Intramolecular N–H, O–H, and S–H Insertion Reactions. Synthesis of Heterocycles from α-Diazo β-Keto Esters

Mikel P. Moyer, Paul L. Feldman, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, California 94720

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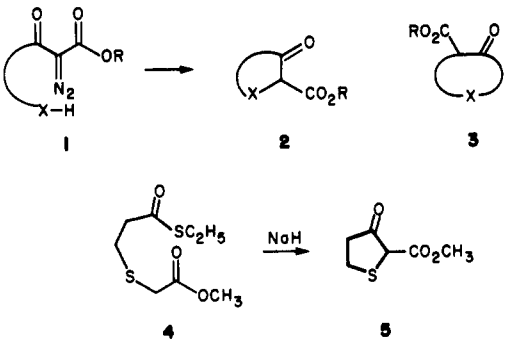
Several aspects of the $Rh_2(OAc)_4$-catalyzed intramolecular N–H, O–H, and S–H insertion reactions have been studied. Examination of the effect of ring size revealed that four-, five- and six-membered nitrogen heterocycles can be efficiently prepared from the corresponding α-diazo β-keto ester precursors (**9a–c**), whereas competing C–H insertion prevented formation of the seven-membered heterocycle. Variations in solvent, temperature, and catalyst concentration were found to play an important role in determining the product distribution in the cyclization of the 6-carbamoyl 2-diazo 3-keto ester **9c**. The intramolecular X–H insertion reaction has also been successful in the synthesis of oxygen (**39**) and sulfur (**49**) heterocycles as well as a heterocycle containing two (N, O) heteroatoms (**34**).

Transition-metal-mediated carbon–carbon bond-forming reactions from various diazo precursors have been extensively utilized in carbocycle synthesis. The intramolecular versions of cyclopropanation and C–H insertion reactions have been used in the synthesis of both theoretically interesting compounds and natural products. 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.[2-5]

Recently, $Rh_2(OAc)_4$ has been used to catalyze intramolecular C–H insertion reactions of α-diazo β-keto esters into freely rotating aliphatic side chains.[3b] This work was significant because the regioselectivity of C–H insertion was determined on a conformationally mobile side chain rather than on a constrained system in which ring size is determined by the proximity of the diazo function to the C–H bond. The results demonstrated that (a) there is a kinetic preference for five-membered ring formation and (b) C–H insertion into a more substituted carbon is faster than into a less substituted one for the same ring size. Even though five-membered ring formation is favored with conformationally mobile side chains, there are many examples of C–H insertion giving both four- and six-membered rings depending upon the substrate.[1,3a] The regioselectivity one obtains in a particular molecule depends upon the type of diazo function, substitution of the carbon where insertion takes place, steric factors, and the reagent used to promote the reaction.

Scheme I



The use of diazo carbonyl precursors to prepare heterocycles has been limited. Cyclopropanation[6] and C–H insertion[1,3a] have been used to synthesize lactones, and C–H insertions employing α-diazoamides have served extensively to synthesize β-lactams.[1,7] Intermolecular examples of O–H insertion reactions have shown $Rh_2(OAc)_4$ to be the most efficient catalyst for intermolecular insertion between ethyl diazoacetate and a variety of alcohols[8] and C–H insertion not to be competitive with ether formation.[9] The $Rh_2(OAc)_4$-mediated X–H insertion was extended to include N–H and S–H insertions by coupling ethyl diazoacetate with aniline and thiophenol.[10] Subsequently, the S–H insertion reaction was used as an efficient means of synthesizing α-(phenylthio) ketones from the corresponding α-diazoketones.[11] There have been a number of examples of $Rh_2(OAc)_4$-catalyzed intramolecular N–H insertions as a key step in the synthesis of various β-lactams.[5] With one exception, all intramolecular X–H insertion reactions catalyzed by $Rh_2(OAc)_4$ involve insertion into amide N–H bonds.[12] This methodology has also been used

(1) Burke, S. D.; Grieco, P. A. *Org. React.* **1979**, *26*, 361.
(2) A general review on carbenoid reactions is presented in: Wulfman, D. S.; Poling, B. "Reactive Intermediates"; Abramovitch, R. A., Ed.; Plenum Press: New York, 1980, Vol. 1, p 321.
(3) Recent studies on carbenoid C–H insertion are given in: (a) Cane, D. E.; Thomas, P. J. *J. Am. Chem. Soc.* **1984**, *106*, 5295. (b) Taber, D. F.; Petty, E. H. *J. Org. Chem.* **1982**, *47*, 4808. (c) Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935. (d) Taber, D. F.; Petty, E. H.; Raman, K. *J. Am. Chem. Soc.* **1985**, *107*, 196. (e) Demonceau, A.; Noels, A. F.; Hubert, A. J.; Teyssie, P. *J. Chem. Soc., Chem. Commun.* **1981**, 688. (f) Taber, D. F.; Ruckle, R. E.; Jr. *Tetrahedron Lett.* **1985**, *26*, 3059.
(4) Recent studies on carbenoid cyclopropanation are found in: (a) Doyle, M. P.; Dorow, R. L.; Buhro, W. E.; Griffin, J. H.; Tamblyn, W. H.; Trudell, M. L. *Organometallics* **1984**, *3*, 44. (b) Doyle, M. P.; van Leusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787. (c) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem.* **1980**, *45*, 695.
(5) Carbenoids have been used for intramolecular X–H insertion: (a) Cama, L. D.; Christensen, B. G. *Tetrahedron Lett.* **1978**, 4233. (b) Ratcliffe, R. W.; Salzmann, T. N.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 31. (c) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. *Tetrahedron Lett.* **1980**, *21*, 1193. (d) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783. (e) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G. Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6163. (f) Yamamoto, S.; Itani, H.; Takahashi, H.; Tsuji, T.; Nagata, W. *Tetrahedron Lett.* **1984**, *25*, 4545. (g) Campbell, M. M.; Jasys, V. J. *Heterocycles* **1981**, *16*, 1487. (h) Moody, C. J.; Pearson, C. J.; Lawton, G. *Tetrahedron Lett.* **1985**, *26*, 3171.
(6) A leading reference on intramolecular cyclopropanation with diazo esters is: Hudlicky, T.; Reddy, D. B.; Govindan, S. V.; Kulp, T.; Still, B.; Sheth, J. P. *J. Org. Chem.* **1983**, *48*, 3422.
(7) Bright, G. M.; Dee, M. F.; Kellogg, M. S. *Heterocycles* **1980**, *14*, 1251.
(8) Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1973**, 2233.
(9) Noels, A. F.; Demonceau, A.; Petiniot, N.; Hubert, A. J.; Teyssie, P. *Tetrahedron* **1982**, *38*, 2733.
(10) Paulissen, R.; Hayez, E.; Hubert, A. J.; Teyssie, P. *Tetrahedron Lett.* **1974**, 607.
(11) McKervey, M. A.; Ratananukul, P. *Tetrahedron Lett.* **1982**, *23*, 2509.
(12) A $Rh_2(OAc)_4$-catalyzed intramolecular OH insertion has been reported in the synthesis of oxazinones; however, stoichiometric quantities of BF_3·Et_2O were found to be better in promoting the insertion. McClure, D. E.; Lumma, P. K.; Arison, B. H.; Jones, J. H.; Baldwin, J. J. *J. Org. Chem.* **1983**, *48*, 2675.

0022-3263/85/1950-5223$01.50/0

with two heteroatoms in the ring to synthesize oxapenams[5g] and oxacephams[5a,f] and has led to anomalous results when applied to aza analogues.[13]

We have examined several aspects of the intramolecular X–H insertion reaction in order to increase its utility and now present our results. By determining the effect of ring size on the N–H insertion reaction we have shown that intramolecular N–H insertion reactions can provide good yields of various sized aza rings. Also, the versatility of the reaction has been demonstrated by synthesizing heterocycles containing one (N, O, S) and two (O, N) heteroatoms in the ring. Finally, the effect of solvent, temperature, and catalyst stoichiometry on the outcome of one N–H insertion reaction has been studied.

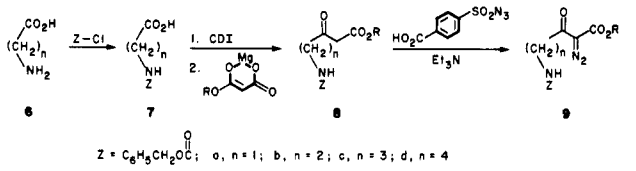
Results and Discussion

To facilitate investigation of the fundamental aspects of the carbenoid insertion reaction we utilized substrates devoid of unnecessary functionality. Thus, the synthetic objective was to construct substrates of general type 1 (Scheme I) in which the heteroatom to undergo insertion is tethered to the α-diazo β-keto ester with carbon chains of various lengths to allow investigation of the effect of ring size. The products that would result from successful X–H insertion are functionalized heterocycles of type 2. The potential synthetic applicability of these compounds prompted a literature review to determine whether heterocycles of this type are known and, if so, how efficient has been their construction.

Heterocycles of general structure 2 in the past have been almost invariably prepared via Dieckmann cyclization of the appropriate diester. Their construction suffers the same limitations present in any unsymmetrical Dieckmann cyclization, namely the difficulty in obtaining regiochemical control and the need for strongly basic conditions. The problem of regiocontrol has been resolved to some extent by manipulation of reaction conditions to give either kinetic or thermodynamic control or by differentiation of the esters to make one carbonyl more susceptible to nucleophilic attack. The strongly basic conditions cannot be avoided.

By judicious choice of reaction conditions it was demonstrated that 2-carboxy-3-oxopyrrolidines[14] (type 2) could be obtained via Dieckmann condensation. Previously, the thermodynamically more stable 4-carboxy-3-oxopyrrolidines (type 3) had been the exclusive products because the reaction had been conducted under equilibrating conditions (sodium ethoxide in ethanol at reflux). Upon utilization of nonequilibrating conditions (potassium *tert*-butoxide in toluene at 0 °C), the kinetic isomer became the preponderant product; however, the 4-carboxy isomer was still formed in significant amounts (40%). A similar kinetically controlled Dieckmann cyclization was used in the preparation of a 2-carboxy-3-oxopiperidine[15] derivative but only in very poor yield (25%). Also, a kinetically controlled Dieckmann condensation was utilized in the synthesis of a 2-carboxy-3-oxotetrahydrothiophene.[16] In this case, the pure product could not be isolated free of contamination with the isomeric 4-carboxy compound. Thus, although some degree of regiochemical selectivity is possible through control of reaction parameters, the classical Dieckmann condensation often produces a regioisomeric mixture and frequently gives low yields of the desired product when applied to the construction of heterocycles of type 2.

Scheme II



A more successful approach to the problem of regiochemical control has been to differentiate the two carboxyl functions such that one mode of Dieckmann closure is favored over the other. A direction-controlled Dieckmann type cyclization using half-thiol diesters has been successfully employed in the synthesis of both carbocycles and heterocycles.[17] For example, the tetrahydrothiophene 5 was prepared from half-thiol diester 4 in 74% yield by treatment with sodium hydride in THF. An analogous N-protected 2-carboxy-3-oxopyrrolidine derivative has also been prepared by using this methodology. In spite of this progress in obtaining regioselective syntheses of heterocycles of type 2, a need still remains for a general, mild, and regiospecific method for constructing such heterocycles. The discussion that follows describes such a method. Information is also presented that will facilitate extension of this methodology to more complicated heterocyclic compounds.

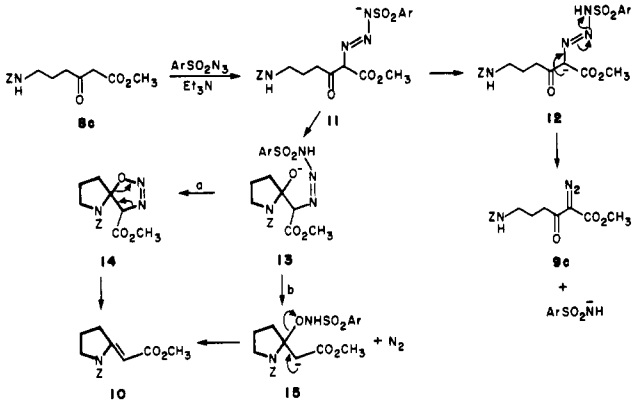
N–H Insertion Reactions. A general and efficient synthetic route to N–H insertion substrates **9a–d**, potential precursors of four-, five-, six- and seven-membered nitrogen-containing heterocycles, is outlined in Scheme II. The readily available amino acids **6a–d** were first converted to the corresponding benzyl carbamates **7a–d** by a modified Schotten–Baumann procedure. Initial attempts at conversion of the protected amino acids to β-keto esters **8a–d** involved Claisen condensations on the corresponding methyl esters of **7a–d**. The harsh conditions and low yields (10–40%) made this method synthetically unacceptable. A far more satisfactory method involved activation of the carboxyl by treatment with *N,N'*-carbonyldiimidazole, followed by treating the resulting imidazolide with the dianion of hydrogen methyl malonate.[18] Good yields (70–95%) and mild reaction conditions make this the method of choice for forming β-keto esters **8a–d**.

The diazo group was introduced by diazo transfer from (*p*-carboxyphenyl)sulfonyl azide[19] since the *p*-carboxybenzenesulfonamide that results from the diazo transfer can be removed via a simple alkaline wash. Although all of the diazo compounds (**9a-d**) were stable to purification by silica gel chromatography, in most cases this was unnecessary due to the absence of byproducts, and yields were generally 80–95%.

Initially, β-keto ester **8c** presented difficulties in the diazo transfer reaction. When (*p*-carboxyphenyl) sulfonyl azide was added to a solution of **8c** in acetonitrile, the diazo transfer reagent remained insoluble until dropwise addition of triethylamine formed its triethylammonium salt. Although the desired diazo compound was formed to some extent, a less polar material was the major component.

(13) An attempt to accomplish an intramolecular N–H insertion on 2-substituted 1,2-diazetidin-3-ones is described by: Taylor, E. C.; Davies, H. M. L. *J. Org. Chem.* **1984**, *49*, 113.
(14) Blake, J.; Willson, C. D.; Rapoport, H. *J. Am. Chem. Soc.* **1964**, *86*, 5293.
(15) Plieninger, H.; Leonhäuser, S. *Chem. Ber.* **1959**, *92*, 1579.
(16) Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc.* **1946**, *68*, 2229.
(17) Yamada, Y.; Ishii, T.; Kimura, M.; Hosaka, K. *Tetrahedron Lett.* **1981**, *22*, 1353.
(18) (a) Cox, M. T.; Jackson, A. H.; Kenner, G. W.; McCombie, S. W.; Smith, K. M. *J. Chem. Soc. Perkin Trans. 1* **1974**, 516. (b) Bram, G.; Vilkas, M. *Bull. Soc. Chim. Fr.* **1964**, 945. (c) Bates, H. A.; Rapoport, H. *J. Am. Chem. Soc.* **1979**, *101*, 1259.
(19) Hendrickson, J. B.; Wolf, W. A. *J. Org. Chem.* **1968**, *33*, 3610.

Scheme III



The infrared spectrum of this material contained no diazo or N–H stretch, while mass spectral evidence indicated a molecular weight of 275, which is 16 mass units less than the starting material, β-keto ester **8c**. The ^1H NMR also indicated the absence of an N–H and contained one vinylic hydrogen coupled (J = 1.9 Hz) to a two-proton absorbance at 3.16 ppm. These data are consistent with pyrrolidine **10** (Scheme III), whose structure was further supported by fully proton decoupled ^{13}C NMR and ^{13}C NMR using a distortionless enhancement by polarization transfer (DEPT) pulse sequence to allow complete assignment of carbon resonances.[20] The structure was unambiguously established by hydrogenolysis of the benzyl carbamate to give methyl 2-pyrrolidinylidene acetate, which was spectrally identical (except for the ester resonances) with the analogous ethyl ester prepared via a different route.[21]

With the structure of **10** established, the remaining question was the route by which it was formed. Formally, **10** arises by condensation of the carbamate with the ketone of the β-keto ester followed by elimination of water. To test whether we were observing simply a base-catalyzed reaction, β-keto ester **8c** was treated with triethylamine but no reaction occurred. Similarly, when **8c** was treated with triethylamine and *p*-carboxybenzenesulfonamide, the other component of the reaction mixture, we recovered only starting material. Extended reaction time did not change the product ratio, indicating that **10** does not come from further reaction of **9c**. These limited data suggest that the **10** was formed from a diazo intermediate. The proposed mechanism for diazo transfer is shown in Scheme III (**8c** → **11** → **12** → **9c**). The path to **10** must branch at intermediate **11**, since proton transfer to give **12** would effectively protect the carbonyl from nucleophilic attack. Two possible routes from **11** to **10** are shown in Scheme III.

A seemingly minor change in conditions allowed formation of the desired diazo compound **9c** in good yield. By adding the triethylamine all in one portion, instead of dropwise, **9c** can be reproducibly isolated in 80–90% yield. Even under our best conditions, **10** is still formed in small amounts (5–10%). We have seen no previous mention of this type of reaction and have not observed it with any of the other substrates.

Dissolution of α-diazo β-keto ester **9a** in benzene followed by addition of 0.6 mol % of $Rh_2(OAc)_4$ and immediate immersion of the reaction vessel into a preheated oil bath (80–90 °C) caused a rapid disappearance of starting material with concomitant formation of a very polar product (silica gel TLC). Isolation of this material by column chromatography followed by spectroscopic analysis led to the postulate that it was diester **17**. This was subsequently confirmed by independent synthesis of **17** via alkylation of Z-glycine methyl ester (**18**) with methyl bromoacetate.

Table I. Effect of Solvent, Temperature, and Amount of $Rh_2(OAc)_4$ on the Cyclization of 9c

entry	solvent	temp, °C	$Rh_2(OAc)_4$, mol %	product distribn,[a] % 20	21	10
1	C_6H_6	80	5	67	<5	<5
2	C_6H_6	80	1.5	44	10	<5
3	C_6H_6	20	1.5	<5	<5	10
4	$C_6H_5CH_3$	111	1.5	56	7	<5
5	CH_2Cl_2	20	1.5	21	<5	5
6	$ClCH_2CH_2Cl$	83	1.5	no cyclized matl		
7	THF	66	1.5	no cyclized matl		

[a] Yield of isolated product.

The most likely explanation for the formation of **17** is the acid-catalyzed ring opening of the intermediate 2-carboxy-3-oxoazetidine (**16**) during silica gel chromatography using methanol in the eluent. This extreme lability toward nucleophilic ring opening is a consequence of ring strain in **16**. Independent evidence for ring strain is reflected in the infrared carbonyl absorbance that occurs at 1835 cm^{-1}. To avoid any opportunity for nucleophilic ring opening, the reaction mixture was filtered through a small plug of Celite to remove the catalyst, and the filtrate was evaporated to give analytically pure **16** in quantitative yield. While 3-oxoazetidine derivatives have been synthesized previously,[22] the 2-carboxy-3-oxoazetidines are unknown.

The rhodium acetate catalyzed cyclization of **9b** to give the 2-carboxy-3-oxopyrrolidine **19** was performed in the manner described above. The product, isolated in essentially quantitative yield, exhibited a very complex ^1H NMR spectrum that initially confused structure determination. The infrared spectrum no longer contained an N–H stretch, implying that cyclization had occurred. Upon inspection of molecular models, it became apparent that the complexity of the ^1H NMR spectrum could be attributed to hindered rotation of both the carbamate and ester groups. Examination of the ^1H NMR spectrum as a function of temperature confirmed this attribution. Although complete coalescence of the rotamers was not achieved, at 65 °C the spectrum was sufficiently simple to allow proton assignments to be made and the structure to be determined with the help of the fully proton decoupled ^{13}C spectrum and the ^{13}C DEPT pulse sequence.

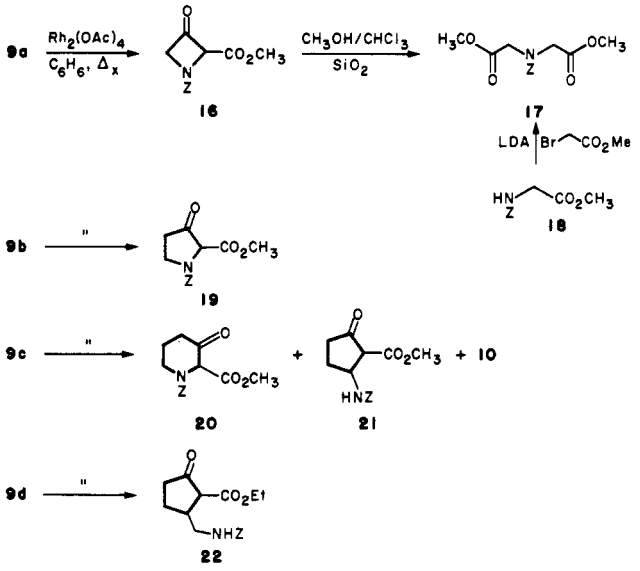
As discussed earlier, intramolecular C–H insertion to form five-membered carbocycles is a very facile reaction. In diazo compound **9c**, the opportunity exists for just such a reaction, as well as for competitive N–H insertion, leading to a six-membered heterocycle. Little pertinent information exists in the literature concerning such a competition.[5c] Our example differs from previous work[3b,c] in that a heteroatom is attached to the carbon that could suffer insertion; however, there are no data to predict what effect, if any, this would have. We discovered that the product distribution from this reaction is quite dependent on the reaction parameters employed with solvent, temperature, and amount of catalyst being particularly important.

(20) Doddrell, D. M.; Pegg, D. T.; Bendall, M. R. *J. Magn. Reson.* **1982**, *48*, 323. The DEPT pulse sequence we used inverted the CH_2s and left the CHs and CH_3s upright. Quaternary carbons are not seen with this technique.

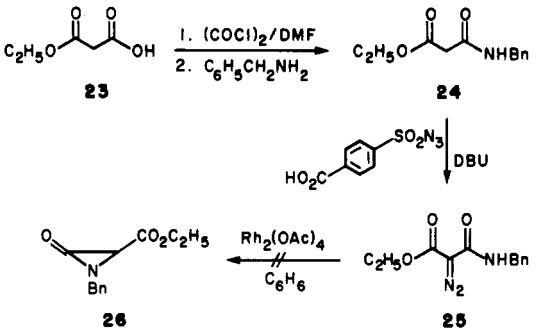
(21) (a) Pinnick, H. W.; Chang, Y.-H. *J. Org. Chem.* **1978**, *43*, 4662. (b) Luly, J. R.; Rapoport, H. *J. Am. Chem. Soc.* **1983**, *105*, 2859.

(22) (a) Chatterjee, S. S.; Shoeb, A. *Synthesis* **1973**, 153 and references therein. (b) Morimoto, A.; Okutani, T.; Masuda, K. *Chem. Pharm. Bull.* **1973**, *21*, 228.

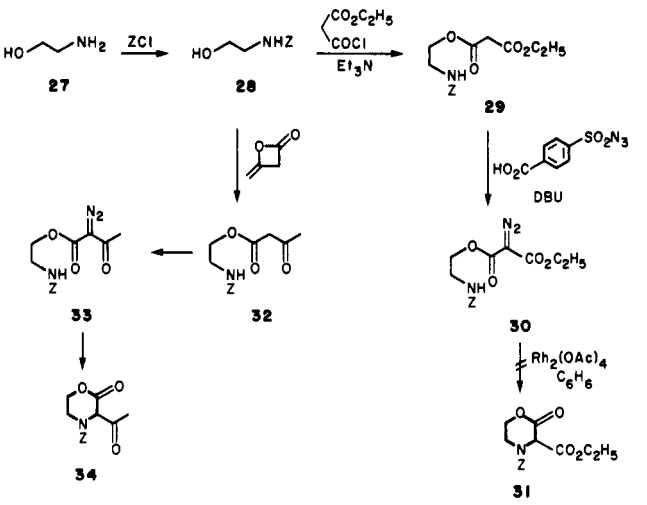
Scheme IV



Scheme V



Scheme VI



Three cyclization products have been identified from these reactions of **9c**: the N–H insertion product **20**, the C–H insertion product **21**, and **10**, the same byproduct that was formed during the diazo transfer reaction. The structure determination of **20** and **21** was similar to that already discussed for pyrrolidine **19**. As shown in Table I, seemingly minor changes in reaction conditions can result in major changes in the product ratio. The optimum conditions (entry 1) gave the desired 3-oxopiperidine derivative in 67% yield with only trace amounts of the other cyclization products. Reduction of the amount of $Rh_2(OAc)_4$ (entry 2) led to a significant decrease in the yield of the N–H insertion product, while lowering the reaction temperature decreased the yield of **20** and **21** to only trace amounts. To maximize formation of **20**, the reaction is performed by dissolving diazo compound **9c** in benzene, followed by addition of $Rh_2(OAc)_4$ and then immediate immersion of the reaction vessel into a preheated oil bath. To test whether even higher temperatures would be advantageous, the reaction was performed in refluxing toluene; however, this did not increase the yield of **20**. A few other solvents (entries 5–7) gave uniformly poor results. It was interesting, however, that some N–H insertion product was formed in methylene chloride at room temperature, whereas in benzene at room temperature no **20** was formed.

The most important information to come from this brief examination of reaction parameters would seem to be that changes in solvent, temperature, and amount of catalyst profoundly influence the product distribution in this reaction. Unfortunately, the basis for this influence is not readily apparent. The formation of pyrrolidine **10** is quite surprising as it must arise by a net reduction of diazo compound **9c**. We have been unable to formulate a reasonable mechanism for its production under these conditions.

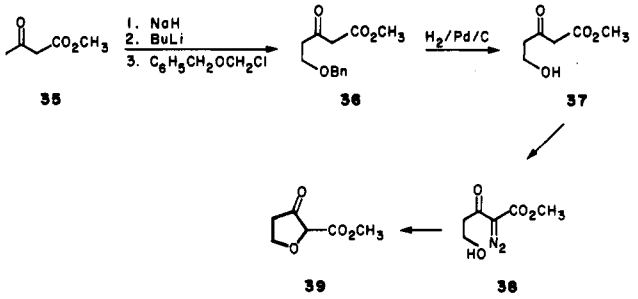
Diazo compound **9d** provided an even more extreme test for the competitive N–H insertion reaction. This substrate presents the option for five- and six-membered C–H insertion in addition to N–H insertion, leading to a seven-membered ring. When heated at reflux in benzene with 1.5 mol % of $Rh_2(OAc)_4$, **9d** produced cyclopentanone **22** in 39% yield as the only cyclization product. Thus, the kinetic preference for five-membered ring formation completely overwhelms any tendency for N–H insertion. The reactions of **9a–d** are collected in Scheme IV.

To examine whether $Rh_2(OAc)_4$-catalyzed N–H insertion could be used in the synthesis of aziridinones, the cyclization substrate **25** was prepared from ethyl hydrogen malonate[23] via amide **24**. The conversion of amide **24** to diazo compound **25** was sluggish when the standard diazo transfer conditions were used; however, utilization of DBU[12] instead of triethylamine increased the reaction rate and allowed efficient construction of **25**. It should be noted that there are several differences in this cyclization attempt other than ring size. All of our previous substrates have been α-diazo β-keto esters while **25** is an α-diazo β-amido ester. In addition, the insertion would be into an amide, rather than a carbamate, N–H. With these differences in mind, **25** was dissolved in benzene, $Rh_2(OAc)_4$ (1.5 mol %) was added, and the reaction was placed in an oil bath preheated to 80–90 °C. The starting material was rapidly consumed, however, no aziridinone was detected in the crude reaction mixture. We were unable to identify any of the products, thus, it is impossible to say whether insertion did occur and the multitude of products results from thermal decomposition of the aziridinone[24] or the reaction took an entirely different course. The thermal instability of aziridinones is well documented, with the actual mode of decomposition being very substrate dependent.[24]

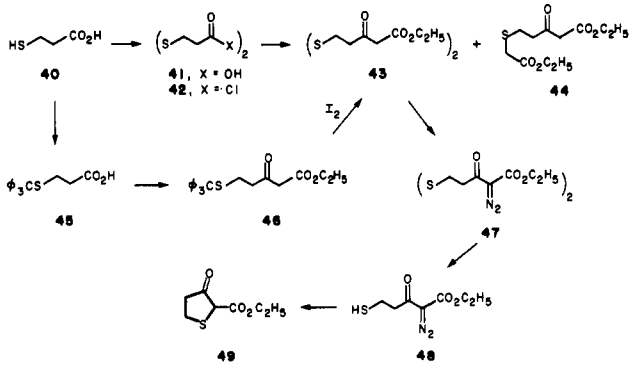
Extension of the carbenoid insertion methodology to heterocycles containing two heteroatoms was next investigated. To this end, benzyl carbamate **28** (Scheme VI) was acylated with the acid chloride of ethyl hydrogen malonate to give the substituted malonate **29**. Diazo

(23) Strube, R. E. "Organic Syntheses"; Wiley: New York, 1963; Collect. Vol. IV, p 417.
(24) Lengyel, I.; Sheehan, J. C. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 25 and references therein.

Scheme VII



Scheme VIII



transfer was accomplished with (*p*-carboxyphenyl)sufonyl azide and DBU in acetonitrile. This diazo compound has some important differences from the closest analogue previously investigated, diazo compound **9c**. The presence of the oxygen in the chain between the diazo group and the N–H could influence conformational mobility by virtue of its dipole moment and certainly has an influence on the reactivity of the diazo group, making it more reactive than an α-diazo β-keto ester because of the decreased delocalization of electron density into the β-dicarbonyl system. When **30** was treated with 5 mol % of $Rh_2(OAc)_4$ at 50 °C in benzene, it was completely consumed after 2 h and the products were isolated by column chromatography. Although the exact structures were not determined, it was clear no N–H insertion had occurred by virtue of the presence of an N–H in the IR and ^1H NMR spectra of all of the products.

Conversion of the protected amino alcohol **28** into acetoacetic acid derivative **32** using diketene and triethylamine allowed us to investigate the possibility of having two heteroatoms in the newly formed ring, while retaining the β-keto ester stabilized diazo group. Thus, **32** was converted to diazo compound **33** under standard conditions, and treatment with 5 mol % of $Rh_2(OAc)_4$ in refluxing benzene did indeed produce the desired morpholine derivative **34**. While the yield was poor (16%), isolation of **34** does show the potential of this methodology for construction of heterocycles of this type. In light of the previously demonstrated sensitivity of the carbenoid insertion reaction to subtle changes in reaction conditions, it is quite likely that the yield of this reaction could be significantly improved by further study of the reaction parameters.

O–H and S–H Insertion Reactions. In order to demonstrate the feasibility of intramolecular O–H and S–H insertion, 2-(methoxycarbonyl)-3-oxotetrahydrofuran (**39**) and 2-(ethoxycarbonyl)-3-oxotetrahydrothiophene (**49**) were synthesized. The oxygen heterocycle has not been reported previously, but there have been several syntheses of derivatives of **49** via Dieckmann methodology.[16,17,25]

The precursor to the furanone, methyl 5-hydroxy-3-oxopentanoate (**37**), was prepared by two different routes. Even though the nucleophilic addition of the dianion of methyl acetoacetate to formaldehyde is known,[26] it proceeds in poor yield, and we found it more convenient to synthesize **37** by the two-step procedure outlined in Scheme VII. Treatment of the dianion of methyl acetoacetate with (benzyloxy)methyl chloride gave **36** in 60–70% yield.[26] Deprotection of the alcohol by hydrogenolysis[27] and diazo transfer using the standard conditions gave **38**. Refluxing **38** with 1.5 mol % of $Rh_2(OAc)_4$ in benzene for 20 min produced **39** in quantitative yield. The structure of **39** was readily determined from the spectral data.

Several routes were pursued to synthesize the 3-oxotetrahydrothiophene precursor ethyl 5-mercapto-3-oxopentanoate. Claisen condensation of methyl 3-mercaptopropionate with the anion of methyl acetate gave the desired methyl 5-mercapto-3-oxopentanoate but in very poor yield. Three of the byproducts of this reaction were the disulfide of the β-keto ester, the mixed disulfide from educt and product, and methyl acetoacetate. Since the results from the Claisen reaction were so poor, another route to the precursor of **49** was explored.

As disulfide formation was complicating β-keto ester formation, we decided to protect the thiol as the disulfide, form the β-keto ester, and then mildly cleave the disulfide. Treatment of 3-mercaptopropionic acid with H_2O_2/H_2O produced the disulfide in nearly quantitative yield.[28] However, utilization of standard methods for β-keto ester formation yielded complex product mixtures. As shown in Scheme VIII the major product from activating the diacid as the diacid chloride followed by quenching with the dianion of ethyl hydrogen malonate was **44**. This result was not surprising since quenching lithium enolates with disulfides is a standard method of synthesizing α-alkylthio ketones or esters.[29]

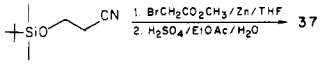
Next we sought to protect the mercaptan with a group stable to base yet easily removed under acid or neutral conditions. The *p*-methylbenzyl group is stable to base yet can be removed with liquid HF.[30] Protection of the thiol of 3-mercaptopropionic acid was straightforward;[31] however, the benzyl group was not removed with neat HF.

Thiol protection of 3-mercaptopropionic acid with the acid-labile trityl group was accomplished in 91% yield by treatment with triphenylmethanol/BF_3·Et_2O in acetic acid.[32] Homologation to the β-keto ester was uneventful, and after unsuccessfully trying to remove the trityl group with TFA or HBr/HOAc, successful deprotection followed

(25) An interesting synthesis of 2-alkyl-3-oxotetrahydrothiophene from 4-(alkylthio)-1-diazobutan-2-one is the only example of a carbenoid reaction used to synthesize any of the heterocycles we have made. This reaction proceeds via intramolecular carbenoid addition to sulfur to give an intermediate cyclic sulfur ylide that then rearranges to the product either via a [2,3] sigmatropic shift or a Stevens rearrangement, depending upon the alkylthio group. Kondo, K.; Ojima, I. *J. Chem. Soc., Chem. Commun.* **1972**, 860.

(26) Taylor, E. C.; LaMattina, J. L. *J. Org. Chem.* **1978**, *43*, 1200.

(27) Another route (Bellassoued, M.; Gaudemar, M. *J. Organomet. Chem.* **1974**, *81*, 139) outlined below employed the Blaise reaction for synthesizing **37**; however, we found it less satisfactory than the scheme described in the text.



(28) Danehy, J. P.; Kreuz, J. A. *J. Am. Chem. Soc.* **1961**, *83*, 1109.

(29) Trost, B. M.; Salzmann, T. N. *J. Am. Chem. Soc.* **1973**, *95*, 6840.

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(31) A similar procedure to that used to protect cysteine was employed by: Erickson, B. W.; Merrifield, R. B. *J. Am. Chem. Soc.* **1973**, *95*, 3750.

(32) Zee-Cheng, K.-Y.; Cheng, C. C. *J. Med. Chem.* **1970**, *13*, 414.

by disulfide formation was accomplished in 75% yield by treating **46** with I_2 in CH_2Cl_2/EtOH.[33] Since diazo transfer is conducted under basic conditions and base has promoted disulfide formation in the Claisen route, we elected to do the diazo transfer on **43** and then cleave the disulfide linkage. Diazo transfer was effected in 78% yield and cleavage of the S–S bond with an excess of dithioerythritol in aqueous basic acetonitrile proceeded to **48** in 59% yield. If the reaction lifetime was more than 15 min, many byproducts were formed. Treatment of **48** with 1.5 mol % of $Rh_2(OAc)_4$ in benzene at reflux gave analytically pure **49** in 73% yield. Since the β-keto ester exists both in the keto and enol form, the ^1H NMR spectrum was complicated. However, the structure was readily confirmed by the ^{13}C DEPT experiment. The inverted methylene carbons resonate at 25.4, 38.8, and 62.3 ppm, and the methine resonates at 52.1 ppm.

In all of the previous carbenoid closures the solution at the end of the reaction was the emerald green of crystalline $Rh_2(OAc)_4$. However, at the end of the intramolecular S–H insertion reaction the solution was deep red. We suggest that the thiol group of the starting material, and possibly the sulfide of the product, is coordinating with the open sites of the catalyst.[34] Stable, variously colored adducts of $Rh_2(OAc)_4$ and a variety of Lewis bases have been synthesized,[35] and we found that stirring a benzene solution of $Rh_2(OAc)_4$ with methyl 3-mercaptopropionate at room temperature gave a rose red solution.

Summary

The rhodium acetate catalyzed carbenoid insertion reaction has been demonstrated to be a mild, efficient, and regiospecific method for the construction of azetidine, pyrrolidine, piperidine, tetrahydrofuran, and tetrahydrothiophene derivatives containing functionality suitable for further synthetic manipulations. Competing C–H insertion becomes a problem only when attempting to form larger than six-membered heterocycles. This methodology has also proven successful in the construction of heterocycles containing two heteroatoms. Thus, the rhodium acetate catalyzed carbenoid insertion reaction should be useful in the construction of a wide variety of heterocyclic ring systems.

Experimental Section

General Procedures. Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) was distilled from sodium/benzophenone immediately prior to use. Melting points are uncorrected. ^{13}C NMR and DEPT experiments were conducted with the aid of a Bruker Am-500 spectrometer (500.13 MHz) equipped with an Aspect 3000 computer. Chemical shifts, recorded in $CDCl_3$, are expressed in ppm downfield from internal tetramethylsilane. Significant ^1H NMR data are tabulated in the following order: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in Hertz. The notation (i) is used to indicate inverted signals in the ^{13}C NMR DEPT experiment. Elemental analysis were performed by the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA. Column chromatography was performed with 63–200-μm silica gel 60 (EM Reagents). Analytical thin-layer chromatography (TLC) was done with aluminum-backed silica plates (E. Merck).

β-Keto Ester Formation. General Procedure. To a solution of the protected amino acid[36] in THF was added *N,N'*-carbonyldiimidazole (120 mol %) and the resulting solution stirred for 12 h at room temperature. Treatment of hydrogen methyl malonate (150 mol %) with isopropylmagnesium bromide (300 mol %) at 0 °C for 0.5 h, then at room temperature for 0.5 h and finally at 40 °C for 0.5 h, generated the dianion as its magnesium chelate. To this solution at 0 °C was added the imidazolide solution, and a gummy precipitate began to form immediately. After warming to room temperature and stirring for 4 h, the reaction was poured into ice-cold 1 M H_3PO_4. Extraction with ethyl acetate was followed by washing the combined organics with saturated $NaHCO_3$ and saturated NaCl and drying over $MgSO_4$. Evaporation of the solvent left the crude β-keto ester. If purification was necessary, it was accomplished by column chromatography on silica gel.

Methyl 4-[(Benzyloxycarbonyl)amino]-3-oxobutanoate (8a). Purification by column chromatography (hexanes/EtOAc, 1/1) gave **8a** in 71% yield: mp 53.5–55 °C; IR (CH_2Cl_2) 3440, 3020, 1720 cm^{-1}; ^1H NMR δ 7.34 (s, 5 H), 5.6 (br s, 1 H), 5.10 (s, 2 H), 4.17 (d, 2 H, J = 5.1), 3.72 (s, 3 H), 3.48 (s, 2 H). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.9; H, 5.7; N, 5.3. Found: C, 58.8; H, 6.0; N, 5.3.

Methyl 5-[(Benzyloxycarbonyl)amino]-3-oxopentanoate (8b). No purification was needed for this material obtained in 91% yield: IR (neat) 3440, 1720 cm^{-1}; ^1H NMR δ 7.34 (s, 5 H), 5.28 (br s, 1 H), 5.08 (s, 2 H), 3.72 (s, 3 H), 3.45 (br s, 4 H), 2.80 (t, 2 H, J = 5.6). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0. Found: C, 60.1; H, 6.2; N, 5.0.

Methyl 6-[(Benzyloxycarbonyl)amino]-3-oxohexanoate (8c). Purification by column chromatography (CH_2Cl_2/EtOAc, 9/1) gave **8c** in 74% yield: IR ($CHCl_3$) 3440, 2940, 1740, 1700 cm^{-1}; ^1H NMR δ 7.3 (s, 5 H), 5.1 (s, 2 H), 5.0 (m, 1 H), 3.7 (s, 3 H), 3.4 (s, 2 H), 3.2 (m, 2 H), 2.6 (t, 2 H, J = 7.1), 1.8 (m, 2 H). Anal. Calcd for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.5; N, 4.8. Found: C, 61.0; H, 6.6; N, 4.8.

Ethyl 7-[(Benzyloxycarbonyl)amino]-3-oxoheptanoate (8d). The product was obtained in 90% yield substituting ethyl for hydrogen methyl malonate: IR (neat) 3435, 2975, 1720 cm^{-1}; ^1H NMR δ 7.23 (s, 5 H), 5.06 (s, 2 H), 4.8 (br s, 1 H), 4.15 (q, 2 H, J = 2.2), 3.39 (s, 2 H), 3.14 (dd, 2 H, J = 12.6, 6.3), 2.54 (t, 2 H, J = 6.7), 1.50 (m, 4 H), 1.24 (t, 3 H, J = 7.2). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.5; H, 7.2; N, 4.4. Found: C, 63.4; H, 7.3; N, 4.3.

Diazo Transfer Reaction. General Procedure. The diazo transfer reactions were performed with (*p*-carboxyphenyl)sulfonyl azide as the diazo transfer reagent according to the published procedure.[19]

Methyl 4-[(Benzyloxycarbonyl)amino]-2-diazo-3-oxobutanoate (9a). The material was chromatographed twice (hexanes/CH_2Cl_2/EtOAc, 2/1/1) to give a light yellow solid in 73% yield: mp 84.5–86 °C; IR (neat) 3550, 2950, 2130, 1720, 1700, 1660 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H), 5.48 (br s, 1 H), 5.11 (s, 2 H), 4.46 (d, 2 H, J = 5.4), 3.84 (s, 3 H).

Methyl 5-[(Benzyloxycarbonyl)amino]-2-diazo-3-oxopentanoate (9b). The product was obtained in 84% yield and was used without purification: IR (neat) 3360, 2950, 2125, 1715, 1700, 1645 cm^{-1}; ^1H NMR δ 7.32 (m, 5 H), 5.35 (br s, 1 H), 5.08 (s, 2 H), 3.83 (s, 3 H), 3.52 (m, 2 H), 3.07 (t, 2 H, J = 5.9).

Methyl 6-[(Benzyloxycarbonyl)amino]-2-diazo-3-oxohexanoate (9c). Purification by column chromatography (CH_2Cl_2/EtOAc, 9/1) gave **9c** in 81% yield: IR ($CHCl_3$) 3440, 3000, 2140, 1710 cm^{-1}; ^1H NMR δ 7.35 (s, 5 H), 5.09 (s, 2 H), 5.02 (m, 1 H), 3.83 (s, 3 H), 3.23 (m, 2 H), 2.89 (t, 2 H, J = 7.1), 1.86 (m, 2 H).

Methyl Z-*N*-(benzyloxycarbonyl)-2-pyrrolidinylideneacetate (10) was isolated in 8% yield: IR ($CHCl_3$) 3020, 1740, 1700 cm^{-1}; ^1H NMR δ 7.23 (s, 5 H), 6.56 (t, 1 H, J = 1.9), 5.20

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(34) Upon stirring **48** with 5 mol % of $Rh_2(OAc)_4$ in benzene at room temperature no conversion to **49** was noted by TLC; however, the solution turned rose red. This supports **48** coordinating with $Rh_2(OAc)_4$; however, we cannot rule out that **49** also coordinates with the catalyst after it is formed.

(35) The authors found that dimethyl sulfide formed a rose red complex with $Rh_2(OAc)_4$; however, hydrogen sulfide did not react. Johnson, S. A.; Hunt, H. R.; Neumann, H. M. *Inorg. Chem.* **1963**, *2*, 960.

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(s, 2 H), 3.73 (t, 2 H, J = 7.7), 3.65 (s, 3 H), 3.16 (dt, 2 H, J = 7.7, 1.9), 1.89 (m, 2 H): ^{13}C NMR δ 169.2, 157.3, 152.7, 135.6, 128.8, 128.6, 128.4, 128.2, 128.0, 96.5, 67.7, 50.8, 49.6, 31.6, 21.1; mass spectrum, m/e 275 (M^+). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.2; N, 5.1. Found: C, 65.5; H, 6.2; N, 5.1.

Ethyl 7-[(benzyloxycarbonyl)amino]-2-diazo-3-oxoheptanoate (9d) was obtained in quantitative yield: IR (neat) 3360, 2940, 2130, 1720, 1705, 1635 cm^{-1}; ^{1}H NMR δ 7.33 (s, 5 H), 5.06 (s, 2 H), 4.95 (br s, 1 H), 4.25 (q, 2 H, J = 7.1), 3.18 (m, 2 H), 2.83 (t, 2 H, J = 7.0), 1.16 (m, 4 H), 1.29 (t, 3 H, J = 7.1).

$Rh_2(OAc)_4$-Catalyzed Carbenoid Insertion Reaction. General Procedure. The $Rh_2(OAc)_4$ (see specific example for amount) was added to a solution of the α-diazo β-keto ester in benzene (ca. 0.05 M). The mixture was immediately immersed in a preheated oil bath (80–90 °C) until TLC indicated that starting material was completely consumed. The reaction was then filtered through Celite and the filtrate evaporated. If necessary the crude product was purified by column chromatography on silica gel.

1-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-3-oxoazetidine (16) was prepared with 0.6 mol % of $Rh_2(OAc)_4$. The crude product was isolated in pure form as a viscous light yellow oil: IR (neat) 2970, 1835, 1755, 1660 cm^{-1}; ^{1}H NMR δ 7.34 (s, 5 H), 5.46 (d, 1 H, J = 3.1), 5.18 (dd, 2 H, J = 15.5, 12.2), 4.9 (m, 2 H), 3.78 (s, 3 H). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.3; H, 5.0; N, 5.3. Found: C, 59.3; H, 5.0; N, 5.3. Chromatography of **16** on silica ($CH_3OH/CHCl_3$, 1/19) gave **17** as a yellow oil in 17% yield: IR (neat) 2975, 1745, 1705 cm^{-1}; ^{1}H NMR δ 7.33 (m, 5 H), 5.15 (s, 2 H), 4.2 (s, 2 H), 4.12 (s, 2 H), 3.74 (s, 3 H), 3.67 (s, 3 H). Anal. Calcd for $C_{14}H_{17}NO_6$: C, 57.0; H, 5.8; N, 4.7. Found: C, 56.6; H, 6.0; N, 4.6.

1-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-3-oxopyrrolidine (19) was prepared with 0.6 mol % of $Rh_2(OAc)_4$. Column chromatography on silica gel (hexanes/EtOAc/CH_2Cl_2, 2/1/1) gave **19** as a yellow oil in 90% yield: IR (neat) 2975, 1765, 1740, 1700 cm^{-1}. The ^{1}H NMR and ^{13}C NMR DEPT are complicated by rotamers and show multiple signals for some carbons: ^{1}H NMR δ 7.3 (m, 5 H), 5.24–5.10 (m, 2 H), 4.65 and 4.59 (2 s, 1 H total) 4.02–3.8 (m, 2 H), 3.82 and 3.65 (2 s, 3 H total), 2.70 (m, 2 H); ^{13}C NMR DEPT δ 128.4, 128.2, 128.1, 128.0, 127.8, 67.6 (i), 67.5 (i), 65.3, 65.1, 53.2, 53.0, 42.1 (i), 36.8 (i), 36.1 (i); mass spectrum, m/e 277 (M^+, 0.91). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.7; H, 5.5; N, 5.1. Found: C, 60.7; H, 5.4; N, 5.1.

1-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-3-oxopiperidine (20) was prepared with 5 mol % of $Rh_2(OAc)_4$ in refluxing benzene. The product was isolated by column chromatoraphy on silica gel (CH_2Cl_2/EtOAc, 9/1) to give **20** in 67% yield. The ^{1}H NMR is complicated by rotamers: IR ($CHCl_3$) 2960, 1710 cm^{-1}; ^{1}H NMR (enol) δ 7.3 (m, 5 H), 5.2 (m, 2 H), 4.0–4.2 (m, ~1 H), 3.7 and 3.8 (2 s, 3 H total), 3.4–3.6 (m, ~1 H), 2.4 and 2.6 (2 t, 2 H total, J = 6.4, 6.1), 1.95 (m, 2 H); mass spectrum m/e 291 (M^+). Anal. Calcd for $C_{15}H_{17}NO_5$: C, 61.9; H, 5.9; N, 4.8. Found: C, 61.6; H, 5.7; N, 4.7.

3-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)-cyclopentanone (21): IR ($CHCl_3$) 3460, 2960, 1740, 1710 cm^{-1}: ^{1}H NMR (complicated by diastereomers and rotamers) δ 7.35 (s, 5 H), 5.1–5.2 (m, 2 H), 4.9 (m, 1 H), 3.5–3.9 (m, 5 H), 2.5–2.8 (m, 2 H), 2.1 (m, 2 H); mass spectrum for $C_{15}H_{17}NO_5$, calcd m/e 291.1108, found m/e 291.1107.

3-[[(Benzyloxycarbonyl)amino]methyl]-2-(ethoxycarbonyl)cyclopentanone (22) was prepared with 1.5 mol % of $Rh_2(OAc)_4$. The crude product was chromatographed on silica gel (hexanes/EtOAc, 7/3) to obtain the second of three UV-active materials as a yellow oil in 39% yield: IR (neat) 3330, 2970, 1750–1680 cm^{-1}; ^{1}H NMR δ 7.3 (s, 5 H), 5.1 (s, 2 H), 5.0 (br s, 1 H), 4.17 (q, 2 H, J = 7.2), 3.48 (m, 2 H), 2.98, 2.93, (2 s, 1 H total), 2.8 (m, 1 H), 2.5–2.1 (m, 3 H), 1.6 (m, 1 H), 1.35 (t, 3 H, J = 7.2); ^{13}C NMR and ^{13}C NMR DEPT, combined, δ 210.3, 169.1, 156.5, 136.5, 128.5, 128.2, 128.1, 66.9 (i), 61.7 (i), 59.5, 44.5 (i), 41.7, 38.1 (i), 24.8 (i), 14.2; mass spectrum, m/e 319 (M^+, 0.15). Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.9; H, 6.6; N, 4.4. Found: C, 63.9; H, 6.7; N, 4.3.

Ethyl *N*-Benzylmalonamate (24). To ethyl hydrogen malonate (1.00 g, 7.6 mmol) in dry CH_2Cl_2 at 0 °C was added one drop of DMF and then oxalyl chloride (1.01 g, 8.0 mmol). The solution was stirred at 0 °C for 1 h at which time it was added to a solution of benzylamine (1.63 g, 15.2 mmol) in CH_2Cl_2. After 2 h the reaction was diluted with more CH_2Cl_2 and washed with 1 M H_3PO_4, saturated $NaHCO_3$, and saturated NaCl. After drying ($MgSO_4$), the solvent was evaporated, leaving a white solid that was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 3/1) to give **24** (0.93 g, 55%) as a white solid: mp 51–53 °C (lit.[37] mp 46–49 °C); IR ($CHCl_3$) 3360, 2980, 2130, 1715, 1670 cm^{-1}; ^{1}H NMR δ 7.5 (br s, 1 H), 7.3 (m, 5 H), 4.52 (d, 2 H, J = 6), 4.23 (q, 2 H, J = 7.2), 3.40 (s, 2 H), 1.23 (t, 3 H, J = 7.2).

Ethyl *N*-Benzyl-α-diazomalonamate (25). Exposure of **24** to the standard diazo transfer conditions gave **25** in 80% yield: IR ($CHCl_3$) 3360, 2980, 2130, 1715, 1670 cm^{-1}; ^{1}H NMR δ 8.2 (br s, 1 H), 7.3 (m, 5 H), 4.55 (d, 2 H, J = 5.8), 4.3 (q, 2 H, J = 7.1), 1.35 (t, 3 H, J = 7.1).

2-[(Benzyloxycarbonyl)amino]ethyl Ethyl Malonate (29). To ethyl hydrogen malonate (2.02 g, 15.3 mmol) in dry CH_2Cl_2 at 0 °C was added one drop of DMF and then oxalyl chloride (2.14 g, 16.8 mmol). The soltuion was stirred at 0 °C for 1 h and then added to a solution of 2-[(benzyloxycarbonyl)amino]ethanol (**28**) (1.00 g, 5.1 mmol) and triethylamine (3.14 g, 31.0 mmol) in dry CH_2Cl_2. After 2 h the reaction mixture was diluted with more CH_2Cl_2, washed with H_2O, 1 M H_3PO_4, saturated $NaHCO_3$, and saturated NaCl, dried over $MgSO_4$, and evaporated. The crude product was purified by column chromatography (silica gel, CH_2Cl_2/EtOAc, 3/1) to give malonate **29** (1.32 g, 80%): IR ($CHCl_3$) 3460, 3000, 1720 cm^{-1}; ^{1}H NMR δ 7.27 (s, 5 H), 5.2 (br m, 1 H), 5.03 (s, 2 H), 4.15 (m, 4 H), 3.40 (q, 2 H, J = 5.4), 3.30 (s, 2 H), 1.19 (t, 3 H, J = 7.1). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.2; H, 6.2; N, 4.5. Found: C, 58.1; H, 6.2; N, 4.5.

2-[(Benzyloxycarbonyl)amino]ethyl Ethyl α-Diazomalonate (30). The diazo compound was prepared from **29** in quantitative yield via the standard procedure except for the substitution of DBU for triethylamine: IR ($CHCl_3$) 3460, 3000, 2140, 1750, 1710 cm^{-1}; ^{1}H NMR δ 7.34 (s, 5 H), 5.25 (m, 1 H), 5.10 (s, 2 H), 4.27 (m, 4 H), 3.50 (m, 2 H), 1.28 (t, 3 H, J = 5.3).

2-[(Benzyloxycarbonyl)amino]ethyl 3-Oxobutanoate (32). Freshly distilled diketene (0.42 g, 5.0 mmol) was added to a solution of 2-[(benzyloxycarbonyl)amino] ethanol[38] (**28**; 0.82 g, 4.2 mmol) and triethylamine (2 drops) in CH_2Cl_2 at room temperature. After 6 h the reaction mixture was diluted with more CH_2Cl_2, washed with H_2O, 1 M H_3PO_4, saturated $NaHCO_3$, and saturated NaCl, and dried over $MgSO_4$. Evaporation and column chromatography of the residue on silica gel (CH_2Cl_2/EtOAc, 3/1) gave β-keto ester **32**: 0.89 g (75%); IR ($CHCl_3$) 3460, 1715 cm^{-1}; ^{1}H NMR δ 7.35 (s, 5 H), 5.24 (br t, 1 H), 5.11 (s, 2 H), 4.24 (t, 2 H, J = 5.1), 3.47 (m, 4 H), 2.25 (s, 3 H). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0. Found: C, 60.0; H, 6.2; N, 5.0.

2-[(Benzyloxycarbonyl)amino]ethyl 2-Diazo-3-oxobutanoate (33). The diazo group was introduced by the published procedure[12] with DBU substituted for triethylamine. Purification by column chromatography on silica gel (CH_2Cl_2/EtOAc, 3/1) gave **33** in 79% yield: IR ($CHCl_3$) 3460, 3000, 2140, 1720 cm^{-1}; ^{1}H NMR δ 7.35 (s, 5 H), 5.11 (s, 2 H), 5.0 (br t, 1 H), 4.32 (t, 2 H, J = 5.2), 3.52 (q, 2 H, J = 5.3), 2.46 (s, 3 H).

***N*-(Benzyloxycarbonyl)-2-(methoxycarbonyl)-3-oxomorpholine (34).** The carbenoid insertion reaction was performed as described above, using 5 mol % of $Rh_2(OAc)_4$. The cyclized product was isolated by column chromatography (silica gel, CH_2Cl_2/EtOAc, 3/1) in 16% yield: IR ($CHCl_3$) 2980, 1715 cm^{-1}; ^{1}H NMR δ 7.36 (s, 5 H), 5.30 and 5.40 (2 s, 1 H total), 5.15 (m, 2 H), 4.4 (m, 2 H), 3.8 (m, 2H), 2.29 and 2.47 (2 s, 3 H total). Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.6; H, 5.5; N, 5.1. Found: C, 60.7; H, 5.5; N, 4.9.

Methyl 5-Hydroxy-3-oxopentanoate[28] (37). To methyl 5-(benzyloxy)-3-oxopentanoate[28] (**36**; 1.50 g, 6.0 mmol) in CH_3OH was added 10% Pd/C (0.15 g). The suspension was stirred under 1 atm of H_2 for 20 h, and then the catalyst was removed by filtration and the filtrate was evaporated. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9/1) to give **37** in 47% yield: IR (neat) 3400–3500, 2950, 1730, 1710 cm^{-1}; ^{1}H NMR δ 3.80 (br m, 2 H), 3.68 (s, 3 H), 3.47 (s, 2

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H), 2.9 (br s, 1 H), 2.74 (t, 2 H, J = 5.5).

Methyl 2-Diazo-5-hydroxy-3-oxopentanoate (38). The diazo transfer reaction was performed on **37** in the standard manner to give **38** in 77% yield after purification by column chromatography on silica gel (CH_2Cl_2/EtOAc, 9/1): IR ($CHCl_3$) 3400–3600, 2960, 2140, 1720 cm^{-1}; ^1H NMR δ 3.92 (br m, 2 H), 3.85 (s, 3 H), 3.11 (t, 2 H, J = 5.5), 2.9 (br s, 1 H).

2-(Methoxycarbonyl)-3-oxotetrahydrofuran (39). The carbenoid insertion reaction was performed with 1.5 mol % of $Rh_2(OAc)_4$ as described above to give **39** in quantitative yield: IR ($CHCl_3$) 2960, 1740 cm^{-1}; ^1H NMR δ 4.3–4.6 (m, 3 H), 3.78 (s, 3 H), 2.59 (t, 2 H, J = 7.8); mass spectrum for $C_6H_8O_4$, calcd m/e 144.0423, found m/e 144.0420.

Ethyl 5-(*S*-trityl)-3-oxopentanoate (46) was prepared by the general procedure for synthesizing β-keto esters. The crude product was pure enough to use in the next reaction; for analysis the material was chromatographed (hexanes/EtOAc, 1/1): 88% yield; mp 97–98 °C; IR ($CDCl_3$) 2890, 1730, 1710 cm^{-1}; ^1H NMR δ 7.48–7.2 (m, 15 H), 4.15 (q, 2 H, J = 7.2), 3.28 (s, 2 H), 2.43 (m, 4 H), 1.25 (t, 3 H, J = 7.1). Anal. Calcd for $C_{26}H_{26}O_3S$: C, 74.6; H, 6.3. Found: C, 75.0; H, 6.2.

Bis(ethyl 3-oxo-5-mercaptopentanoate) (43). To **46** (2.0 g, 4.78 mmol) in CH_2Cl_2/EtOH (2/1, 30 mL) was added iodine (2.7 g, 10.6 mmol). The solution was stirred at room temperature for 40 min and then diluted with saturated $NaHSO_3$ and extracted with ether. The ether solution was dried (Na_2SO_4), evaporated, and chromatographed on silica gel (hexanes/EtOAc, 7/3). Isolation of the lowest R_f spot gave **43** as a yellow mobile oil (627 mg, 75%): IR ($CDCl_3$) 2980, 1735, 1715 cm^{-1}; ^1H NMR δ 4.16 (q, 4 H, J = 7.1), 3.46 (s, 4 H), 2.96 (t, 4 H, J = 6.6), 2.85 (t, 4 H, J = 6.6), 1.25 (t, 6 H, J = 7.1). Anal. Calcd for $C_{14}H_{22}O_6S_2$: C, 48.0; H, 6.3. Found: C, 47.9; H, 6.3.

Bis(ethyl 2-diazo-3-oxo-5-mercaptopentanoate) (47) was prepared by the general procedure for diazo transfer reactions. The crude product was chromatographed twice (hexanes/EtOAc, 7/3) to give **47** as a yellow oil in 78% yield: IR ($CDCl_3$) 2980, 2140, 1705, 1640 cm^{-1}; ^1H NMR δ 4.26 (q, 4 H, J = 7.1), 3.23 (t, 4 H, J = 7.1), 2.92 (t, 4 H, J = 7.1), 1.28 (t, 6 H, J = 7.1).

Ethyl 2-Diazo-3-oxo-5-mercaptopentanoate (48). To **47** (514 mg, 1.28 mmol) dissolved in acetonitrile (2 mL) and aqueous potassium carbonate (0.5 mL, 0.2 M) was added dithioerythritol (395 mg, 2.56 mmol). The solution was stirred at room temperature for 15 min and then added to an ether/water mixture. The aqueous layer was extracted several times with ether, and then the organics were dried (Na_2SO_4) and evaporated to give an oil. Chromatography on silica gel (hexanes/EtOAc, 7/3) led to isolation of the material with the highest R_f as a light yellow oil: 305 mg (59%); IR ($CDCl_3$) 2980, 2135, 1708, 1640 cm^{-1}; ^1H NMR δ 4.31 (q, 2 H, J = 7.1), 3.20 (t, 2 H, J = 6.7), 2.79 (m, 2 H), 1.69 (t, 1 H, J = 8.4), 1.34 (t, 3 H, J = 7.1).

2-(Ethoxycarbonyl)-3-oxotetrahydrothiophene (49) was prepared by the general procedure for $Rh_2(OAc)_4$-catalyzed X–H carbenoid insertions. The solution was refluxed for 1 h, with 1.5 mol % of $Rh_2(OAc)_4$ in benzene, concentrated in vacuo, dissolved in CH_2Cl_2, and then filtered through silica gel to remove the red rhodium residues. The oil obtained on evaporation was Kugelrohr distilled (50 °C (~0.5 mm)) to give **49** as a colorless oil in 73% yield: IR (CH_2Cl_2) 2960, 1740, 1720 cm^{-1}; ^1H NMR δ 4.23 (m, 2 H), 4.01 (s, 1 H), 3.33 (m, 1 H), 3.08 (m, 1 H), 2.90 (m, 1 H), 2.67 (m, 1 H), 1.30 (t, 3 H, J = 7.2); ^{13}C NMR DEPT δ 62.3 (i), 52.1, 38.8 (i), 25.4 (i), 14.1; mass spectrum, m/e 174 (M^+, 56.65). Anal. Calcd for $C_7H_{10}O_3S$: C, 48.3; H, 5.8. Found: C, 48.4; H, 5.9.

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Registry No. **6a**, 56-40-6; **6b**, 107-95-9; **6c**, 56-12-2; **6d**, 660-88-8; **7a**, 1138-80-3; **7b**, 2304-94-1; **7c**, 5105-78-2; **7d**, 23135-50-4; **8a**, 82961-77-1; **8a** (imidazolide), 99017-59-1; **8b**, 99017-63-7; **8b** (imidazolide), 99017-60-4; **8c**, 84446-29-7; **8c** (imidazolide), 99017-61-5; **8d**, 99017-64-8; **8d** (imidazolide), 99017-62-6; **9a**, 99017-65-9; **9b**, 99017-66-0; **9c**, 99017-67-1; **9d**, 99017-69-3; **10**, 99017-68-2; **16**, 99017-70-6; **17**, 99017-88-6; **19**, 92249-27-9; **20**, 99017-71-7; **21**, 99017-72-8; **22**, 99017-73-9; **24**, 29689-63-2; **25**, 99017-74-0; **28**, 77987-49-6; **29**, 99017-75-1; **30**, 99017-76-2; **32**, 99017-77-3; **33**, 99017-78-4; **34**, 99017-79-5; **36**, 99017-80-8; **37**, 99017-81-9; **38**, 99017-82-0; **39**, 99017-83-1; **40**, 107-96-0; **43**, 99017-85-3; **45**, 27144-18-9; **46**, 99017-84-2; **47**, 99017-86-4; **48**, 99017-87-5; **49**, 80278-79-1; $MeOCOCH_2CO_2H$, 16695-14-0; $EtOCOCH_2CO_2H$, 1071-46-1; (MeOCOCHCOO)Mg, 57907-72-9; diketene, 674-82-8.

Phase-Transfer Catalysis by Poly(ethylene glycol)s of β-Thioethyl Chloride Reactions

J. Milton Harris,* M. Steven Paley, M. R. Sedaghat-Herati, and Samuel P. McManus

Department of Chemistry, University of Alabama in Huntsville, Huntsville, Alabama 35899

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Neighboring sulfur participation is a facile process for β-thioethyl derivatives. In the present work we examine the ability of phase-transfer catalysis by poly(ethylene glycol)s to make direct substitution, elimination, and oxidation competitive with neighboring sulfur participation for reaction of mustard chlorohydrin (1).

There has been much recent interest in the use of poly(ethylene glycol) (PEG) and its derivatives as phase-transfer agents.[1-8] In the present work we describe our use of these agents for catalysis of reactions of β-thioalkyl chlorides. These processes are of interest because of the difficulty in achieving reactions other than neighboring sulfur assisted (k_Δ) displacement in ionizing media. Thus we have shown that neighboring group participation by sulfur (and accompanying carbon scrambling) is much more facile than direct solvolytic displacement (a k_s process).[9] This inertness toward direct nucleophilic substitution is especially interesting in view of the facility with

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