Advantageous Syntheses of Diazo Compounds by Oxidation of Hydrazones with Lead Tetraacetate in Basic Environments

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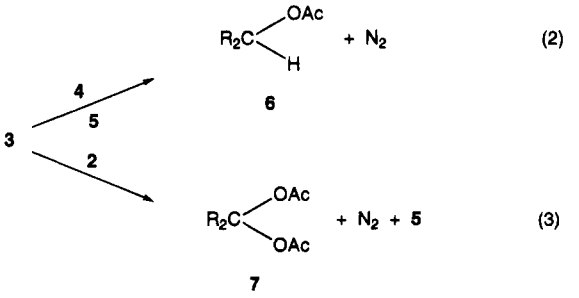
Varied sensitive diazo compounds **3** are produced efficiently and safely in 3–6 g quantities by oxidation (eq 1) of hydrazones **1** at −78 °C with lead tetraacetate (**2**) in triethylamine/chloroform, *N*-methylmorpholine/dimethylformamide, tetramethylguanidine (**8**)/dimethylformamide, and tetramethylguanidine/methylene chloride, respectively, upon use of appropriate workup and handling techniques. New and improved nonhazardous procedures have been developed for preparing and handling hydrazones **1** from aldehydes and ketones in reactions with excess hydrazine.

Hydrazones ($R_2C{=}NNH_2$) are oxidized to diazo compounds ($R_2C{=}N_2$)[1a] by yellow mercury(II) oxide,[1b] silver(I) oxide,[1c] manganese dioxide,[1d] nickel peroxide (NiO_2),[1e] sodium or calcium hypochlorite,[1f] iodine,[1g] barium manganate ($BaMnO_4$),[1h] mercury(II) acetamide [$Hg(HNCOCH_3)_2$],[1i] mercury(II) trifluoroacetate [$Hg(O_2CCF_3)_2$],[1j] phenyliodine(III) diacetate [$C_6H_5I(OAc)_2$],[1k] phenyldipyridinioiodine(III) bis(trifluoromethanesulfonate) [$C_6H_5I(NC_5H_5)_2(O_3SCF_3)_2$],[1l] chlorine dioxide,[1m] hydrogen peroxide,[1n] peracetic acid,[1o] and oxygen.[1p] Many of the oxidants are effective for syntheses of highly stabilized or sterically protected diazo compounds. The above methodologies are usually quite unsatisfactory, however, for preparing diazo compounds which are acid, heat, light, or oxidatively sensitive in that the conversions and yields are poor, the oxidations occur too slowly, and maintenance, separation, isolation, and utilization of the diazo products are difficult.

Of present relevance is that highly-stabilized diazo compounds **3** such as dicyanodiazomethane [$(NC)_2C{=}N_2$],[2a] bis(trifluoromethyl)diazomethane [$(CF_3)_2C{=}N_2$],[2b] methyl α-diazo-(*para*-substituted-phenyl)acetates [*Zp*-$C_6H_4C(N_2)CO_2CH_3$; Z = OCH_3 and H],[2c] methyl α-diazo-(*para*-substituted-phenyl)acetonitriles [*Zp*-$C_6H_4C(N_2)CN$, *Zp* = H and Cl],[2d] and tetrabromodiazocyclopentadiene [$C_4Br_4C{=}N_2$][2l] are obtained efficiently by oxidation (eq 1) of their precursor hydrazones **1** with lead tetraacetate (**2**) in acetonitrile, methylene chloride, or tetrahydrofuran at 0 °C. The method has not been satisfactorily extend-

$$\underset{\mathbf{1}}{R_2C{=}N{-}NH_2} + \underset{\mathbf{2}}{Pb(OAc)_4} \longrightarrow \underset{\mathbf{3}}{R_2C{=}N{=}N} + \underset{\mathbf{4}}{2\,HOAc} + \underset{\mathbf{5}}{Pb(OAc)_2} \qquad (1)$$

able to synthesis of less-stable diazo compounds **3**[2a] because of their rapid decomposition (eq 2) by acetic acid (**4**) and lead diacetate (**5**) to acetates **6**[3a] and their conversions (eq 3) to *gem*-diacetoxy compounds (**7**) by **2**.[3b] It is now reported that varied hydrazones **1** are oxidized



(2)

(3)

efficiently and safely to sensitive diazo compounds (**3**, Table 1) by **2** at −78 °C in the following basic environments:[4] triethylamine/chloroform, *N*-methylmorpholine/dimethylformamide, tetramethylguanidine (**8**)[5]/dimethylformamide (Scheme 1), and tetramethylguanidine (**8**)/methylene chloride (Scheme 1), respectively.[6] The latter two oxidation methods are highlighted in the present summary because they are of greater value for preparing and separating sensitive diazo compounds **3** in quantity. The tetramethylguanidine (**8**)/dimethylformamide pro-

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(1) (a) For review of recent literature of oxidation of hydrazones **1** to diazo compounds **3**, see Böshar, M.; Fink, J.; Heydt, H.; Wagner, O.; Regitz, M. *Methoden Der Organischen Chemie (Höuben-Weyl)*; Klaman, D., Hagemann, H., Eds.; Georg Thieme Verlag: New York, 1990; *E14B*, pp 996–1010. A specific reference for conversion of **1** to **3** by each of the oxidants is (b) Smith, L. I.; Howard, K. L. *Organic Syntheses*; Wiley: New York, 1955; Coll. Vol. II, p 352. (c) Reimlinger, H. *Ber.* **1964**, *97*, 3493. (d) Schroeder, W.; Katz, L. *J. Org. Chem.* **1954**, *19*, 718. (e) Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* **1966**, 730. (f) Morrison, H.; Danishefsky, S.; Yates, P. *J. Org. Chem.* **1961**, *26*, 2617. (g) Barton, D. H. R.; O'Brien, R. E.; Sternhell, S. *J. Chem. Soc.* **1962**, 470. (h) Guziec, F. S.; Murphy, C. J.; Cullen, E. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 107. (i) Forster, M. O.; Zimmerli, A. *J. Chem. Soc.* **1910**, *97*, 2171. (j) Newman, M. S.; Arkell, A. *J. Org. Chem.* **1959**, *24*, 385. (k) Sharefkin, J. G.; Saltzman, H. *Org. Synth.* **1963**, *43*, 62. (l) Weiss, R.; Seubert, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 891. (m) Handoo, K. L.; Handoo, S. K.; Gadru, K.; Kaul, A. *Tetrahedron Lett.* **1985**, *26*, 1765. (n) Fahr, E. *Ann.* **1959**, *627*, 213. (o) Adamson, J. R.; Bywood, R.; Eastlick, D. T.; Gallagher, G.; Walker, D.; Wilson, E. M. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2030. (p) Staudinger, H.; Gaule, A. *Ber.* **1916**, *49*, 1951.

(2) (a) Ciganek, E. *J. Am. Chem. Soc.* **1965**, *87*, 652. (b) Gale, D. M.; Middleton, W. J.; Krespan, C. G. *J. Am. Chem. Soc.* **1965**, *87*, 657. (c) Ciganek, E. *J. Org. Chem.* **1970**, *35*, 862. (d) Bernard, R. E. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1967. (e) McBee, E. T.; Sienkowski, K. J. *J. Org. Chem.* **1973**, *38*, 1340.

(3) (a) Cationic decomposition of **3** in **4** is catalyzed by **5**. (b) Jakubowitsch, A. J.; Makarow, S. P.; Ginsberg, W. A.; Gawrilow, G. W.; Merkulowa, J. N. *Izr. Akad. Nauk SSR* **1950**, *72*, 69. (c) Jakubowitsch, A. J.; Merkulowa, J. N.; Makarow, S. P.; Gawrilow, G. W. *J. Gen. Chem.* **1952**, *22* (84), 2060. (d) Hensel, R. H. *Ber.* **1952**, *88*, 527.

(4) In the present work addition of acetophenone hydrazone to **5** (1.40–1.45 mole ratio) in methylene chloride at 25 to −20 °C following literature procedures[2a,c] results in evolution of nitrogen (90–53%) and gives no 1-diazo-1-phenylethane. At −78 °C 1-diazo-1-phenylethane is obtained in 14% yield; inverse addition gives yields of 22–27%.

(5) Tetramethylguanidine (**8**) is manufactured by American Cyanamid, Wayne, NJ, and is obtained from many chemical suppliers.

(6) The present authors were led to the present methodologies by private communication from R. E. Bernard[2e] that highly-stabilized diazo compounds **3** are preparable from **1** and **2** in the presence of pyridine.

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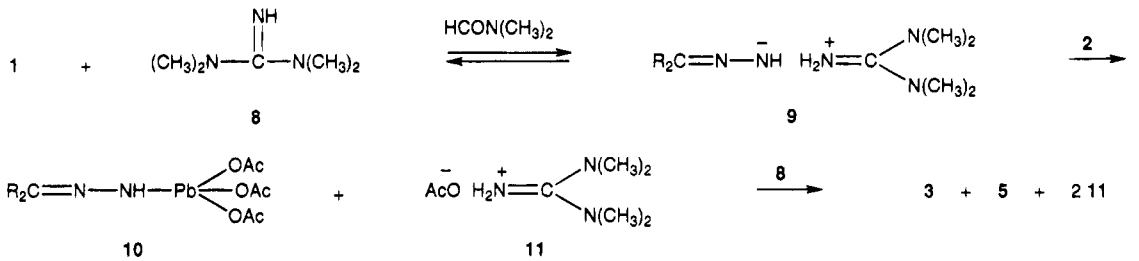
Table 1. Conversions of Aldehydes and Ketones to Hydrazones 1 and Oxidation of 1 by Lead Tetraacetate (2) to Diazo Compounds 3

hydrazones 1	yield, %[a]	diazo compounds 3	yield, %[b]	yield, %[c]	yield, %[d]	yield, %[e]
pentanal[10a]	78[f]	1-diazopentane[11a]		81	52	
3-methylbutanal[10b]	78[f]	1-diazo-3-methylbutane[11a]	54	87	53	
3-pentanone[10c]	70[f]	3-diazopentane[11b]	56	56	77	50
3,3-dimethyl-2-butanone[10d]	83[g]	2-diazo-3,3-dimethylbutane[11c,d]	80	86	97	67
5-hexen-2-one[10b]	≫26	2-diazo-5-hexene[11e]			90	
cyclopropyl methyl ketone[10e]	60[h]	1-cyclopropyl-1-diazoethane[11f]			100	53
dicyclopropyl ketone[10f]	73[g]	dicyclopropyldiazomethane[11g]			89	65
cyclopentanone[10c,g]	64[h]	diazocyclopentane[11h]	40		99	74
cyclohexanone[10c,h,i]	60[h]	diazocyclohexane[11h]	52	83	91	56
camphor[10j,k]	92[g]	2-diazocamphane[11i]			91	80
cyclooctanone[10l,m]	67[h]	diazocyclooctane[11j]			94	70
4-methoxybenzaldehyde[10n]	78[g]	(4-methoxyphenyl)diazomethane[11k]	68	58	86	75
4-nitrobenzaldehyde[10o]	94[f,g]	(4-nitrophenyl)diazomethane[11l]			84	80[i]
acetophenone[10p,q]	100[g]	1-diazo-1-phenylethane[11m]			96	96
α-tetralone[10o,r]	76[g]	1-diazotetralin[11h]	57			
dibenzyl ketone[10m,s]	62[g]	2-diazo-1,3-diphenylpropane[11e]			96	96
benzophenone[10o,t]	*i*	diphenyldiazomethane[11m]	77		100	
xanthone[10u]	*i*	9-diazoxanthene[11o]			69	
perinaphthenone[10v]	*j*	1-diazoperinaphthene[11e]			83	

[a] Yields of **1** by reactions of the aldehydes and ketones with hydrazine (6–10 mole ratio) by the method indicated. [b] Yields of **3** from addition of excess **2** (2.3–2.8 mmol) to **1** (2.1–2.5 mmol) in triethylamine (10 mL) and chloroform (30–40 mL) at −78 °C. [c] Yields of **3** obtained by adding excess **2** (2.3–4.1 mmol) to **1** (2.1–2.9 mmol) in *N*-methylmorpholine (15–25 mL) and dimethylformamide (15–25 mL) at −78 °C. [d] All reactions were conducted on small scale by addition of excess **2** (2.2–3.3 mmol) in one portion to **1** (2.0–3.0 mmol) in **8** (9–11 mL) and dimethylformamide (25–38 mL) at −78 °C and stirring the mixture for 15–60 min at −78 °C, followed by manometric analysis of **3** for N_2. [e] Except when noted, yield of **3** (3–6 g) by addition of **2** to **1** in **8** and dimethylformamide at −78 °C as described in text. [f] Prepared by method A. [g] Prepared by method B. [h] Prepared by method C. [i] Reaction of the hydrazone **1** with **2** (1.1 mole ratio) in **8** (10 mL) and methylene chloride (100 mL) at −78 °C. [j] Obtained as gifts.

Scheme 1



cedure is simpler and usually more efficient; the tetramethylguanidine (**8**)/methylene chloride methodology is preferable for preparing **3** which are not soluble in hydrocarbon solvents. Because of the losses in handling and extraction of **3**, the yields are greater on small than on large scale in either method. Also, as will be summarized, advantageous methods for synthesis of **1** of various types for conversions to **3** have been developed.

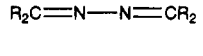
Diazo compounds (**3**, Table 1) are usually readily obtained in 81–100% yields as indicated in eq 3 upon addition of solid **2** in portions and with stirring to varied hydrazones **1** at −78 °C in **8** and dimethylformamide. The dimethylformamide, a cosolvent, greatly increases the solubility of **2** in the reaction mixture. Tetramethylguanidine (**8**), a strong neutral base ($pK_B = -0.2$),[7a] accelerates oxidation of **1** presumably by formation of their conjugate bases **9**,[7b,c] is not oxidized by **2** and protects **3** from decomposition by the **4** and **5** formed in the oxidation–reduction sequence (Scheme 1). Conversions of **1** to **3** are complete in 20–30 min or sooner at −78 °C, and the reaction products can be kept cold for extended periods without serious change. Oxidations of **1** by **2** to **3** (Scheme 1) are much faster than conversions of **3** by **2** to **7** (eq 2) at −78 °C.

A most important feature of the hydrazone **1**/lead tetraacetate (**2**)/tetramethylguanidine (**8**) synthetic method (Scheme 1) is that **3** can usually be extracted efficiently along with **8** and some dimethylformamide into cold pentane or hexane. Washing the hydrocarbon extracts with 30% aqueous potassium hydroxide at ~−35 °C removes essentially all of the dimethylformamide and most of the **8**. The **8** remaining is of great advantage in that cationic decompositions of **3** in the hydrocarbon solvents are retarded by the **8** present. The **8** in the pentane or hexane solutions of **3** can be removed simply when desired by adding dry ice and filtering the large crystals of the carbon dioxide adduct of **8** that form rapidly. The yield in a specific synthesis is obtainable upon injection of an aliquot of a cold hydrocarbon solution of **3** into a cold aqueous solution of sulfuric acid and determining the volume of nitrogen evolved. The remaining hydrocarbon solutions can often be stored at −20 °C to −78 °C for days and then used for many synthetic reactions of **3**. The solutions have also been frequently evaporated at reduced pressures to concentrate **3** without serious decomposition. Various procedures for preparing and handling **3** in different quantities safely are described in the Experimental Section.

Hydrazones **1** are usually obtained by reactions of hydrazine with aldehydes and ketones or their *N,N*-

(7) (a) Angyal, S. J.; Warburton, W. K. *J. Chem. Soc.* **1951**, 2492. (b) 4-Nitrobenzaldehyde, xanthone, and fluorenone hydrazones give intensely colored solutions in **8**. (c) The abilities of **8** to catalyze and improve conversion of **1** to **3** by other oxidants have not been studied.

dimethylhydrazones.[8a,b] Such syntheses, in particular those from highly reactive aldehydes, suffer serious complications in that azines **12** and hexahydrotetrazines **13** are formed. Further, attempted purifications of nonstabilized or unhindered **1** by distillation, chromatography, and/or recrystallization frequently make them worse. Preparations of **1** are improved by reactions of aldehydes and ketones with excess hydrazine in refluxing



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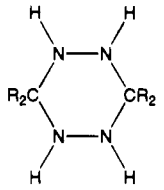

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ethanol when catalyzed by triethylamine in quantity.[1g] Hydrazones **1** are now found to be obtained even more advantageously (Table 1) by adding an aldehyde or ketone to a 6–10 molar excess of 97% anhydrous hydrazine at 20–25 °C. If the two reactants are immiscible, ethanol or methanol is used as a solubilizing solvent. For most unhindered aliphatic and aromatic aldehydes and reactive aliphatic ketones, conversions to **1** are essentially complete upon mixing the reagents (method A). When the carbonyl compound is an arylalkyl, aryl, bicyclic, or a long-chain dialkyl ketone, efficient production of **1** may require 2–50 h of reflux in the alcohol solvent (method B). Isolation of **1** is effected upon addition of sodium chloride, extraction into pentane, ethyl ether, or methylene chloride, washing the extracts with aqueous sodium chloride solutions, and concentration at −20 to 0 °C at reduced pressure. Such **1** are usually 90–95% pure by NMR and satisfactory for oxidation to **3** by **2**. Using the above methodologies, cyclopentanone, cyclohexanone, cyclooctanone, and cyclopropyl methyl ketone react with hydrazine to give water-soluble adducts[9] that are not readily extracted by the organic solvents. These latter ketones are satisfactorily converted however to their hydrazones **1** by reactions with hydrazine hydrate and barium oxide in refluxing ethanol, extractions into ethyl ether, drying the product solutions over solid sodium hydroxide, and reduced pressure distillations (method C).

Experimental Section

Materials. Triethylamine, *N*-methylmorpholine, and tetramethylguanidine (**8**) were distilled over barium oxide. Chloroform (reagent grade) was passed over neutral alumina to remove the ethanol present. Dimethylformamide, methylene chloride, hydrazine, and all hydrocarbon solvents were of reagent grade. All of the above reactants and solvents were saturated with and stored over dry nitrogen.

Fresh lead tetraacetate (**2**, G.F. Smith Chemical Co.) was dried for at least one day in darkness at room temperature at 0.3–0.6 mmHg before use. The equivalents of lead(IV) per gram of oxidant were determined by dissolving **2** (0.1 g) in glacial acetic acid (15 mL) and then adding a solution of potassium iodide (0.5 g) and sodium acetate (13 g) in water (65 mL). The iodine produced was back-titrated with standard sodium thiosulfate solution (~0.0100 N) to a starch endpoint. The sulfuric acid (~30% by weight) used for manometric decomposition of **3** was saturated with nitrogen.

General Procedures for Preparation of Hydrazones (1). Representative procedures used for preparing the hydrazones **1** in Table 1 are detailed as follows.

Method A. Pentanal Hydrazone. Pentanal (28.7 g, 0.33 mol) was added dropwise to rapidly stirred anhydrous hydrazine (110 g, 3.33 mmol) at room temperature. The reaction was complete after the last portion of the aldehyde had been added (57 min). Stirring the mixture was continued and pentane (200 mL) and powdered sodium chloride (15 g) were added. A three-phase liquid system was produced. The upper two phases (top, pentane; middle, pentanal hydrazone and some hydrazine) were drawn off and extracted with saturated sodium chloride solution (3 × 25 mL). The pentane solution was dried through Drierite and then concentrated at reduced pressure. Removal of the remaining solvent under vacuum (0 °C/5 mmHg) yielded pentanal hydrazone (26.0 g, 78%) as a slightly yellow turbid oil. The product was rapidly suction-filtered, bottled, and stored as a white solid at −78 °C. The IR and NMR spectra for the hydrazone were recorded. Accurate determination of the purity of the product failed because of rapid conversion of the hydrazone to 3,6-dibutylhexahydro-1,2,4,5-tetrazine.

Method B. 3,3-Dimethyl-2-butanone Hydrazone. 3,3-Dimethyl-2-butanone (33.3 g, 0.33 mol), 97% anhydrous hydrazine (64.0 g, 2.0 mol), and absolute methanol (40 mL) were refluxed 2.5 h. The reaction mixture was cooled and extracted with pentane (200 mL). The pentane extract was washed with saturated sodium chloride solution (3 × 100 mL), dried through Drierite, and stripped *in vacuo* to give 3,3-dimethyl-2-butanone hydrazone (31.4 g, 82.5%) as a colorless oil, 93% pure by ^{1}H NMR. The hydrazone is indefinitely stable upon storage at −20 °C.

Method B. Camphor Hydrazone. A mixture of camphor (50.7 g, 0.33 mol), 97% anhydrous hydrazine (64 g, 20 mol),

(8) (a) Recent literature of preparation of **1** is summarized by Dumic, M.; Koruncev, D.; Koracevic, K.; Polak, L.; Kolbah, D. *Methoden der Organischen Chemie* (Höuben-Weyl); Klaman, D., Hageman, H., Eds.; Georg Thieme Verlag: New York, 1990; *E14b*, pp 434–712. (b) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677.

(9) Such adducts may have structures of $R_2C(NHNH_2)_2$ and $R_2C(OH)(NHNH_2)$.

(10) For references for previous preparation or discussion of the stabilities of the indicated hydrazones **1**, see (a) Kauffmann, Th.; Ruckelshauss, G.; Schulz, *J. Angew. Chem.* **1963**, *75*, 1204. (b) Hydrazones of 3-methylbutanal, 5-hexen-2-one, and 2-methylbenzaldehyde have not been previously reported. These hydrazones, when prepared in acceptable purities, undergo rapid change of 0–25 °C and must be kept cold (~78 °C) to avoid extensive change. The IR and NMR spectra of these hydrazones are available. (c) Giese, B.; Erfort, U. *Chem. Ber.* **1983**, *116* (3), 1240. (d) Berg, C. *J. Chem. Soc., Chem. Commun.* **1974**, *4*, 122. (e) Herrmann, W. A.; Weber, C.; Ziegler, M. L.; Rahl, C. *Chem. Ber.* **1984**, *117* (3), 875. (f) Hart, H.; Curtis, O. E., Jr. *J. Am. Chem. Soc.* **1956**, *78*, 112. (g) Giese, H.; Erfort, U. *Angew. Chem.* **1982**, *94* 133. (h) Perkin, W. H.; Plant, S. G. *J. Chem. Soc.* **1925**, *127*, 1138. (i) Heyns, K.; Heine, A. *Ann.* **1957**, *604*, 133. (j) Barton, D. H. R.; McGhie, J. F.; Balton, P. L. *J. Chem. Soc. C* **1970**, 1033. (k) Wolff, L. *Ann.* **1912**, *394*, 86. (l) El-Abadelah, M. M.; Hussein, A. Q.; Awardellah, A. M. *Heterocycles* **1989**, *29* (10), 1957. (m) Rozen, S.; Zamir, D. *J. Org. Chem.* **1991**, *56* (15), 4695. (n) El-Kerdawy, M. M.; El-Kousy, S. *J. Drug. Res.* **1973**, *5* (1), 143. (o) Newkome, G. R.; Fishel, D. L. *J. Org. Chem.* **1966**, *31*, 677. (p) Staudinger, H.; Gaule, A. *Ber.* **1916**, *49*, 198. (q) Lach, C.; Stach, K. *Ber.* **1943**, *76*, 1252. (r) Nishinaga, A.; Yamazaki, S.; Matsuura, T. *Tetrahedron Lett.* **1986**, *27*, 2649. (s) Bywood, R.; Gallagher, G.; Sharma, G. K.; Walker, D. *J. Chem. Soc. Perkin Trans. 1* **1975**, 2019. (t) Kaiser, E. M.; Henoch, F. E.; Hauser, Ch. R. *J. Am. Chem. Soc.* **1968**, *90*, 7287. (u) Schonberg, A.; Singer, E. *Chem. Ber.* **1968**, *101*, 3445. (v) Newman, M. S., Department of Chemistry, The Ohio State University, Columbus, OH.

(11) (a) Kaufman, G. M.; Smith, J. A.; vander Stouw, G. G.; Shechter, H. *J. Am. Chem. Soc.* **1965**, *87*, 936. (b) Bekhazi, M.; Smith, P. J.; Warkentin, J. J. *Can. J. Chem.* **1984**, *62*, 1646. (c) Friedman, L.; Shechter, H. *J. Am. Chem. Soc.* **1959**, *81*, 5512. (d) Kaufman, G. M. Ph.D. Dissertation, The Ohio State University, Columbus, OH, 1967. (e) These diazo compounds are new compounds. (f) Majchrzak, M. W.; Bekhazi, I.; Tse-Sheepy, I.; Warkentin, J. *J. Org. Chem.* **1989**, *54*, 1842. (g) Ensslin, H. M.; Hanack, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 1702. (h) Heyns, K.; Heins, A. *Ann.* **1957**, *604*, 133. (i) Heubaum, U.; Noyes, W. A. *J. Am. Chem. Soc.* **1930**, *52*, 5070. (j) Wojnarovits, L. *Proc. Tihany Symp. Radiat. Chem.* **1982**, *5* (1), 529. (k) Kamaike, K.; Tsuchiya, H.; Imai, K.; Takaku, H. *Tetrahedron* **1986**, *42*, 4701. (l) Davies, H. M.; Schwarz, M. *J. Org. Chem.* **1965**, *30*, 1242. (m) Meinwald, J.; Gassman, P. G.; Miller, E. G. *J. Am. Chem. Soc.* **1959**, *81*, 4751. (n) Callot, H. J.; Cromer, R.; Louti, A.; Metz, B.; Chevrier, B. *J. Am. Chem. Soc.* **1987**, *109* (10), 2946. (o) Latif, N.; Fathy, I. *Can. J. Chem.* **1959**, *37*, 865.

and absolute methanol (88 mL) was refluxed 50 h. The hydrazonation reaction was followed to completion by observing the disappearance of the carbonyl IR band of camphor (1740 cm^{-1}). The reaction mixture was then cooled and extracted with pentane (400 mL). After the resulting two-phase system had been extracted further with saturated aqueous sodium chloride (200 mL), the pentane layer was washed with additional sodium chloride solution (2×200 mL) and dried through a cone of Drierite. Rotary (40 °C) and vacuum aspiration of the pentane solution left crude camphor hydrazone (50.9 g, 92.0%) as a white solid, mp 41.2–48.5 °C. Rapid vacuum distillation of the crude hydrazone yielded only a slightly purer product, mp 43–54 °C. The distilled material (41.9 g) was recrystallized upon solution in warm ether (50 mL), adding 30–60 °C petroleum ether (120 mL), and cooling the solution to 0 °C and then to −78 °C. Filtration and vacuum desiccation of the white solid (fine needles) yielded camphor hydrazone (26.1 g, 47%), mp 54.5–57.0 °C. The hydrazone is satisfactorily storable at −20 °C in a sealed ampule.

Method C. Cyclohexanone Hydrazone. Cyclohexanone (34.3 g, 0.35 mol) was added dropwise in 25 min to a stirred mixture of freshly distilled hydrazine hydrate (19.5 g, 0.39 mol), ethanol (20 mL), and barium oxide (13.8 g, 0.09 mol) heated to 110 °C. After the mixture had been refluxed 4 h and then cooled, ether was added. The solution was filtered and stored overnight at −20 °C over sodium hydroxide pellets. Upon removal of the ether by rotary evaporation, rapid distillation of the resulting liquid at reduced pressure gave cyclohexanone hydrazone (24.8 g, 63%) as a colorless oil, bp 60–70 °C (1.9 mmHg). The hydrazone is 96% pure by ^1H NMR and storable as a solid at −78 °C.

Reaction of 1,1-Dimethylhydrazones and Hydrazine. 3,3-Dimethyl-2-butanone Hydrazone. 3,3-Dimethyl-2-butanone 1,1-dimethylhydrazone (17.9 g, 0.13 mol, bp 52–54 °C at 50 mmHg), 97% anhydrous hydrazine (16.6 g, 0.52 mol), and absolute ethanol (20 mL) were refluxed 16 h. The mixture was cooled, and water (75 mL) was added. The aqueous solution was extracted with ether (3 × 30 mL). The combined ether extract was washed with water (30 mL), dried over sodium sulfate and Drierite, and filtered. Removal of the ether at reduced pressure yielded 3,3-dimethyl-2-butanone hydrazone (10.3 g, 70%) as a colorless oil (~100% pure) with IR and ^1H NMR properties essentially identical with those from 3,3-dimethyl-2-butanone hydrazone prepared by method B.

Oxidation of 1 by 2 to 3. Techniques. Small Scale. Diazo compounds **3** (Table 1) can be prepared simply on small scale (0.2–0.6 g, ~3 mmol) by adding solid **2** (3.0–3.6 mmol) in one portion to a solution of **1** (~3 mmol) at −78 °C in a solvent (25–30 mL of dimethylformamide or methylene chloride) containing the chosen base (10–15 mL of **8**, *N*-methylmorpholine, or triethylamine). The yield of **3** in such an experiment can be determined by syringing the reaction solution at −78 °C into an enclosed stirred mixture of sulfuric acid (~30% by weight and of known volume) and pentane, hexane, or methylene chloride (~15 mL) at 0 °C which had been saturated previously with nitrogen and incorporated into an appropriate monostatic and barometric system for measuring the volume of nitrogen evolved. The moles of nitrogen evolved by decomposition of **3** and then the yield of **3** are calculated by routine use of the gas law and stoichiometric relationships. The methodology described is particularly valuable for determining proper conditions for efficient oxidation of a particular hydrazone **1** to its diazo compound **3**. For preparation of **3** for use in small quantities, the procedures usable are directly analogous to that which will be detailed for large scale synthesis.

Large Scale. General Procedures. Lead tetraacetate (**2**, 0.033 mmol) is added at a slow, steady rate in 20–40 min to a well-stirred solution of **1** (3–6 g, ~0.03 mmol), **8** (10–15 mL), and dimethylformamide (30–40 mL) at −78 °C. The reaction mixture is stirred additionally for 10–20 min at −78 °C and then extracted with hexane (2 × 100 mL portions) at −78 °C. The combined hydrocarbon extracts are washed at −78 °C with cold 30% aqueous potassium hydroxide (50 mL; −35 °C). Dry ice (several small pieces) is added to the hydrocarbon solution of **3**, and the resulting precipitate from carbon dioxide and **8** is suction-filtered. The solution of **3** is degassed at reduced pressure and stored over potassium hydroxide pellets, and then, when necessary, an aliquot can be analyzed manometrically for **3**. The solution of **3** can either be used as such, stored in the dark cold, or concentrated under vacuum. The alternate oxidation procedure in methylene chloride (100 mL) involves addition of **2** (0.033 mmol) with stirring to **1** (3–6 g, 0.03 mmol) and **8** (~10 mL) at −78 °C. After 15–35 min at −78 °C, the reaction mixture is shaken with cold 30% aqueous potassium hydroxide (3 × 25 mL) and suction-filtered through Celite to remove lead hydroxide. Upon separating the aqueous phase, the methylene chloride solution of **3** is washed with cold 2% aqueous potassium hydroxide (3 × 25 mL), dried over potassium carbonate, stored cold, analyzed for **3**, and used purposely.

1-Diazopentane. Pentanal (2.84 g, 0.0033 mol) was added in 5 min to stirred 97% anhydrous hydrazine (10.5 g, 0.0329 mol) at 55 °C. The reaction was continued 45 min at 55–65 °C. After the mixture had been cooled to room temperature, methylene chloride (100 mL) was added. The solution was washed with saturated aqueous sodium chloride (3 × 25 mL), dried over potassium carbonate, and concentrated under reduced pressure to a volume of ~10–20 mL. Dimethylformamide (37 mL) was added, and the remaining methylene chloride was removed by vacuum volatization.

The solution of pentanal hydrazone in dimethylformamide was cooled to −78 °C (15 min) and diluted with cold tetramethylguanidine (**8**, 13 mL). Lead tetraacetate (18.6 g, 0.00363 mol) was added in 10 min, and the mixture was stirred 35 min at −78 °C. The reaction solution was diluted with cold hexane (3 × 100 mL) and extracted at −78 °C using siphoning techniques. The combined cold hexane extracts were washed with cold (−30 °C) 30% aqueous potassium hydroxide (2 × 25 mL), small pieces of dry ice were added, and the solution was then filtered. An aliquot of the yellow solution of 1-diazopentane in hexane was injected into sulfuric acid (30%, 50 mL)/hexane (15 mL); the nitrogen evolved corresponds to a 52% yield of the diazoalkane. The infrared spectrum of the hexane solution exhibits strong absorption at 2060 cm^{-1} for its diazo group. 1-Diazopentane is stable in hexane for several days.

5-Diazo-1-hexene. A mixture of 5-hexen-2-one hydrazone (3.05 g, 0.0272 mol), tetramethylguanidine (**8**, 13 mL), and dimethylformamide (37 mL) was stirred at −78 °C (20 min), and lead tetraacetate (**2**, 14.6 g, 0.0274 mol) was added in 20 min. After 30 min (−78 °C), the mixture was stirred with three portions of cold hexane (total volume of hexane ~250 mL). After each extraction the hexane solution was siphoned at −78 °C into a receiver at −78 °C. The combined cold extracts (−78 °C) were washed with cold, 30% potassium hydroxide solution (2 × 25 mL, −30 °C), dry ice was added, and the mixture was rapidly filtered. Carbon dioxide was removed by aspirating the solution for ~5 min. Aliquots of the mixture were injected into a sulfuric acid/hexane mixture. The nitrogen evolved corresponds to a 62% yield of 5-diazo-1-hexene. The diazo compound in hexane has an IR absorption for its diazo group at 2044 cm^{-1}. Solutions of 5-diazo-1-hexene decolorize rapidly at room temperature.

(2-Methylphenyl)diazomethane. To stirred 97% anhydrous hydrazine (10 mL, ~0.306 mol) at 60 °C was added 2-methylbenzaldehyde (3.73 g, 0.0278 mol) in 6 min by syringe. The mixture was stirred for 45 min at 50–60 °C, cooled, and then taken into methylene chloride (100 mL). After the resulting two-phase mixture had been washed with saturated aqueous sodium chloride (3 × 25 mL), the methylene chloride solution (lower phase) was dried over potassium carbonate and rotary-evaporated to ~10–15 mL. Dimethylformamide (37 mL) was added, and the remaining methylene chloride was stripped.

Tetramethylguanidine (10 mL) was syringed into the solution of the hydrazone, and the mixture was cooled to −78 °C (15 min). Lead tetraacetate (**2**, 15.7 g, 0.0306 mol) was added in 15 min (−78 °C). The reaction mixture was stirred further for 35 min and then shaken with cold, 30% potassium hydroxide (100 mL). Lead hydroxide was removed by suction filtration through Celite in a cold Buchner funnel. The two-phase filtrate (−78 °C) was transferred to a cold separatory

funnel, and the aqueous (upper) layer was removed. The methylene chloride solution was washed with cold, 2% potassium hydroxide solution (4 × 200 mL) and then dried over potassium carbonate. An aliquot of the diazoalkane solution was injected into a sulfuric acid/methylene chloride mixture and the nitrogen evolved was measured. (2-Methylphenyl)-diazomethane was obtained in 75% yield. The IR spectrum of the methylene chloride solution revealed intense absorption for a diazo group at 2065 cm^{-1}. Solutions of (2-methylphenyl)-diazomethane are stable at room temperature in light for weeks.

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Supporting Information Available: Copies of ^1H NMR spectra of new hydrazones (3 pages). This material is contained on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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