shown by GLC analysis and ^{13}C NMR to contain **5a** (10%), unknown compounds (12%), and **3a** (78%). The data (GLC and ^{13}C NMR) are identical with those from the products from reaction of 1 with methanol at room temperature.

Acknowledgment. We acknowledge grants from the Research Committee of the New Zealand Universities Grants Committee and helpful discussions with Professor M. A. Battiste.

Supplementary Material Available: ^{13}C and ^{1}H NMR spectra for compounds 1, **3a-d**, **5a,b**, **6a,b**, **12**, **14a-c**, **16a,b**, and **18a,b** (26 pages). Ordering information is given on any current masthead page.

Reaction of Carbonyl Compounds with Ethyl Lithiodiazoacetate. Studies Dealing with the Rhodium(II)-Catalyzed Behavior of the Resulting Adducts†

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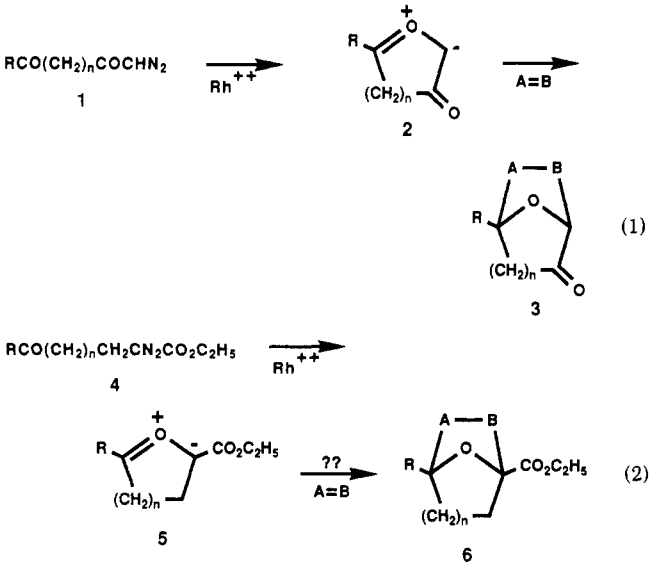
The carbenoid intermediate derived by treating ethyl 2-diazo-4-phthalimidobutyrate with rhodium(II) octanoate undergoes transannular cyclization onto the adjacent imido carbonyl group. The resulting cyclic carbonyl ylide dipole was trapped with several dipolarophiles. In an attempt to prepare related substrates for cyclization studies, the reaction of ethyl lithiodiazoacetate with various aldehydes and ketones was studied. Treatment of the α-diazo-β-hydroxy ester derived from acetone or cyclopentanone with rhodium(II) octanoate gave rise to a β-keto ester. The exclusive phenyl shift encountered with acetophenone is in keeping with migration to an electron-deficient center. The reaction works well with acrolein, leading to high yields of 3-oxo-4-pentenoate. The 1,2-hydrogen shift pathway was found to proceed much faster than intramolecular cyclopropanation. Dehydration of the α-diazo-β-hydroxy esters generates vinyl diazo esters, which readily cyclize to 1*H*-pyrazoles on thermolysis.

α-Diazo carbonyl compounds have found numerous applications in organic synthesis, and their use in either heterocyclic or carbocyclic ring formation is well documented.[1-14] Most of the early work has centered on the cyclopropanation and C-H insertion reactions of the resulting carbenes or metallocarbenoids.[15-18] Recently, we described the formation of oxabicyclo compounds from the rhodium(II) acetate catalyzed reaction of 1-diazoalkanediones.[19] The reaction involves the formation of a rhodium carbenoid and subsequent transannular cyclization of the electrophilic carbon onto the adjacent keto group to generate a cyclic carbonyl ylide followed by 1,3-dipolar cycloaddition (eq 1).[20,21] The ease with which α-diazo ketones 1 undergo this tandem cyclization-cycloaddition sequence suggested that a similar transformation should also occur with the related α-diazo keto ester system 4 (eq 2). We thought that this latter reaction could be of some synthetic value as it permits for the synthesis of novel functionalized THF derivatives of type **6**. The importance of tetrahydrofuran ring systems in natural products, interwoven with their rich diversity of molecular architecture, has continued to challenge the current level of synthetic methodologies.[22-25] Although a variety of methods exist



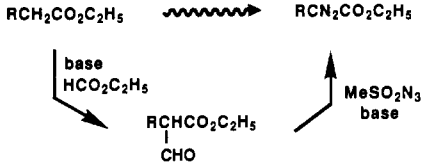
†Dedicated with respect and admiration to Professor Ernest Wenkert, one of the leading pioneers in the area of diazocarbonyl chemistry, on the occasion of his 65th birthday.

(1) Burke, S. D.; Grieco, P. A. *Org. React. (N.Y.)* **1979**, *26*, 361.
(2) Trost, B. M.; Vladauchick, W. C. *J. Org. Chem.* **1979**, *44*, 148.
(3) Dave, V.; Warnhoff, E. W. *Org. React. (N.Y.)* **1970**, *18*, 217.
(4) Meier, H.; Zeller, K. P. *Angew. Chem., Int. Ed. Engl.* **1979**, *14*, 32.
(5) Wenkert, E.; Alonso, M. E.; Buckwalter, B. L.; Sanchez, E. L. *J. Am. Chem. Soc.* **1983**, *105*, 2021.
(6) Moody, C. J. *Organic Reaction Mechanisms*; Wiley: London, 1983; Chapter 6.
(7) Vogel, E.; Reel, H. *J. Am. Chem. Soc.* **1972**, *94*, 4388.
(8) Doering, W. V. E.; Pomerantz, M. *Tetrahedron Lett.* **1964**, 961.
(9) Stork, G.; Ficini, J. *J. Am. Chem. Soc.* **1961**, *83*, 4678.
(10) Corey, E. J.; Achiwa, K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318.
(11) White, J. D.; Torii, S.; Nogami, J. *Tetrahedron Lett.* **1974**, 2879.
(12) Saltzmann, T. N.; Ratcliff, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161.
(13) Ratcliff, R. W.; Saltzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31.
(14) Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422.
(15) Doyle, M. P. *Acc. Chem. Res.* **1986**, *19*, 348; *Chem. Rev.* **1986**, *86*, 919.
(16) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196.
(17) Maas, G. *Topics in Current Chemistry*; Springer-Verlag: Berlin, West Germany, 1987.
(18) Taylor, K. G. *Tetrahedron* **1982**, *38*, 159.
(19) Padwa, A.; Carter, S. P.; Nimmesgern, H. *J. Org. Chem.* **1986**, *51*, 1157. Padwa, A.; Carter, S. P.; Nimmesgern, H.; Stull, P. *J. Am. Chem. Soc.* **1988**, *110*, 2984. Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Org. Chem.* **1988**, *53*, 2875.
(20) Ibata, T.; Motoyama, T.; Hamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2298.
(21) Gillon, A.; Ovadia, D.; Kapon, M.; Bien, S. *Tetrahedron* **1982**, *38*, 1477.

for tetrahydrofuran synthesis,[26] few of these are based on an annulation strategy.[27-30] One of our goals is to develop new methodologies for the construction of O-heterocycles with primary consideration given to mechanistic pathways that would allow a secure means of incorporating centers of stereochemistry. With these interests in mind, we were intrigued by the untapped potential of the rhodium(II)-induced tandem cyclization–cycloaddition reaction of α-diazo esters. Thus, we decided to explore the synthesis and transition-catalyzed behavior of diazo esters related to **4**. In this paper, we describe the results we obtained from using ethyl diazoacetate as a reagent for the preparation of a series of α-diazo esters.

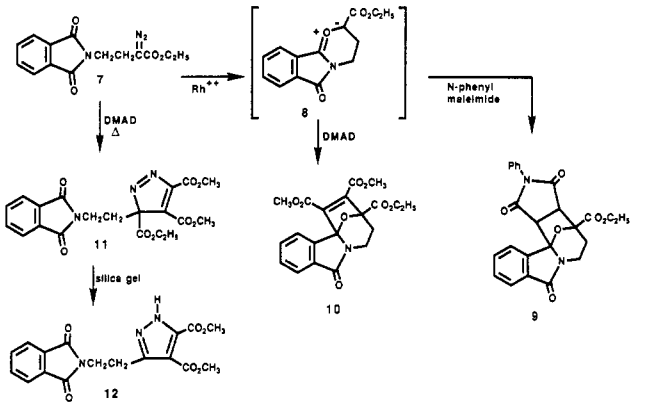
Results and Discussion

For the initial development and subsequent application of our fundamental strategy, we needed an efficient method to generate a diazo group adjacent to an ester functionality. The base-catalyzed transfer of a diazo moiety



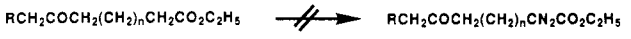
to a methylene group adjacent to one or more electron-withdrawing groups is a well-established and powerful synthetic tool.[31-36] The most commonly used reagents for diazo transfer have been *p*-toluenesulfonyl (tosyl) azide[31] or mesyl azide,[37] although examples of diazo transfer to β-dicarbonyl systems by other reagents have been reported.[38] While the diazo transfer reaction works extremely well for cases in which the reaction site is activated by two adjacent carbonyl functions, it generally fails in cases where the methylene group is activated by a single carbalkoxy group.[39] This difficulty can be overcome by treating the ester anion with ethyl formate so as to produce the diactivated species. Reaction of this material with mesyl azide now occurs, proceeding onto the desired diazo ester by a subsequent cleavage of the formyl group.

Our own investigations began with diazo phthalimide derivative **7**, which was of interest in our long-range goal of planned synthesis of alkaloids. This material was prepared in the standard way using ethyl formate and mesyl azide. Treatment of **7** with *N*-phenylmaleimide in the presence of rhodium octanoate at 25 °C afforded cycloadduct **9** in 92% yield. A similar reaction of **7** with

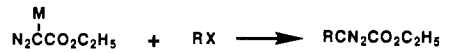


dimethyl acetylenedicarboxylate gave cycloadduct **10** (79%), which is derived from the six-ring dipole **8**. In the absence of a catalyst, **7** undergoes facile 1,3-dipolar cycloaddition with DMAD across the diazo group to give 3*H*-pyrazole **11** in high yield.[40] This material undergoes hydrolysis and decarboxylation on silica gel chromatography, affording a sample of 1*H*-pyrazole **12** in 59% yield.

Application of the (*ethyl formate activation*)–(*mesyl azide diazotization*)–(*base deformylation*) sequence to a series of simple keto esters was unsuccessful. The problem with these systems is that enolate formation adjacent to the keto group competes with ester activation, giving rise to a complex mixture of diazo compounds.



In looking for an alternate route to circumvent this problem, we were attracted by the possibility of reacting an organometallic derivative of a diazo compound with an alkyl halide to give the diazo ester in a single step. Various

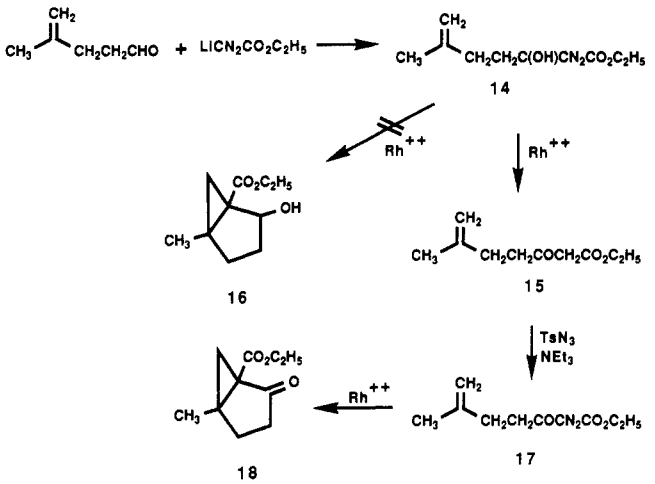


organometallic derivatives of diazo compounds are known, and ethyl diazoacetate, in particular, is easily metalated.[41] Ethyl lithiodiazoacetate is stable in solution at low temperature. This reagent has been reported to react with electrophiles such as alkyl halides, lactones, acid chlorides, and carbonyl compounds,[41-44] and therefore this seemed like a sensible method for preparing a variety of α-diazo esters.

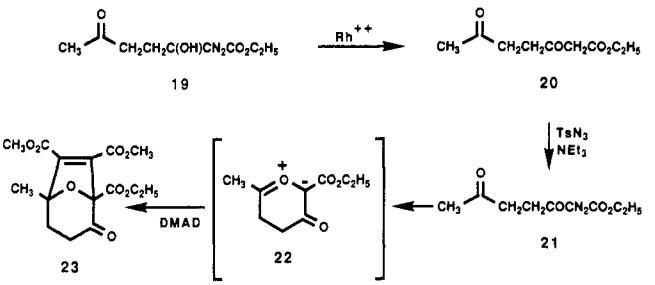
We found that commercially available ethyl diazoacetate could easily be metalated by addition to a solution of LDA in tetrahydrofuran at −110 °C. The resulting solution was treated with various alkyl halides (allyl iodide, methyl iodide, *n*-butyl bromide, benzyl bromide, etc.) and then allowed to warm to −20 °C. The reaction mixture was quenched by the addition of acetic acid followed by standard aqueous workup. Although the iodides react with ethyl lithiodiazoacetate to give the expected diazo ester

(22) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309.
(23) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, Chapter 6.
(24) Semple, J. E.; Joullie, M. M. *Heterocycles* **1980**, *14*, 1825.
(25) Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950.
(26) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2.
(27) Piers, E.; Karunaratne, V. J. *J. Org. Chem.* **1983**, *48*, 1774.
(28) Magnus, P.; Gange, D.; Bass, L.; Arnold, E. V.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *102*, 2134. Gange, D.; Magnus, P. *J. Am. Chem. Soc.* **1978**, *100*, 7746.
(29) Bruckner, C.; Reissig, H. U. *J. Org. Chem.* **1988**, *53*, 2440.
(30) Trost, B. M.; King, S. A.; Schmidt, T. *J. Am. Chem. Soc.* **1989**, *111*, 5902.
(31) Regitz, M. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 733.
(32) Taber, D. F.; Schuchardt, J. L. *J. Am. Chem. Soc.* **1985**, *107*, 5289.
(33) Chen, E. Y. *J. Org. Chem.* **1984**, *49*, 3245.
(34) Crow, W. D.; Gosney, I.; Ormiston, R. A. *J. Chem. Soc., Chem. Commun.* **1983**, 643.
(35) Adams, J. L.; Metcalf, B. W. *Tetrahedron Lett.* **1984**, 919.
(36) Regitz, M.; Menz, F. *Chem. Ber.* **1968**, *101*, 2622.
(37) Taber, D. F.; Ruckle, R. E.; Hennessy, M. J. *J. Org. Chem.* **1986**, *51*, 4077.
(38) Cavender, C. J.; Shiner, V. G. *J. Org. Chem.* **1972**, *37*, 3567. Balli, H.; Low, R.; Muller, V.; Rempfler, H.; Sezen-Gezgin, G. *Helv. Chim. Acta* **1978**, *61*, 97. Kokel, G.; Viehe, H. G. *Angew. Chem.* **1980**, *92*, 754. Hazen, G. G.; Weinstock, L. M.; Connell, R.; Bollinger, F. W. *Synth. Commun.* **1981**, *11*, 947. Lombardo, L.; Mander, L. M. *Synthesis* **1980**, 368. Herbranson, D. E.; Hawley, M. D. *J. Electroanal. Chem. Interfacial Electrochem.* **1983**, *144*, 423. Baum, J. S.; Shook, D. A.; Davies, H. M. L.; Smith, H. D. *Synth. Commun.* **1987**, *17*, 1709.
(39) Hendrickson, J. B.; Wolff, W. A. *J. Org. Chem.* **1968**, *33*, 3610.
(40) Regitz, M.; Heydt, H. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 1.
(41) For a review of organometallic derivatives of diazo compounds, see: Kruglaya, O. A.; Vyazankin, N. S. *Russ. Chem. Rev. (Engl. Transl.)* **1980**, *49*, 357.
(42) Wenkert, E.; McPherson, C. A. *J. Am. Chem. Soc.* **1972**, *94*, 8084.
(43) Nagao, K.; Chiba, M.; Kim, S. W. *Synthesis* **1983**, 197.
(44) Heslin, J. C.; Moody, C. J.; Slawin, A. M. Z.; William, D. *Tetrahedron Lett.* **1986**, 1403. Moody, C. J.; Taylor, R. J. *J. Chem. Soc., Perkin Trans 1* **1989**, 721.

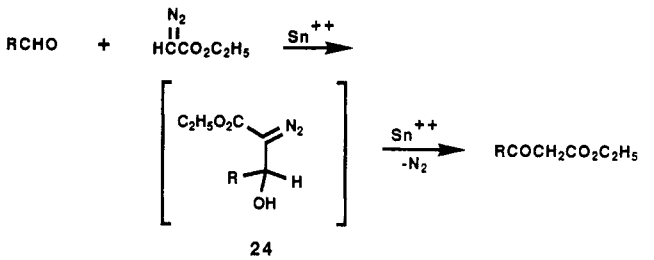
(ca. 35%), the other alkyl halides only afforded poor yields (5–20%) of the desired product. Aldehydes and ketones, on the other hand, react readily with ethyl lithiodiazoacetate to give diazo alcohols in good to excellent yield (see Experimental Section). It is well-known that unsaturated α-diazo carbonyl compounds undergo intramolecular cyclopropanation, giving access to novel bicyclic and polycyclic molecules.[1] The cyclopropane moiety formed by this intramolecular carbenoid-to-olefin addition has often been used for further transformations, such as thermal rearrangement, acid-catalyzed or nucleophilic ring-opening, and hydrogenolysis.[17] A general review of intramolecular diazo carbonyl reactions appeared in 1979,[1] and since then, many further publications on the transition-metal-catalyzed reactions have extended the scope of this methodology.[45-49] Recent work indicates that a number of catalyzed reactions of α-diazo carbonyl compounds that traditionally have been brought about by copper salts can be improved on substantially by the use of rhodium(II) carboxylates.[50-52] Consequently, this led us to study the rhodium(II) acetate catalyzed reaction of **14** with the hope that the intramolecular cyclopropanation reaction would proceed at a faster rate than the competitive 1,2-hydrogen shift pathway.[43] We found, however, that the only material produced corresponded to β-keto ester **15** derived by 1,2-hydrogen migration from the rhodium carbenoid intermediate. Similar results were also encountered with related copper catalysts.[53] It should be pointed out that diazo ester **17** does indeed undergo ready intramolecular cyclopropanation. Thus, treatment of **17** with rhodium(II) acetate gave bicyclo[3.1.0]hexan-2-one **18** in 75% yield.



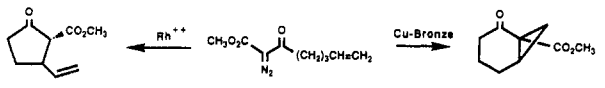
The rhodium(II)-catalyzed decomposition of diazo carbonyl compounds is believed to involve a metallocarbenoid intermediate (e.g., $R_2C{=}RhLn$) which retains the properties associated with free carbenes.[47] The carbenoid carbon is highly electrophilic and in an appropriate acyclic substrate would be expected to be intercepted intramolecularly by a suitably disposed nucleophilic atom. We reasoned that cyclization of the carbenoid center on a neighboring carbonyl group might be faster than the 1,2-hydrogen shift that was encountered with diazo ester **14**. This led us to try to prepare the closely related keto diazo ester system **19** so as to study its rhodium-catalyzed behavior. Unfortunately, all attempts to synthesize **19** using ethyl lithiodiazoacetate and 4-oxopentanal failed to give any characterizable material. Consequently, we were not able to establish whether cyclization on the more nucleophilic carbonyl group is preferred over the 1,2-hydrogen shift. In contrast to the complex mixture of products that was produced upon reaction with ethyl lithiodiazoacetate, reaction of 4-oxopentanal with ethyl diazoacetate and tin chloride afforded **20** in 85% isolated yield.[55] Diazo transfer to **20** using tosyl azide in acetonitrile in the presence of triethylamine proceeded readily to give diazo ester **21**. The rhodium(II)-induced cyclization of **19** produced carbonyl ylide dipole **22**, which was smoothly trapped with DMAD to give cycloadduct **23** in excellent yield.



While our work was in progress, Holmquist and Roskamp reported that aldehydes are efficiently converted into β-keto esters by reaction with ethyl diazoacetate in the presence of tin(II) chloride.[55] More than likely, the reaction proceeds via a transient 2-diazo-3-hydroxy ethyl ester **24** intermediate analogous to that generated by using ethyl lithiodiazoacetate. Although β-keto esters can be prepared by a variety of methods,[56] only a few of them



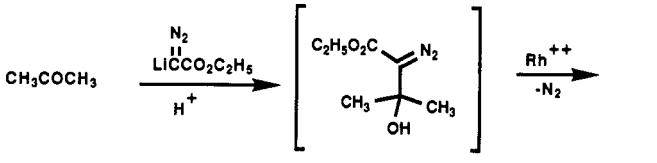
(45) Wulfman, D. S.; Poling, B. *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980; Vol. 1, p 321.
(46) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, *3*, 44. Doyle, M. P.; Tamblyn, W. H.; Bagheri, V. *J. Org. Chem.* **1981**, *46*, 5094.
(47) Anciaux, A. J.; Hubert, A. Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.
(48) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3171.
(49) Moyer, M. P.; Feldman, P. L.; Rapoport, H. *J. Org. Chem.* **1985**, *50*, 5223.
(50) Singh, A. K.; Bakshi, R. K.; Corey, E. J. *J. Am. Chem. Soc.* **1987**, *109*, 6187.
(51) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1982**, 2509.
(52) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688.
(53) Taber and co-workers[16] have noted a preference for intramolecular cyclopropanation by copper carbenoids versus insertion by rhodium carbenoids derived from the nearly identical diazo esters outlined below:[54]



(54) Taber, D. F.; Saleh, S. A.; Korsmeyer, R. W. *J. Org. Chem.* **1980**, *45*, 4699.
(55) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.
(56) Schaefer, J.; Bloomfield, J. *Org. React. (N.Y.)* **1967**, *15*, 1. Rathke, M. *Org. React. (N.Y.)* **1975**, *22*, 423. Balasubrahmanyam, S. N.; Balasubramanian, M. *Organic Syntheses*; Wiley: New York, 1973; Vol. V, p 439. Claisen, L.; Lowman, O. *Ber. Dtsch. Chem. Ges.* **1887**, *20*, 651. Kocienski, P.; Stocks, M.; Donald, D.; Cooper, M.; Manners, A. *Tetrahedron Lett.* **1988**, 4481. Pelliciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959. Pellicciari, R.; Natalini, B.; Fringuelli, R.; Ceccherelli, P. *J. Chem. Soc., Perkin Trans. 1* **1985**, 493. Wenkert, E.; McPherson, A. *J. Am. Chem. Soc.* **1972**, *94*, 8084. Ikota, N.; Takamura, N.; Young, S.; Ganem, B. *Tetrahedron Lett.* **1981**, 4163.

show high regioselectivity when applied to unsymmetrical ketones.[57-62] Recent work in the literature indicates that a number of catalyzed reactions of α-diazo carbonyl compounds that traditionally have been brought about by copper or other metal salts can be improved on substantially through the use of rhodium(II) carboxylates.[46-51] Consequently, we decided to investigate the rhodium(II) carboxylate induced rearrangement of a series of 2-diazo-3-hydroxy 3,3-disubstituted ethyl esters prepared from the reaction of several ketones with the lithiodiazoacetate. Although an earlier paper by Kim and co-workers reported on the rearrangement using various Lewis acids and metal salts, there was no mention of using a rhodium(II) carboxylate as the catalyst.[63]

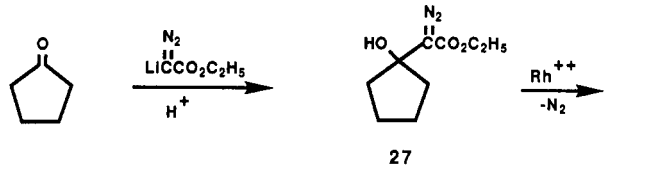
We found that the symmetrical hydroxy diazo esters **25** and **27** smoothly rearrange to the expected β-keto esters **26** and **28** in quantitative yield. The unsymmetrical alcohol **29** was regiospecifically converted to β-keto ester **30** when treated with a catalytic amount of rhodium acetate in methylene chloride. No detectable quantities of the other



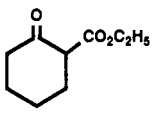
25

$CH_3COCH(CH_3)CO_2C_2H_5$

26



27



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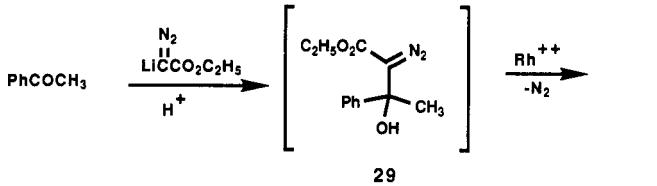
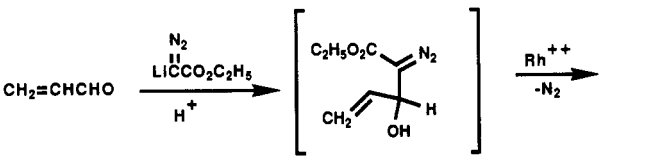


29

$CH_3COCH(Ph)CO_2C_2H_5$

30

regioisomer could be found in the crude reaction mixture. In this case, the reaction involves an exclusive phenyl shift, which is in keeping with migration to an electron-deficient center. This simple method for β-keto ester formation is further illustrated by the synthesis of ethyl 3-oxo-4-pentenoate (**32**). Very recently, Zibuck and Streiber have reported on the large-scale preparation of this interesting reagent.[64] Even though the synthesis and use of this compound as an annelating agent is well-known,[65-72] the above workers developed a short, practical synthesis of **32** that could be carried out in 100-mmol lots.[64] The procedure involves the base-induced reaction of ethyl acetate with acrolein followed by Jones oxidation. We have also been able to prepare keto ester **32** in 87% overall yield (vs 79% via the Zibuck method[64]). As shown, treatment of acrolein with ethyl lithiodiazoacetate gave alcohol **31** which, without purification, was quantitatively converted to **32** upon exposure to rhodium(II) acetate in methylene chloride at 25 °C.



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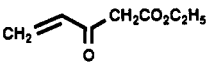
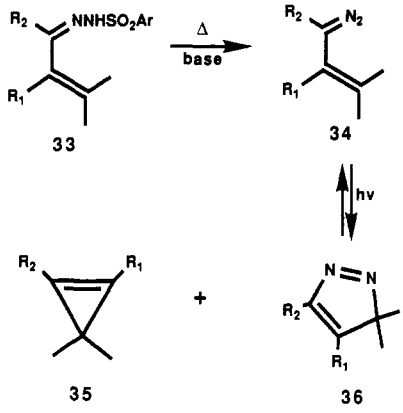


32

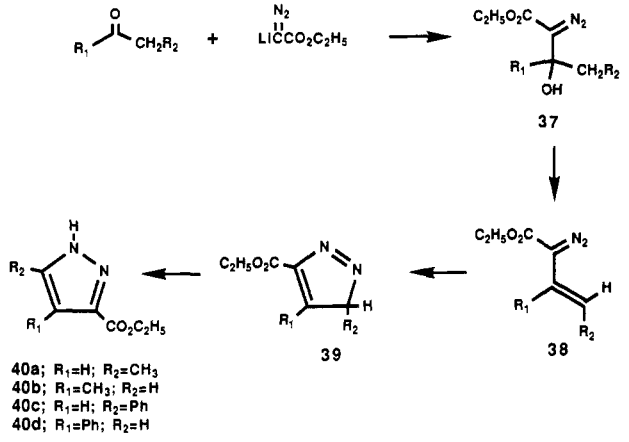
While the interaction of ethyl diazoacetate and aldehydes or ketones accompanied by nitrogen extrusion has been known for a long time,[73] there have not been many reports dealing with the chemistry of the resulting α-diazo-β-hydroxy carbonyl compounds. One observation by Wenkert is especially interesting since it suggests that these diazo hydroxy esters could be used to prepare 1*H*-pyrazoles.[42] During the course of our studies with ethyl diazoacetate and various carbonyl compounds, we found that the initially formed diazo alcohol could be readily dehydrated with phosphoryl chloride in pyridine to give vinyl diazo esters in good yield (see Experimental Section). Vinyldiazomethanes **34** are generally synthesized either by heating the tosylhydrazone salts of ketones **33** or by irradiating the corresponding 3*H*-pyrazole **36** with filtered light to avoid photochemical decomposition of the diazo compound.[74] Thermolysis of vinyldiazomethanes, on the other hand, gives 3*H*-pyrazoles **36** and cyclopropenes **35** as products.[75] The ratio of these two substrates is very dependent on the substituent pattern.[76] The 3*H*-pyrazoles **36** can also be obtained by 1,3-dipolar cycloaddition of disubstituted diazoalkanes onto electrophilic acetylenes.[77]

(57) Mock, W. L.; Hartman, M. E. *J. Org. Chem.* **1977**, *42*, 459.
(58) Hashimoto, N.; Aoyama, T.; Shioiri, T. *Tetrahedron Lett.* **1980**, 4619.
(59) Tchoubar, B. *Bull. Soc. Chim. Fr.* **1949**, 164.
(60) Taguchi, H.; Yamamoto, H.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 1588.
(61) Cohen, T.; Kuhn, D.; Falck, J. R. *J. Am. Chem. Soc.* **1975**, *97*, 4749.
(62) Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* **1976**, *41*, 2073.
(63) Nagao, K.; Chiba, M.; Kim, S. W. *Synthesis* **1983**, 197.
(64) Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717.
(65) Pelletier, S. W.; Chapopell, R. L.; Prabhakar, S. *J. Am. Chem. Soc.* **1968**, *90*, 2889. Stork, G.; Guthikonda, R. N. *J. Am. Chem. Soc.* **1972**, *94*, 5109.
(66) Wenkert, E.; Alonso, A.; Bredenberg, J.; Kaneko, C.; Tahara, A. *J. Am. Chem. Soc.* **1964**, *86*, 2038.
(67) Stork, G.; Guthikonda, R. *Tetrahedron Lett.* **1972**, *13*, 2755.
(68) Pichat, L.; Beaucourt, J. *Synthesis* **1973**, 537.
(69) Trost, B. M.; Kunz, R. A. *J. Org. Chem.* **1974**, *39*, 2648.
(70) Orisini, F.; Pelizzoni, F.; Destro, R. *Gazz. Chim. Ital.* **1978**, *108*, 693.
(71) van den Goorbergh, J.; van der Gen, A. *Tetrahedron Lett.* **1980**, 3621.
(72) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959.
(73) Curtius, T.; Buchner, E. *Ber. Dtsch. Chem. Ges.* **1885**, *178*, 2371. Schlotterbeck, F. *Ibid.* **1907**, *40*, 3000; **1909**, *42*, 2565. Dieckmann, F. *Ibid.* **1910**, *43*, 1024. Kharasch, M.; Rudy, T.; Nudenberg, W.; Buchi, G. *J. Org. Chem.* **1952**, *18*, 1030. Gutsche, C. D.; Hillman, M. *J. Am. Chem. Soc.* **1954**, *76*, 2236.
(74) Pincock, J. A.; Mathur, N. C. *J. Org. Chem.* **1982**, *47*, 3699.
(75) Brewbaker, J. L.; Hart, H. *J. Am. Chem. Soc.* **1969**, *91*, 711.
(76) Closs, G. L. In *Advances in Alicyclic Chemistry*; Hart, H., Karabatsos, G. J., Eds.; Academic Press: New York, 1966; Vol. 1, p 53.
(77) Franck-Neumann, M.; Lohmann, J. J. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 323. Buchecker, C. D.; Franck-Neumann, M. *Tetrahedron* **1983**, *39*, 1247; **1984**, *40*, 2909.



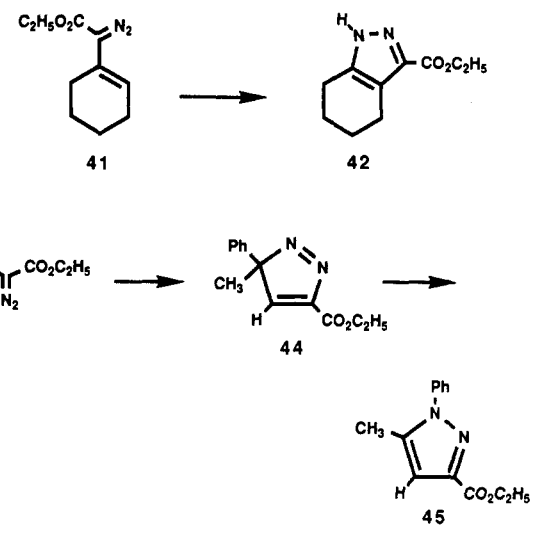
Their construction by this method, however, suffers from the same limitations present in the cycloaddition reaction with any unsymmetrical dipolarophile, namely, the difficulty in obtaining high regiochemical control.

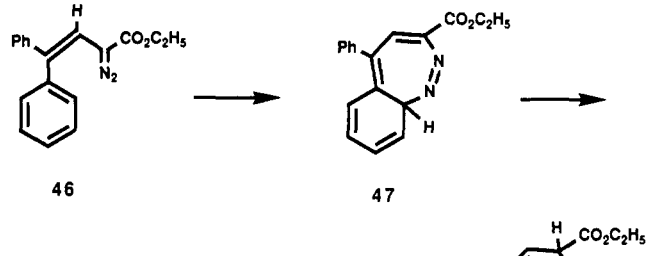
Having prepared a variety of vinyl diazo esters of type **38** by the dehydration of diazo alcohol **37**, we investigated their thermal behavior. Heating the vinyl diazo ester in



octane at 110 °C gave rise to the 1*H*-pyrazole system in excellent yield. No signs of any cyclopropenes could be detected in the crude reaction mixture. The formation of the 1*H*-pyrazole ring proceeds by an initial 6π-electrocyclization followed by a subsequent 1,5-hydrogen shift of the initially formed 3*H*-pyrazole. It should be noted that the production of five-membered rings by 6π-electrocyclization of 1,5-dipoles is well precedented and represents an important principle in heterocyclic chemistry.[78,79] An interesting aspect of this sequence is that, by varying the nature of the carbonyl group employed in the condensation reaction with ethyl lithiodiazoacetate, it is possible to prepare different regioisomeric pyrazoles (i.e., **40a** vs **40b**, or **40c** vs. **40d**). When α-methyl phenylacetaldehyde was used, the initially formed vinyl diazo ester **43** was also found to cyclize to a 1*H*-pyrazole (i.e., **45**) upon thermolysis. In this case, the transient 3*H*-pyrazole intermediate **44** undergoes the well-known van Alphen–Huttel rearrangement, which involves a 1,5-sigmatropic phenyl shift.[80,81]

In contrast to the above results, thermolysis of the diphenyl-substituted vinyl diazo ester **46** results in cyclization to provide substrate **48** in 70% yield as the exclusive product. The formation of **48** from **46** is an example of





a dipolar 1,7-electrocyclization at a benzene ring. Earlier

work from our laboratory[82] showed that 3*H*-2-benzazepines are produced from styryl nitrile ylides, and Sharp and his co-workers[84,84] have extensively investigated the formation of 3*H*-1,2-benzodiazpines from β-aryl-α,β-unsaturated diazoalkanes. Robertson and Sharp have pointed out that the helical conformation required for antarafacial 8π-electrocyclization with these systems can be easily attained.[84] In the present case, this is the preferred mode of reaction. The primary product **47** rearranges to benzodiazepine **48** by a [1,5]-shift of hydrogen.

In conclusion, the reaction of ethyl lithiodiazoacetate with aldehydes and ketones provides a simple one-step route to β-hydroxy-α-diazo esters. The subsequent rhodium carbenoid mediated reaction gives β-keto esters in excellent yield. Dehydration of the α-diazo-β-hydroxy ester, on the other hand, generates vinyl diazo esters, which readily cyclize to 1*H*-pyrazoles on thermolysis. Extension of the scope and synthetic potential of these reactions is being further investigated.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 283 infrared spectrometer. Proton NMR spectra were obtained on a Varian EM-390, a Nicolet 360, and a GE QE-300 spectrometer. ^{13}C NMR spectra were

(78) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181.
(79) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947.
(80) Van Alphen, J. *Recl. Trav. Chim. Pays-Bas* **1943**, *62*, 485.
(81) Huttel, R.; Reidl, J.; Martin, H.; Franke, K. *Chem. Ber.* **1960**, *93*, 1425.
(82) Padwa, A.; Smolanoff, J.; Tremper, A. *J. Am. Chem. Soc.* **1975**, *97*, 4682.
(83) Sharp, J. T.; Findlay, R. H.; Thorogood, P. B. *J. Chem. Soc., Perkin Trans. 1* **1975**, 102.
(84) Robertson, I. R.; Sharp, J. T. *Tetrahedron* **1984**, *40*, 3095.

recorded on an GE QE-300 (75 MHz) spectrometer. Microanalyses were performed at Atlantic Microlabs, Atlanta, GA. Mass spectra were determined with a VG MM-7070S mass spectrometer at an ionizing voltage of 70 eV.

Preparation and Rhodium(II) Octanoate Catalyzed Reaction of Ethyl 2-Diazo-4-phthalimidobutyrate (7) with *N*-Phenylmaleimide. A suspension containing 54 g of potassium phthalimide and 71 g of ethyl 4-bromobutyrate in 300 mL of dry dimethyl formamide was heated at reflux and maintained for 24 h. The reaction mixture was cooled to 25 °C, poured into water, and extracted with ether. The combined organic extracts were washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure, to give 84 g of a pale yellow solid, which was recrystallized from methylene chloride–hexane, to give 47.3 g (63%) of ethyl 4-phthalimidobutyrate as a white solid: mp 64–65 °C; IR ($CDCl_3$) 3020, 3000, 1780, 1720, 1620, 1480, 1430, 1400, 1380, 1200, 1120, 1040, 900, and 720 cm^{-1}; NMR ($CDCl_3$, 90 MHz) δ 1.23 (t, 3 H, J = 7 Hz), 1.85–2.17 (m, 2 H), 2.23–2.56 (m, 2 H), 3.77 (t, 2 H, J = 7 Hz), 4.10 (q, 2 H, J = 7 Hz), and 7.63–7.97 (m, 4 H).

To a suspension of sodium hydride (97 mg of a 60% suspension in oil) in 3 mL of dry benzene at 0 °C was added one drop of anhydrous ethanol, followed by the dropwise addition of 211 mg of the above phthalimidobutyrate and 180 mg of ethyl formate. The reaction mixture was allowed to warm to 25 °C and was stirred for 12 h, after which 490 mg of mesyl azide was introduced. Stirring was continued for 4 h, and then the mixture was quenched with water, washed with a 10% sodium hydroxide solution, dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the residue by flash silica gel chromatography using a 30% ethyl acetate–hexane mixture afforded 162 mg (69%) of ethyl 2-diazo-4-phthalimidobutyrate (7) as a yellow oil: IR (neat) 3000, 2100, 1780, 1720, 1680, 1470, 1400, 1340, 1150, 1090, 1030, 980, 950 and 720 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, 3 H, J = 7.1 Hz), 2.68 (t, 2 H, J = 6.5 Hz), 3.86 (t, 2 H, J = 6.5 Hz), 4.11 (q, 2 H, J = 7.1 Hz), and 7.30–7.47 (m, 4 H); MS 259, 220, 212, 186, 174, 160, 148, 120, and 104; HRMS calcd for $C_{14}H_{13}NO_4$ (M - N_2) 259.0844, found 259.0842.

A solution containing 113 mg of *N*-phenylmaleimide and 5 mg of rhodium(II) octanoate in 0.5 mL of methylene chloride was treated dropwise with a solution containing 37.5 mg of diazo ester 7 in 0.2 mL of methylene chloride. A deep dark red color and gas evolution ensued with each drop followed by rapid color dissipation. Removal of the solvent indicated a 95% yield of the expected cycloadduct 9 as judged by NMR spectroscopy. An analytically pure sample was obtained by recrystallization from methylene chloride–hexane followed by recrystallization from acetone, to give a white solid: mp 239–240 °C; IR ($CHCl_3$) 3100, 2890, 1795, 1760, 1740, 1720, 1610, 1510, 1480, 1420, 1390, 1300, 1290, 1250, 1200, 1080, 1020, 970, 920, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.31 (t, 3 H, J = 7.1 Hz), 2.13 (ddd, 1 H, J = 13.7, 12.1 and 6.8 Hz), 2.42 (dd, 1 H, J = 13.7 and 4.8 Hz), 3.38 (ddd, 1 H, J = 14.5, 12.1, and 4.8 Hz), 3.63 (d, 1 H, J = 7.5 Hz), 3.86 (d, 1 H, J = 7.5 Hz), 4.30 (q, 2 H, J = 7.1 Hz), 4.51 (dd, 1 H, J = 14.5 and 6.8 Hz), and 7.31–7.86 (m, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.3, 29.5, 32.4, 50.1, 52.0, 61.9, 84.7, 94.1, 122.9, 124.6, 125.8, 128.7, 128.8, 130.7, 131.1, 132.0, 136.2, 163.6, 166.8, 171.0, and 172.5. Anal. Calcd for $C_{24}H_{20}N_2O_6$: C, 66.60; H, 4.66; N, 6.48. Found: C, 66.36; H, 4.74; N, 6.41.

Rhodium(II) Octanoate Catalyzed Reaction of Ethyl 2-Diazo-4-phthalimidobutyrate (7) with Dimethyl Acetylenedicarboxylate. To a solution containing 22 mg of dimethyl acetylenedicarboxylate and 5 mg of rhodium(II) octanoate in 0.2 mL of dry methylene chloride was slowly added a solution containing 37 mg of diazo ester 7 in 0.5 mL of methylene chloride. A deep red solution ensued, which rapidly faded with each additional drop. Removal of the solvent indicated a 79% yield of the expected cycloadduct 10 by NMR analysis. An analytically pure sample was obtained by flash silica gel chromatography using a 30% ethyl acetate–hexane mixture as the eluent, to give ethyl 10,11-dicarbomethoxy-9,11a-epoxy-7,8,9,11a-tetrahydro-5-oxo-5*H*-azepino[2,1-*a*]isoindole-9-carboxylate (10) as a colorless oil: IR (neat) 2800, 1760, 1740, 1720, 1635, 1625, 1470, 1440, 1410, 1260, 1180, 1100, 1000, 960, 770, and 700 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, 3 H, J = 7.1 Hz), 2.28 (dd, 1 H, J = 13.6 and 5.6 Hz), 2.41 (ddd, 1 H, J = 13.5, 11.6, and 7.07 Hz), 3.34 (ddd, 1 H, J = 13.5, 11.6, and 5.6 Hz), 3.53 (s, 3 H), 3.88 (s, 3 H), 4.28 (q, 2 H, J = 7.1 Hz), 4.36 (dd, 1 H, J = 13.6 and 7.07 Hz), 7.53–7.63 (m, 3 H), and 7.80–7.83 (m, 1 H); MS 401 (M^+), 369, 355, 342, 328, 295, 268, 240 (base), 208, 182, 160, and 120; HRMS calcd for $C_{20}H_{19}NO_8$ 401.1110, found 401.1093. Anal. Calcd for $C_{20}H_{19}NO_8$: C, 59.83; H, 4.77; N, 3.49. Found: C, 59.78; H, 4.74; N, 3.41.

A solution containing 48 mg of diazo ester 7 and 29 mg of dimethyl acetylenedicarboxylate was stirred in 0.5 mL of deuteriochloroform for 12 h in the absence of a rhodium catalyst. Removal of the solvent left a colorless oil, whose structure was assigned as 3*H*-pyrazole 11 on the basis of its spectral properties: IR ($CDCl_3$) 3040, 2970, 1770, 1750, 1740, 1710, 1580, 1470, 1440, 1400, 1380, 1280, 1060, 1010, 960, and 880 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 1.40 (t, 3 H, J = 7.1 Hz), 3.55 (s, 3 H), 3.81 (s, 3 H), 3.55 (m, 2 H), 4.03 (t, 2 H, J = 6.5 Hz), 4.50 (q, 2 H, J = 7.1 Hz), and 7.63–7.73 (m, 4 H). The structure of the unstable 3*H*-pyrazole 11 was confirmed by isomerization to pyrazole 12 in 59% yield, which occurred upon silica gel chromatography: IR ($CHCl_3$) 3440, 2980, 1740, 1720, 1400, 1310, 1240, 1120, and 1050 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 3.32 (t, 2 H, J = 6.8 Hz), 3.83 (s, 3 H), 3.91 (s, 3 H), 4.03 (t, 2 H, J = 6.8 Hz), 7.24–7.71 (m, 2 H), and 7.78 (m, 2 H); MS 357 (M^+), 325, 296, 210, 160 (base), 122, 104, and 77; HRMS calcd for $C_{17}H_{15}N_3O_6$ 357.0960, found 357.0963. Anal. Calcd for $C_{17}H_{15}N_3O_6$: C, 57.13; H, 4.23; N, 11.76. Found: C, 57.09; H, 4.20; N, 11.64.

Preparation and Rhodium(II)-Catalyzed Reaction of Ethyl 2-Diazo-3-oxo-6-methyl-6-heptenoate (17). To a stirred solution containing 41 g of methyltrihenylphosphonium bromide in 300 mL of tetrahydrofuran was added 50 mL of 2.5 M *n*-butyllithium at room temperature. To the above solution was added 9.6 g of 4-oxo-1-pentanol, and the reaction mixture was stirred at room temperature for 4 h. The solvent was removed under reduced pressure, 200 mL of water was added, and the mixture was extracted with ether. The ether solution was dried over anhydrous sodium sulfate and the solvent was removed under reduced pressure. Vacuum distillation of the residue gave 5.38 g of 2-methyl-1-penten-5-ol (57%) as a colorless liquid:[85] IR (neat) 3370, 3080, 2960, 2890, 1650, 1450, 1380, 1070, 895, and 745 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.70–2.0 (m, 6 H), 2.20 (t, 2 H, J = 7.2 Hz), 3.75 (t, 2 H, J = 6.0 Hz), and 4.82 (s, 2 H).

To a solution containing 10.5 g of pyridinium chlorochromate in 100 mL of methylene chloride was slowly added 4.0 g of 2-methyl-1-penten-5-ol. The reaction mixture was stirred for 3 h at room temperature, and then 100 mL of ether was added. The mixture was passed through a fritted-disk Büchner funnel containing a short pad of silica gel. The residue obtained upon removal of the solvent was passed through a silica gel column using 50-mL portions of ether. The solvent was removed under reduced pressure, and distillation of the residue gave 2.8 g of 4-methyl-4-pentenal (75%) as a colorless oil: IR (neat) 3090, 2990, 2920, 2840, 2740, 1730, 1660, 1450, 1390, 1080, and 900 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.74 (s, 3 H), 2.18 (t, 2 H, J = 7.6 Hz), 2.60 (t, 2 H, J = 7.6 Hz), 4.68 (s, 1 H), 4.76 (s, 1 H), and 9.78 (s, 1 H).

A solution of ethyl lithiodiazoacetate was prepared in the standard manner and was allowed to react with 4-methyl-4-pentenal at −78 °C. After being stirred for 2 h, the mixture was quenched with a saturated ammonium chloride solution. Removal of the solvent after drying over magnesium sulfate left a crude oil, whose NMR spectrum showed the presence of at least three compounds. Extensive silica gel chromatography afforded ethyl 2-diazo-3-hydroxy-6-methyl-6-heptenoate (14) as a clear oil in 30% yield: NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7.0 Hz), 1.62 (s, 3 H), 1.95–2.15 (m, 4 H), 2.85 (d, 1 H, J = 4.5 Hz), 4.24 (q, 2 H, J = 7.0 Hz), and 4.93 (m, 1 H). The above oil was treated with a catalytic amount of rhodium(II) acetate in methylene chloride at 25 °C for 1 h. Workup in the standard manner afforded a 96% yield of a colorless oil, whose structure was assigned as ethyl 6-methyl-3-oxo-6-heptenoate (15):[86] IR (neat) 3090, 2990, 2940, 1750, 1715, 1650, 1450, 1370, 1320, 1250, 1190, 1030, and 900 cm^{-1}; NMR (300 MHZ, $CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz), 1.71 (s, 3 H), 2.28 (t, 2 H, J = 7.2 Hz), 2.67 (t, 2 H, J = 7.2 Hz),

(85) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981.

(86) Rao, V. B.; George, C. F.; Wolff, S.; Agosta, W. *J. Am. Chem. Soc.* **1985**, *107*, 5732.

3.43 (s, 2 H), 4.17 (q, 2 H, J = 7.2 Hz), 4.64 (s, 1 H), and 4.72 (s, 1 H). This same keto ester was also prepared in 98% yield by treating 4-methyl-4-pentenal with ethyl diazoacetate in the presence of tin(II) chloride.

A solution containing 0.7 g of keto ester **15**, 1.24 g of triethylamine, and 0.8 g of tosyl azide in 10 mL of acetonitrile was stirred for 2 h at room temperature. The solvent was removed under reduced pressure, and the crude residue was triturated with ether. The resulting solution was washed with a solution containing 0.3 g of potassium hydroxide in 40 mL of water. The aqueous phase was extracted with ether, and the combined ether extracts were washed with a brine solution and dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was chromatographed on a flash silica gel column using a 5:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 0.73 g (95%) of a yellow oil, whose structure was assigned as ethyl 2-diazo-3-oxo-6-methyl-6-heptenoate (**17**): IR (neat) 3090, 2990, 2940, 2120, 1720, 1660, 1650, 1450, 1380, 1300, 1210, 1130, 890, and 750 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3 H, J = 7.2 Hz), 1.73 (s, 3 H), 2.32 (t, 2 H, J = 7.6 Hz), 2.97 (t, 2 H, J = 7.6 Hz) 4.28 (q, 2 H, J = 7.2 Hz), 4.67 (s, 1 H), and 4.72 (s, 1 H).

A mixture containing 200 mg of the above diazo ester in 2 mL of methylene chloride together with a catalytic amount of rhodium(II) acetate was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a flash silica gel column using a 3:1 hexane–ether mixture as the eluent. The major fraction isolated contained 130 mg (75%) of a colorless oil, whose structure was assigned as ethyl 2-oxo-5-methylbicyclo[3.1.0]hexane-1-carboxylate (**18**): IR (neat) 2990, 2940, 2880, 1730, 1450, 1375, 1250, 1190, 1060, 1000, and 870 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz), 1.30 (s, 3 H), 1.35 (d, 1 H, J = 5.1 Hz), 1.83 (d, 1 H, J = 5.1 Hz), 1.86–2.2 (m, 4 H), and 4.12 (dq, 2 H, J = 7.2 Hz and 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 17.9, 25.7, 28.3, 34.0, 40.4, 44.2, 61.0, 167.2, and 207.7; HRMS calcd for $C_{10}H_{14}O_3$ 182.0943, found 182.0941.

Preparation and Rhodium(II)-Catalyzed Behavior of Ethyl 2-Diazo-3,6-dioxoheptanoate (21). To a stirred solution containing 11.75 g of pyridinium chlorochromate in 100 mL of methylene chloride was slowly added 3.71 g of 1-hydroxy-4-pentanone at room temperature, and the solution was stirred at 25 °C for 2 h. The mixture was passed through a fritted-disk Büchner funnel using a short pad of silica gel. The residue was washed through the column with 50-mL portions of ether. The solvent was removed under reduced pressure, and the residue was rechromatographed on a flash silica gel column using a 4:1 hexane–ethyl acetate mixture as the eluent, to give 2.83 g (78%) of 4-oxopentanal:[87] NMR (90 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.75 (s, 4 H), and 9.85 (s, 1 H).

To a stirred solution containing 505 mg of ethyl diazoacetate in 8 mL of methylene chloride and 84 mg of tin(II) chloride was added 500 mg of 4-oxopentanal in 2 mL of methylene chloride. Nitrogen evolution occurred immediately. The solution was stirred for 2 h, and then the reaction mixture was transferred to a separatory funnel and washed with a saturated brine solution. The organic layers was extracted with ether and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The resulting residue was purified by flash silica gel column chromatography using a 4:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 700 mg (85% yield) of a colorless oil, whose structure was assigned as ethyl 3,6-dioxoheptanoate (**20**): IR (neat) 3600, 2990, 2910, 1740, 1710, 1640, 1410, 1370, 1310, 1190, and 1030 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3 H, J = 7.2 Hz), 2.13 (s, 3 H), 2.65–2.80 (m, 4 H), 3.44 (s, 2 H), and 4.13 (q, 2 H, J = 7.2 Hz).

A solution containing 1.0 g of the above material, 2.2 g of tosyl azide, and 3.1 g of triethylamine in 20 mL of acetonitrile was stirred at room temperature for 4 h according to the general procedure of Regitz.[36] The solvent was removed under reduced pressure, and the residue was triturated with ether. The resulting solution was washed with a 5% aqueous potassium hydroxide solution followed by a saturated brine solution. The solvent was removed under reduced pressure, and the residue was chromatographed on a flash silica gel column using a 3:1 hexane–ethyl acetate mixture as the eluent, to give 1.5 g (70% yield) of ethyl 2-diazo-3,6-dioxoheptanoate (**21**): IR (neat) 2990, 2920, 2120, 1720, 1660, 1450, 1370, 1300, 1130, 1020, and 750 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7.2 Hz), 2.16 (s, 3 H), 2.73 (t, 2 H, J = 6.0 Hz), 3.03 (t, 2 H, J = 6.0 Hz), and 4.25 (q, 2 H, J = 7.2 Hz).

A solution containing 204 mg of the above diazo keto ester and 211 mg of dimethyl acetylenedicarboxylate in 2 mL of toluene was heated to 85 °C. After heating for 5 min, a catalytic amount of rhodium(II) acetate dimer was added. Nitrogen evolution occurred immediately. After being heated for an additional 15 min, the reaction mixture was cooled and the solvent was removed under reduced pressure. The residue was purified by silica gel chromatography using 3:1 hexane–ethyl acetate mixture as the eluent, to give 312 mg (91%) of the expected 1:1 cycloadduct **23** as a thick oil: IR (neat) 2990, 2960, 1730, 1640, 1440, 1380, 1310, 1200, 1100, and 790 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz), 1.67 (s, 3 H), 2.21–2.42 (m, 2 H), 2.50 (ddd, 1 H, J = 17.7, 6.0, and 0.9 Hz), 2.84 (dt, 1 H, J = 17.7 and 9.0 Hz), 3.79 (s, 3 H), 3.80 (s, 3 H), and 4.20–4.40 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 22.4, 32.8, 34.1, 52.6, 52.7, 62.5, 87.7, 93.2, 138.6, 142.5, 161.4, 163.1, 163.2, and 194.4; HRMS calcd for $C_{15}H_{18}O_8$ 326.1001, found 326.0998.

Preparation and Rhodium(II) Acetate Catalyzed Reaction of Ethyl 2-Diazo-3-hydroxy-3-methylbutanoate (25). To a solution containing 5 mL of acetone and 2.0 g of ethyl diazoacetate in 10 mL of dry tetrahydrofuran at −78 °C was added a lithium diisopropylamide solution prepared from 10 mL of a 2.5 M n-butyllithium solution and 3.0 g of diisopropylamine in 5 mL of tetrahydrofuran at −78 °C. The solution was stirred for 1 h at −78 °C and was then quenched by the rapid addition of 20 mL of a 29% aqueous ammonium chloride solution. The reaction mixture was extracted with ether and washed with a saturated sodium bicarbonate solution followed by a brine solution. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a flash silica gel column using a 4:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 2.26 g (75%) of a yellow oil, whose structure was assigned as ethyl 2-diazo-3-hydroxy-3-methylbutanoate (**25**):[88] IR (neat) 3480, 2995, 2945, 2105, 1680, 1460, 1375, 1310, 1080, and 750 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz), 1.47 (s, 6 H), 3.80 (s, 1 H), and 4.19 (q, 2 H, J = 7.2 Hz).

A solution containing 203 mg of the above diazo ester in 2 mL of methylene chloride together with a catalytic amount of rhodium(II) acetate under a nitrogen atmosphere was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the resulting residue consisted of a colorless liquid, whose structure was assigned as ethyl 2-methyl-3-oxobutanoate (**26**) on the basis of its spectral properties:[89] IR (neat) 2990, 2960, 1730, 1715, 1450, 1370, 1260, 1100, and 800 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.20 (t, 3 H, J = 7.2 Hz), 1.29 (d, 3 H, J = 7.2 Hz), 2.19 (s, 3 H), 3.45 (q, 1 H, J = 7.2 Hz), and 4.15 (q, 2 H, J = 7.2 Hz).

Preparation and Rhodium(II)-Catalyzed Reaction of Ethyl 2-Diazo-2-(1-hydroxycyclopentyl)acetate (27). To a stirred solution containing 3.0 g of cyclopentanone and 2.0 g of ethyl diazoacetate in 10 mL of tetrahydrofuran was added a solution of lithium diisopropylamide prepared from 12 mL of a 2.5 M n-butyllithium solution and 3.2 g of diisopropylamine in 5 mL of tetrahydrofuran at −78 °C. The mixture was stirred for 60 min at −78 °C and was then quenched by the rapid addition of 20 mL of a 29% aqueous ammonium chloride solution. The reaction mixture was extracted with ether and washed with a saturated sodium bicarbonate solution followed by a brine solution. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a flash silica gel column using a 5:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 2.94 g (85%) of a yellow oil, whose structure was assigned as ethyl 2-diazo-2-(1-hydroxycyclopentyl)acetate (**27**): IR (neat) 3480, 2980, 2890, 2105, 1690, 1440, 1370, 1300, 1110, and 750 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz),

(87) Aasen, A. J.; Nishidia, T.; Enzell, C. R.; Devreux, M. *Acta Chem. Scand., Ser. B* **1976**, *B30*, 178.

(88) Callot, H. J.; Schaeffer, E. *J. Organomet. Chem.* **1978**, *145*, 91.

(89) Makoto, F.; Tamejiro, H. *J. Am. Chem. Soc.* **1985**, *107*, 8294.

1.65–1.90 (m, 6 H), 1.95–2.10 (m, 2 H), 3.27 (s, 1 H), and 4.22 (q, 2 H, J = 7.2 Hz).

A solution containing 222 mg of the above diazo ester in 2 mL of methylene chloride together with a catalytic amount of rhodium(II) acetate dimer was stirred under a nitrogen atmosphere for 15 min. The reaction was complete after 15 min. The solvent was removed under reduced pressure, and the colorless oil obtained (100%) was assigned as 2-carbethoxycyclohexanone (**28**) on the basis of its spectral properties:[90] IR (neat) 3500, 2960, 2880, 1720, 1660, 1620, 1450, 1410, 1370, 1310, 1220, 1090, and 840 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3 H, J = 7.2 Hz), 1.51–1.72 (m, 4 H), 2.15–2.30 (m, 4 H), 4.18 (q, 2 H, J = 7.2 Hz), and 12.23 (s, 1 H).

Preparation and Rhodium(II) Acetate Catalyzed Reaction of Ethyl 2-Diazo-3-hydroxy-3-phenylbutanoate (29). To a solution containing 1.0 g of acetophenone and 1.0 g of ethyl diazoacetate in 10 mL of tetrahydrofuran was added a lithium diisopropylamide solution prepared from 5 mL of 2.5 M n-butyllithium and 1.3 g of diisopropylamine in 5 mL of tetrahydrofuran at −78 °C. The solution was stirred for 1 h under a nitrogen atmosphere at −78 °C and was then quenched by the rapid addition of 20 mL of a 29% aqueous ammonium chloride solution. The reaction mixture was extracted with ether, and the ether extracts were washed with a saturated sodium bicarbonate solution followed by brine. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a flash silica gel column using a 10:1 hexane–ethyl acetate mixture as the eluent, to give 0.97 g of ethyl 2-diazo-3-hydroxy-3-phenylbutanoate (**29**) (67% yield): IR (neat) 3500, 3070, 2994, 2940, 2105, 1690, 1600, 1500, 1450, 1376, 1310, 1080, 770, and 710 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.21 (t, 3 H, J = 7.2 Hz), 1.69 (s, 3 H), 4.15 (q, 2 H, J = 7.2 Hz), 4.33 (s, 1 H), and 7.1–7.3 (m, 5 H).

A solution containing 206 mg of the above diazo ester in 2 mL of methylene chloride together with a catalytic amount of rhodium(II) acetate dimer was stirred for 1 h at room temperature. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a flash silica gel column using a 10:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 136 mg (75%) of a colorless oil, whose structure was assigned as ethyl 2-phenyl-3-oxobutanoate (**30**) on the basis of its spectral properties:[91] IR (neat) 3080, 2995, 2945, 1730, 1640, 1500, 1460, 1400, 1375, 1270, 1150, 1030, 860, 745, and 710 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz), 2.17 (s, 3 H), 4.19 (q, 2 H, J = 7.2 Hz)8 4.68 (s, 1 H), and 7.1–7.4 (m, 5 H).

Preparation and Rhodium(II) Acetate Catalyzed Reaction of Ethyl 2-Diazo-3-hydroxy-4-pentenoate (31). To a sample containing 1.1 g of acrolein at −78 °C in 10 mL of tetrahydrofuran was added 1.0 g of ethyl diazoacetate. After stirring for several minutes, a lithium diisopropylamide solution (prepared from 5 mL of a 2.5 M n-butyllithium solution and 1.2 g of diisopropylamine in 5 mL of tetrahydrofuran) was added dropwise at −78 °C under a nitrogen atmosphere. The solution was stirred for 1 h and was then quenched with 20 mL of a 29% aqueous ammonium chloride solution. The reaction mixture was extracted with ether, and the ether extracts were washed with a saturated sodium bicarbonate solution followed by a brine solution. The solvent was removed under reduced pressure, and the crude residue was chromatographed on a silica gel column using a 4:1 hexane–ethyl acetate mixture as the eluent. The major fraction contained 1.30 g (87%) of a yellow oil, whose structure was assigned as ethyl 2-diazo-3-hydroxy-4-pentenoate (**31**): IR (neat) 3460, 2990, 2920, 2105, 1685, 1460, 1380, 1295, 1105, 940, and 750 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.26 (t, 3 H, J = 7.2 Hz), 3.07 (s, 1 H), 4.22 (q, 2 H, J = 7.2 Hz), 5.20–5.35 (m, 2 H), 5.45 (d, 1 H, J = 17.4 Hz), and 5.80–6.0 (m, 1 H).

A solution containing 265 mg of the above diazo ester in 2 mL of methylene chloride together with a catalytic amount of rhodium(II) acetate dimer under a nitrogen atmosphere was stirred for 30 min at room temperature. The solvent was removed under reduced pressure, and the colorless oil that was obtained (100%) was identified as ethyl 3-oxo-4-pentenoate (**32**):[64] IR (neat) 2990, 2940, 1746, 1662, 1590, 1425, 1240, 1155, and 820 cm^{-1}; NMR (300 MHz, $CDCl_3$) δ 1.24 (t, 3 H, J = 7.2 Hz), 3.60 (s, 2 H) 4.17 (q, 2 H, J = 7.2 Hz), and 5.9–6.5 (m, 3 H).

General Procedure for the Preparation of Ethyl 2-Diazo-3-hydroxy Carboxylates and Their Conversion to Vinyl Diazo Carboxylates. A solution containing 5.47 g (47 mmol) of ethyl diazoacetate in 150 mL of anhydrous ether and 50 mL of dry tetrahydrofuran was cooled to −110 °C, and 33.6 mL (47 mmol) of a 1.4 M n-butyllithium solution at −78 °C was added to this mixture over a period of 30 min. A solution containing 47 mmol of the freshly distilled aldehyde or ketone in 30 mL of dry tetrahydrofuran was cooled to −70 °C and was then added to the above reaction mixture at −110 °C over a period of 30 min. The mixture was allowed to warm to −25 °C, and a solution containing 2.85 g (47 mmol) of glacial acetic acid in 30 mL of dry tetrahydrofuran, cooled to −20 °C, was added. After warming of the solution to room temperature, the solvent was removed under reduced pressure and the residue was extracted with petroleum ether. The solvent was removed under reduced pressure, to leave behind a red oil. This material was purified by flash silica gel chromatography using a 20% ethyl acetate–hexane mixture as the eluent, to give the pure ethyl 2-diazo-3-hydroxy carboxylate.

To a cooled (−5 to −10 °C) solution containing 10 mmol of the appropriate diazo alcohol in 40 mL of pyridine was added 40 mmol of phosphoryl chloride with stirring. The resulting mixture was stirred at 0 °C for 6 h and at room temperature for an additional 12 h. The mixture was then poured into 100 mL of pentane, and 200 mL of ice–water was added. The pentane layer was separated, and the aqueous layer was extracted with pentane. The combined organic extracts were washed with water, dried over sodium sulfate, and evaporated under reduced pressure, to leave behind an orange oil. The vinyl diazo compound was generally pure enough to be used for the next step although it could be further purified by flash chromatography using a 2% acetone–hexane mixture as the eluent if needed.

Preparation of Ethyl 5-Methyl-1*H*-pyrazole-3-carboxylate (40a). Ethyl 2-diazo-3-hydroxypentanoate (**37a**) was obtained in 73% yield by using 2.73 g of propionaldehyde: NMR (CCl_4, 60 MHz) δ 1.02 (t, 3 H, J = 7.0 Hz), 1.33 (t, 3 H, J = 7.0 Hz), 1.42–1.88 (m, 2 H), 3.79 (br s, 1 H), 4.22 (q, 2 H, J = 7.0 Hz), and 4.68 (m, 1 H); IR (neat) 3610–3205, 3030–2815, 2100, 1705, 1455, 1375, 1300, 1130, 1085, 1015, 950, and 770 cm^{-1}. Ethyl 2-diazo-3-pentenoate (**38a**) was prepared (63%) by the dehydration of 3.44 g of the above alcohol: NMR (CCl_4, 60 MHz) δ 1.31 (t, 3 H, J = 7.0 Hz), 1.85 (d, 3 H, J = 5.5 Hz), 4.21 (q, 2 H, J = 7.0 Hz), and 4.95–5.95 (m, 2 H); IR (neat) 3050–2830, 2080, 1705, 1460, 1375, 1340, 1260, 1175, 1125, 1020, 975, and 780 cm^{-1}.

A solution containing 0.8 g (5.2 mmol) of ethyl 2-diazo-3-pentenoate (**38a**) in 16 mL of n-octane was heated at 110 °C for 1 h. The solution was cooled, and the solvent was removed under reduced pressure. The residue was triturated with hexane, to give 0.7 g of a white crystalline solid (88%), whose structure is assigned as ethyl 5-methyl-1*H*-pyrazole-3-carboxylate (**40a**): mp 81–82 °C; NMR ($CDCl_3$, 60 MHz) δ 1.32 (t, 3 H, J = 7.5 Hz), 2.38 (s, 3 H), 4.18 (q, 2 H, J = 7.5 Hz), 6.58 (s, 1 H), and 11.90 (br s, 1 H); IR ($CHCl_3$) 3390–2705, 1720, 1565, 1475, 1360, 1300, 1265, 1125, 1020, and 990 cm^{-1}; UV (95% ethanol) 218 (ϵ 9700) and 235 nm (5500); MS m/e 154 (M^+), 108, 82, 80, 79, 66, and 54. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.58; H, 6.54; N, 18.14.

Preparation of Ethyl 4-Methyl-1*H*-pyrazole-3-carboxylate (40b). Ethyl 2-diazo-3-hydroxy-3-methylbutyrate (**37b**) was prepared in 84% yield by using 2.7 g of acetone: NMR (CCl_4, 90 MHz) δ 1.29 (t, 3 H, J = 7.0 Hz), 1.45 (s, 6 H), 3.76 (s, 1 H), and 4.26 (q, 2 H, J = 7.0 Hz); IR (neat) 3705–3225, 3075–2900, 2150, 1695, 1460, 1380, 1315, 1190, 1075, 950, 860, and 770 cm^{-1}. Ethyl 2-diazo-3-methyl-3-butenoate (**38b**) was obtained (89%) by the dehydration of 6.9 g of the above alcohol: NMR (CCl_4, 90 MHz) δ 1.28 (t, 3 H, J = 7.5 Hz), 1.91 (d, 3 H, J = 1.0 Hz), 4.22 (q, 2 H, J = 7.5 Hz), 4.86 (q, 1 H, J = 1.0 Hz), 5.30 (s, 1 H); IR (neat) 3125–2855, 2120, 1715, 1620, 1450, 1380, 1350, 1260, 1080, 870, and 770 cm^{-1}.

A solution containing 5.5 g (35 mmol) of ethyl 2-diazo-3-methyl-3-butenoate (**38b**) in 110 mL of n-octane was heated at 110 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. The white solid that precipitated out of solution was recrystallized from benzene, to give 4.5 g (82%) of ethyl 4-methyl-1*H*-pyrazole-3-carboxylate (**40b**): mp 156–157 °C; NMR

(90) Kagan, H. B.; Suen, Y. H. *Bull. Soc. Chim. Fr.* **1966**, 1819.
(91) Wamhoff, H.; Hoffer, G.; Lander, H.; Korte, K. *Justus Liebigs Ann. Chem.* **1969**, *722*, 12.

($CDCl_3$, 90 MHz) δ 1.37 (t, 3 H, J = 7.0 Hz), 2.27 (s, 3 H), 4.42 (q, 2 H, J = 7.0 Hz), 7.46 (s, 1 H), and 11.10 (br s, 1 H); IR ($CHCl_3$) 3470, 3400–2860, 1715, 1565, 1430, 1350, 1305, 1120, and 1065 cm^{-1}; UV (95% ethanol) 221 (ε 8100) and 241 nm (5600); MS m/e 154 (M^+), 125, 109, and 81. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.50; H, 6.56; N, 18.09.

Preparation of Ethyl 5-Phenyl-1*H*-pyrazole-3-carboxylate (40c). Ethyl 2-diazo-3-hydroxy-4-phenylbutyrate (**37c**) was prepared in 68% yield from 5.64 g of phenylacetaldehyde: NMR (CCl_4, 90 MHz) δ 1.19 (t, 3 H, J = 7.5 Hz), 2.89 (d, 2 H, J = 7.0 Hz), 3.51 (d, 1 H, J = 4.5 Hz), 4.12 (q, 2 H, J = 7.5 Hz), 4.76 (dt, 1 H, J = 7.0 and 4.5 Hz), and 7.19 (m, 5 H); IR (neat) 3705–3225, 3175–2795, 2140, 1695, 1505, 1460, 1390, 1300, 1125, 740, and 685 cm^{-1}. Ethyl 2-diazo-4-phenyl-3-butenoate (**38c**) was prepared (58%) by the dehydration of 5.0 g of the above alcohol: NMR (CCl_4, 90 MHz) δ 1.26 (t, 3 H, J = 7.0 Hz), 4.25 (q, 2 H, J = 7.0 Hz), 6.23 (AB, 2 H, J = 16.0 Hz), and 7.02–7.36 (m, 5 H); IR (neat) 3145–2900, 2150, 1715, 1635, 1450, 1375, 1315, 1250, 1110, 945, and 730 cm^{-1}.

A solution containing 0.8 g (3.7 mmol) of ethyl 2-diazo-4-phenyl-3-butenoate (**38c**) in 16 mL of n-octane was heated at 110 °C for 1 h and cooled to 25 °C, and the solvent was concentrated under reduced pressure. The white solid that precipitated from the solution on cooling was filtered, washed with hexane, and recrystallized from benzene, to give 0.65 g (82%) of ethyl 5-phenyl-1*H*-pyrazole-3-carboxylate (**40c**): mp 138–139 °C; NMR ($CDCl_3$, 90 MHz) δ 1.31 (t, 3 H, J = 7.0 Hz), 4.37 (q, 2 H, J = 7.0 Hz), 7.25 (s, 1 H), and 7.45–8.05 (m, 5 H); IR ($CHCl_3$) 3390–2780, 1720, 1565, 1350, 1335, 1100, 1010, and 910 cm^{-1}; UV (95% ethanol) 225 (ε 17 500) and 247 nm (18 000). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.65; H, 5.64; N, 12.92.

Preparation of Ethyl 4-Phenyl-1*H*-pyrazole-3-carboxylate (40d). Ethyl 2-diazo-3-hydroxy-3-phenylbutyrate (**37d**) was prepared in 90% yield by using 5.64 g of acetophenone: NMR (CCl_4, 90 MHz) δ 1.17 (t, 3 H, J = 7.0 Hz), 1.6 (s, 3 H), 4.12 (q, 2 H, J = 7.0 Hz), 4.17 (br s, 1 H), and 7.2–7.95 (m, 5 H); IR (neat) 3705–3280, 3175–2860, 2120, 1695, 1590, 1450, 1365, 1110, 1050, 910, 760, and 690 cm^{-1}. Ethyl 2-diazo-3-phenyl-3-butenoate (**38d**) was prepared (60%) by the dehydration of 2.7 g of the above alcohol: NMR (CCl_4, 90 MHz) δ 1.27 (t, 3 H, J = 7.5 Hz), 4.22 (q, 2 H, J = 7.5 Hz), 5.19 (s, 1 H), 5.78 (s, 1 H), and 7.29 (s, 5 H); IR (neat) 3125–2860, 2130, 1715, 1640, 1605, 1450, 1370, 1250, 1125, 1055, 875, 745, and 700 cm^{-1}.

A solution containing 0.83 g (3.8 mmol) of ethyl 2-diazo-3-phenyl-3-butenoate (**38d**) in 17 mL of n-octane was heated at 110 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. The white crystalline solid that precipitated was recrystallized from benzene, to give 0.5 g (61%) of ethyl 4-phenyl-1*H*-pyrazole-3-carboxylate (**40d**): mp 164–165 °C; NMR ($CDCl_3$, 90 MHz) δ 1.25 (t, 3 H, J = 7.0 Hz), 4.34 (q, 2 H, J = 7.0 Hz), 7.2–7.65 (m, 5 H), 7.83 (s, 1 H), and 10.60 (br s, 1 H); IR ($CHCl_3$) 3470, 3390–2700, 1725, 1615, 1565, 1460, 1380, 1350, 1300, 1155, 1125, 1000, and 915 cm^{-1}; UV (95% ethanol) 234 (ε 7700) and 257 nm (6100); MS m/e 216 (M^+), 170, 114, 89, 77, 63. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.61; H, 5.65; N, 12.88.

Preparation of Ethyl 4,5-Cyclohexa-1*H*-pyrazole-3-carboxylate (42). Ethyl 2-diazo-2-(1-hydroxycyclohexyl)acetate was prepared in 89% yield by using 4.6 g of the cyclohexanone: NMR (CCl_4, 90 MHz) δ 1.20 (t, 3 H, J = 7.0 Hz), 1.2–1.91 (m, 10 H), 3.48 (s, 1 H), and 4.25 (q, 2 H, J = 7.0 Hz); IR (neat) 3705–3205, 3080–2840, 2130, 1695, 1370, 1325, 1170, 1100, 1030, 960, 895, 850, 780, and 740 cm^{-1}. Ethyl 2-diazo-2-(1-cyclohexenyl)acetate (**41**) was prepared (80%) by the dehydration of 8.8 g of the above alcohol: NMR (CCl_4, 90 MHz) δ 1.25 (t, 3 H, J = 7.0 Hz), 1.45–1.89 (m, 4 H), 1.99–2.3 (m, 4 H), 4.18 (q, 2 H, J = 7.0 Hz), and 5.92–6.11 (m, 1 H); IR (neat) 3080–2840, 2130, 1720, 1450, 1385, 1325, 1250, 1150, 1025, 915, 785, and 755 cm^{-1}.

A solution containing 4.7 g (24 mmol) of ethyl 2-diazo-2-(1-cyclohexenyl)acetate (**41**) in 94 mL of octane was heated at 110 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. The white crystalline solid that precipitated was recrystallized from hexane, to give 3.0 g (65%) of ethyl 4,5-cyclohexa-1*H*-pyrazole-3-carboxylate (**42**): mp 90–91 °C; NMR ($CDCl_3$, 90 MHz) δ 1.31 (t, 3 H, J = 7.5 Hz), 1.65–1.9 (m, 4 H), 2.59–2.87 (m, 4 H), 4.35 (nq, 2 H, J = 7.5 Hz), and 10.8 (br s, 1 H); IR ($CHCl_3$) 3510, 3450–3080, 3050–2800, 1720, 1570, 1470, 1400, 1280–1160, 1135, and 1000 cm^{-1}; UV (95% ethanol) 221 (ε 8100) and 241 nm (5600); MS m/e 154 (M^+), 125, 109, 81. Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.50; H, 6.56; N, 18.09.

Preparation of Ethyl 5-Methyl-1-phenyl-1*H*-pyrazole-3-carboxylate (45). Ethyl 2-diazo-3-hydroxy-4-phenylpentanoate was prepared in 62% yield by using 6.3 g of 2-phenylpropionaldehyde: NMR (CCl_4, 60 MHz) δ 1.10 (t, 3 H, J = 7.0 Hz), 1.32 (d, 3 H, J = 7.5 Hz), 2.91 (oct, 1 H, J = 7.5 Hz), 3.82 (d, 1 H, J = 5.0 Hz), 4.03 (q, 2 H, J = 7.0 Hz), 4.62 (dd, 1 H, J = 7.0 and 5.0 Hz), and 7.28 (br s, 5 H); IR (neat) 3625–3205, 3030–2810, 2100, 1755, 1680, 1495, 1450, 1370, 1300, 1125, 1010, 920, 765, and 700 cm^{-1}. Ethyl 2-diazo-4-phenyl-3-pentenoate (**43**) was prepared (71%) by the dehydration of 4.1 g of the above alcohol: NMR (CCl_4, 90 MHz) δ 1.25 (t, 3 H, J = 7.0 Hz), 2.17 (s, 3 H), 4.18 (q, 2 H, J = 7.0 Hz), 5.59 (s, 1 H), and 7.09–7.5 (m, 5 H); IR (neat) 3125–2840, 2090, 1695, 1450, 1370, 1280, 1190, 1125, 1030, 745, and 700 cm^{-1}.

A solution containing 0.46 g (2 mmol) of ethyl 2-diazo-4-phenyl-3-pentenoate (**43**) in 9.2 mL of n-octane was heated at 110 °C for 1 h and cooled to 25 °C, and the solvent was removed under reduced pressure. The residue was purified by flash silica gel chromatography using a 1% acetone–hexane mixture as the eluent, to give 0.4 g (87%) of ethyl 5-methyl-1-phenyl-1*H*-pyrazole-3-carboxylate (**45**) as a yellow oil: bp 73 °C (0.03 mm); NMR (CCl_4), 90 MHz) δ 1.15 (t, 3 H, J = 7.0 Hz), 2.09 (d, 3 H, J = 1.0 Hz), 4.02 (q, 2 H, J = 7.0 Hz), 6.08 (q, 1 H, J = 1.0 Hz), and 7.07–7.6 (m, 5 H); IR (neat) 3115–2790, 1735, 1470, 1380, 1300, 1280–1205, 1100, 1030, 890, 770, 730, and 700 cm^{-1}; UV (95% ethanol) 222 (ε 12 000) and 254 nm (7000); MS m/e 230 (M^+), 201, 172, 161, 145, 133, 105, 77. Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.58; H, 6.24; N, 12.14.

Preparation of Ethyl 5-Phenyl-6,7-benzo-3*H*-1,2-diazepine-3-carboxylate (48). Ethyl 2-diazo-4,4-diphenyl-3-hydroxybutyrate was prepared in 56% yield by using 9.2 g of diphenylacetaldehyde: NMR (CCl_4, 60 MHz) δ 1.12 (t, 3 H, J = 7.0 Hz), 3.19 (d, 1 H, J = 5.0 Hz), 4.01 (q, 2 H, J = 7.0 Hz), 4.04 (d, 1 H, J = 9.0 Hz), 5.21 (dd, 1 H, J = 9.0 and 5.0 Hz), and 6.95–7.41 (m, 10 H); IR (neat) 3705–3250, 3175–2900, 2130, 1695, 1600, 1495, 1365, 1295, 1205, 1100, 820, 745, and 680 cm^{-1}. Ethyl 2-diazo-4,4-diphenyl-3-butenoate (**46**) was prepared (64%) by the dehydration of 3.3 g of the above alcohol: NMR (CCl_4, 60 MHz) δ 1.29 (t, 3 H, J = 7.5 Hz), 4.25 (q, 2 H, J = 7.5 Hz), 6.22 (s, 1 H), and 7.1–7.51 (m, 10 H); IR (neat) 3155–2820, 2095, 1710, 1590, 1450, 1370, 1225, 1090, 1005, 760, and 690 cm^{-1}.

A solution containing 0.7 g (2.4 mmol) of ethyl 2-diazo-4,4-diphenyl-3-butenoate (**46**) in 14 mL of n-octane was heated at 110 °C for 1 h, cooled to 25 °C, and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a 1% acetone–hexane mixture as the eluent, to give 0.5 g (70%) of ethyl 5-phenyl-6,7-benzo-3*H*-1,2-diazepine-3-carboxylate (**48**) as a colorless oil: NMR (CCl_4, 90 MHz) δ 1.28 (t, 3 H, J = 7.0 Hz), 4.08 (q, 2 H, J = 7.0 Hz), 4.31 (d, 1 H, J = 3.0 Hz), and 7.05–7.61 (m, 10 H); IR (neat) 3195–2855, 1735, 1600, 1495, 1450, 1300, 1235, 1090, 755, and 690 cm^{-1}; UV (95% ethanol) 230 (ε 23 000) and 259 nm (6000); MS m/e 292 (M^+), 264, 235, 192, 191, 189, 165, 149, 115, 105, 77, and 63. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.96; H, 5.52; N, 9.58. Found: C, 73.78; H, 5.54; N, 9.32.

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Registry No. **7**, 126579-98-4; **9**, 126579-99-5; **10**, 126580-00-5; **11**, 126580-01-6; **12**, 126580-02-7; **14**, 126580-03-8; **15**, 59697-71-1; **17**, 126580-04-9; **18**, 126580-05-0; **20**, 88459-81-8; **21**, 126580-06-1; **22**, 1655-07-8; **23**, 126580-07-2; **25**, 39910-31-1; **26**, 609-14-3; **27**, 55718-61-1; **29**, 27262-63-1; **30**, 5413-05-8; **31**, 67272-05-3; **32**, 22418-80-0; **37a**, 126580-08-3; **37c**, 126580-09-4; **38a**, 126580-10-7;

38b, 126580-11-8; **38c**, 126580-12-9; **38d**, 126580-13-0; **40a**, 4027-57-0; **40b**, 6076-12-6; **40c**, 5932-30-9; **40d**, 6963-62-8; **41**, 126580-14-1; **42**, 4492-02-8; **43**, 126580-15-2; **45**, 81153-64-2; **46**, 126580-16-3; **48**, 126580-17-4; potassium phthalimide, 1074-82-4; ethyl 4-bromobutyrate, 2969-81-5; ethyl 4-phthalimidobutyrate, 10294-97-0; *N*-phenylmaleimide, 941-69-5; dimethyl acetylenedicarboxylate, 762-42-5; 4-oxo-1-pentanol, 1071-73-4; 2-methyl-1-penten-5-ol, 22508-64-1; 4-methyl-4-pentenal, 3973-43-1; ethyl lithiodiazoacetate, 55718-77-9; ethyl diazoacetate, 623-73-4; 4-oxopentanal, 626-96-0; acetone, 67-64-1; cyclopentanone, 120-92-3; acetophenone, 98-86-2; acrolein, 107-02-8; propionaldehyde, 123-38-6; phenylacetaldehyde, 122-78-1; ethyl 2-diazo-2-(1-hydroxycyclohexyl)acetate, 27262-60-8; cyclohexanone, 108-94-1; ethyl 2-diazo-3-hydroxy-4-phenylpentanoate, 126580-18-5; 2-phenylpropionaldehyde, 93-53-8; ethyl 2-diazo-4,4-diphenyl-3-hydroxybutyrate, 73295-49-5; diphenylacetaldehyde, 947-91-1.

Oxidation of 2-Chloroethyl Sulfides to Sulfoxides by Dimethyl Sulfoxide

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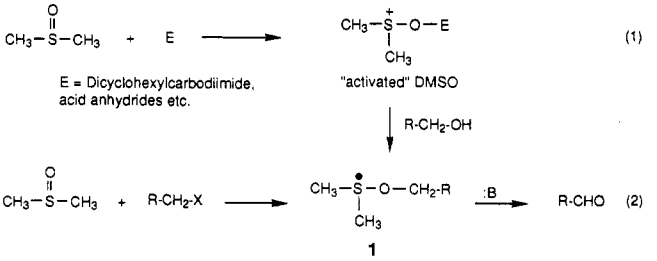
While most organic sulfides were not oxidized by dimethyl sulfoxide (DMSO), the alkyl 2-chloroethyl sulfides and bis(2-chloroethyl) sulfide slowly reacted with DMSO to produce the corresponding sulfoxides at 25–70 °C under nitrogen. The mechanism of the oxidation is proposed to involve nucleophilic substitution by DMSO followed by neighboring sulfur participation to form a transient sulfonium ion with a four-membered ring structure. The sulfonium ion intermediate rapidly reacts with the chloride ion to produce 2-chloroethyl sulfoxides. 2-Hydroxyethyl sulfoxides were also produced, probably due to the presence of a trace amount of water in the DMSO. This reaction demonstrates, for the first time, the unique reactivity of 2-chloroethyl sulfides in DMSO.

Introduction

The versatile chemical nature of dimethyl sulfoxide (DMSO) is well appreciated and has been the subject of many reviews.[1-8] Besides being one of the most prominent members of the family of polar, aprotic solvents,[1] DMSO also functions as a nucleophilic reagent at both the oxygen and sulfur terminals, and thus behaves as either a "hard" or a "soft" base. Because of this characteristic, DMSO has often been used as a mild oxidizing agent in organic synthesis.[2,5,6] The oxidizing capacity of DMSO was shown to be somewhat dependent on its ability to act as a nucleophile.[2] There was also a strong indication that most of the DMSO oxidations involved the same alkoxydimethylsulfonium salt intermediate, **1**.[2] This intermediate can be formed via the activating process illustrated in eq 1. For example, the oxidation of a primary alcohol to an aldehyde usually follows this mechanism.[5,6,8] On the other hand, the oxidation of a primary alkyl halide or tosylate to its corresponding aldehyde, known as the Kornblum reaction,[9-11] usually follows the mechanism descried by eq 2. However, in either case, a base is required in order to achieve the formation of the aldehyde or ketone.



Bis(2-chloroethyl) sulfide (mustard, **2a**), is a toxic chemical agent due to its high reactivity toward proteins and DNAs to induce systematic biochemical and morphological changes in mammalian tissues.[12,13] Its tendency to form a reactive, three-membered ring sulfonium ion in polar media also accounts for its susceptibility to a variety of nucleophiles, including water.[14] Interestingly, its sulfoxide and especially its hydrolysis product, thiodiglycol, are relatively harmless,[12] and these compounds are often goals in the chemical detoxification of mustard. It is the purpose of this study to examine the possible oxidation of mustard and other 2-chloroethyl sulfides by the nucleophilic oxidizing agent, DMSO, in an inert atmosphere and in the absence of any other reagents such as base at relatively mild temperatures.

Results and Discussion

Reaction Products. ^{13}C NMR spectroscopy (see the Experimental Section) was used to monitor the oxidation of 2-chloroethyl sulfides in DMSO. The ^{13}C NMR chemical shifts of several compounds containing alkyl sulfides and their sulfoxides have been reported in the literature.[15,16] It was observed that the chemical shifts of the

(1) Martin, D.; Weise, A.; Niclas, H.-J. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 318.
(2) Epstein, W. W.; Sweat, F. W. *Chem. Rev.* **1967**, *67*, 247.
(3) Durst, T. *Advances in Organic Chemistry: Methods and Results*; Taylor, E. C., Wynberg, H., Eds., Interscience–John Wiley & Sons: New York, 1969; Vol. 6, p 285.
(4) Szmant, H. H. *Dimethyl Sulfoxide, Vol. 1, Basic Concepts of DMSO*; Jacob, S. W., Rosenbaum, E. E., Wood, D. C., Eds.; Marcel Dekker: New York, 1971; pp 1–97.
(5) Moffat, J. G. *Oxidation*; Augustine, R. L., Trecker, D. J., Eds.; Marcel Dekker: New York, 1971; Vol. 2, p 1.
(6) Butterworth, R. F.; Hanessian, S. *Synthesis* **1971**, 70.
(7) Martin, D.; Hauthal, H. G. *Dimethyl Sulfoxide*; Halsted Press, division of John Wiley & Sons: New York, 1975.
(8) Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165.
(9) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.
(10) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113.
(11) Johnson, A. P.; Pelter, A. *J. Chem. Soc.* **1964**, 520.
(12) Anslow, W. P., Jr.; Karnofsky, D. A.; Val Jager, B.; Smith, H. W. *J. Pharmacol. Exp. Ther.* **1948**, *93*, 1.
(13) Peters, R. A.; Wakelin, R. W. *Brit. J. Pharmacol.* **1949**, *4*, 51.
(14) Bartlett, P. D.; Swain, C. G. *J. Am. Chem. Soc.* **1949**, *71*, 1406.
(15) Barbarella, G.; Dembeth, P.; Garbesi, A.; Fava, F. *Org. Magn. Reson.* **1976**, *8*, 108.