacketed distilling reservoir which was cooled by passing cold nitrogen (−130 °C) through the receiver jacket. The mercaptan was then added dropwise to a precooled (0 °C) 250-mL three-neck flask equipped with a single-piece nitrogen inlet vacuum-take-off tube and a coarse glass-frit filtration adapter and charged with 3.30 g (0.42 mol) of lithium hydride in 150 mL of HMPA. The reaction was allowed to proceed for 1 h. The gas-condensing reservoir was then removed under a vigorous stream of nitrogen, the reaction vessel quickly stoppered, the system alternately purged with nitrogen and evacuated, and the reagent then filtered with the aid of a vacuum into a one-neck 250-mL flask attached to the filtration adapter. Upon completion of the transfer, the flask was stoppered with a serum cap, then alternately evacuated and purged with nitrogen, and finally stored in the refrigerator under nitrogen until ready for use. Titration to a phenolphthalein end point gave a value of 1.2 M (we have encountered a range of 1.0 to 1.3 M).

Azo Compounds 2a–e. Only a procedure for the diphenylazo compound **2d** is presented in detail. The synthesis of the other azo compounds is achieved in the same way using the appropriate modifications in reaction time as noted in the text.

Lithium methyl mercaptide (2.10 mmol, 1.2 M in HMPA) was added via syringe to a nitrogen-purged 50 mL one-neck flask equipped with a magnetic stirring bar, a 60-mL addition funnel, and a nitrogen inlet tube and charged with 0.26 g (0.68 mmol) of **1d**. The reaction was allowed to proceed at room temperature for 16 h, at which time the solution was cooled to 0 °C and 0.68 g (2.10 mmol) of potassium ferricyanide dissolved in 20 mL of water was added dropwise; immediate precipitation of yellow salts and gas evolution were noted. The decarboxylation was allowed to proceed for 1 h, and the resulting mixture was then added to 125 mL of pH 6 brine and extracted six times with 100 mL each of pentane. The combined pentane extracts were then washed twice with 300 mL each of pH 6 brine, dried over magnesium sulfate, and concentrated in vacuo to afford 147 mg (82%) of **2d**.

^1H NMR Data for 2a–e. 2a: δ 5.37 (broad q, 2 H, bridgeheads), 1.63 (s, 6 H, CH_3), 1.0–1.7 (m, 4 H, $-CH_2-$). **2b:** δ 5.39 (broad q, 2 H, bridgeheads), 1.9–2.2 (m, 4 H, allylic CH_2), 1.32–1.68 (m, 6 H, cyclohexyl CH_2), 1.32–1.68 (buried under cyclohexyl methylenes), 0.95–1.2 (broad m, 4 H, ethanobridge). **2c:** δ 5.76 (broad s, 1 H, $HCCl{=}C<$), 5.50 (broad s, 1 H, bridgehead), 5.20 (broad s, 1 H, bridgehead), 1.05–1.80 (broad m, 4 H, $-CH_2-$). **2d:** δ 6.98–7.38 (m, 10 H, Ph), 5.39 (broad q, 2 H, bridgeheads), 1.69–1.92 (m, 2 H, $-CH_2-$), 1.05–1.32 (m, 2 H, $-CH_2-$). **2e:** 5.32 (broad q, 2 H, bridgehead), 2.0 (q, 4 H, CH_2CH_3), 0.98 (t, 6 H, CH_2CH_3), 0.8–1.30 (m, 4 H, ethano bridge).

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Registry No.—Lithium methyl mercaptide, 35638-70-1.

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Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution

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We wish to describe a simple absorption chromatography technique for the routine purification of organic compounds. Large scale preparative separations are traditionally carried out by tedious long column chromatography. Although the results are sometimes satisfactory, the technique is always time consuming and frequently gives poor recovery due to band tailing. These problems are especially acute when samples of greater than 1 or 2 g must be separated. In recent years several preparative systems have evolved which reduce separation times to 1–3 h and allow the resolution of components having $\Delta R_f \geq 0.05$ on analytical TLC. Of these, medium pressure chromatography[1] and short column chromatography[2] have been the most successful in our laboratory. We have recently developed a substantially faster technique for the routine purification of reaction products which we call flash chromatography. Although its resolution is only moderate ($\Delta R_f \geq 0.15$), the system is extremely inexpensive to set up and operate and allows separations of samples weighing 0.01–10.0 g[3] in 10–15 min.[4]

Flash chromatography is basically an air pressure driven hybrid of medium pressure and short column chromatography which has been optimized for particularly rapid separations. Optimization studies were carried out under a set of standard conditions[5] using samples of benzyl alcohol on a 20 mm × 5 in. column of silica gel 60 and monitoring the column output with a Tracor 970 ultraviolet detector. Resolution is measured in terms of the ratio of retention time (r) to peak width (w,$w/2$) (Figure 1), and the results are diagrammed in Figures 2–4 for variations in silica gel particle size, eluant flow rate, and sample size.

A number of interesting facts emerge from these data. First, we find that one of the most popular grades of silica gel 60, 70–230 mesh (63–200 μm), gives the poorest resolution of any gel studied under our standard conditions. Second, particle sizes less than 40 μm offer no improvement in resolution with our method of packing.[7] Column performance is quite sensitive to the rate of elution and is best with relatively high eluant flow rates. The solvent head above the adsorbent bed should drop 2.0 ± 0.1 in./min for optimum resolution with mixtures of ethyl acetate/petroleum ether (30–60 °C).[8] Finally, the peak width shows the expected increase with the sample size. Sample recovery was ≥95%.

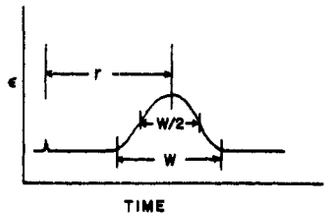

Figure 1. Typical chromatogram.

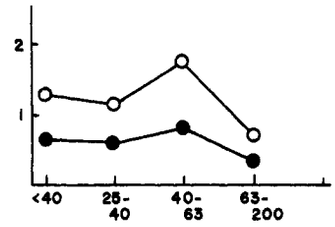

Figure 2. Silica gel particle size[6] (μm): (●) r/w; (○) $r/(w/2)$.

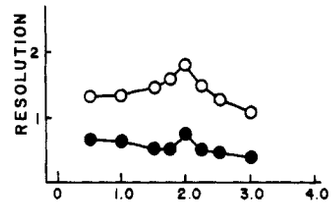

Figure 3. Eluant flow rate (in./min).

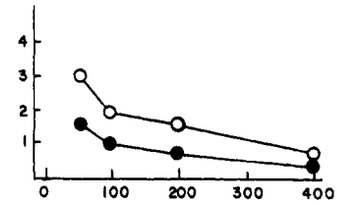

Figure 4. Sample size (mg).

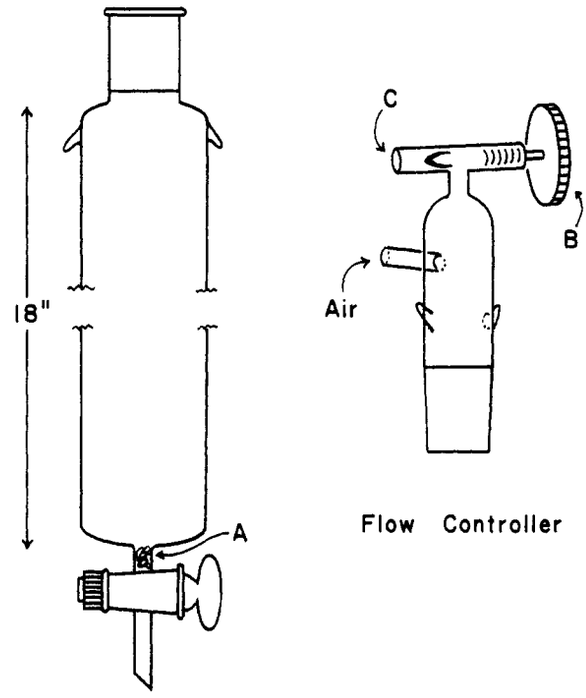

Figure 5.

The apparatus required for this technique consists of a set of chromatography columns and a flow controller valve (below). The column is a flattened bottom 18 in. glass tube fitted with a Teflon stopcock and topped with a 24/40 glass joint. Columns without fritted glass bed supports are generally preferred since they have significantly less dead volume than the standard fritted round-bottom variety. The flow controller

0022-3263/78/1943-2923$01.00/0