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THE ACID PROMOTED DECOMPOSITION OF α-DIAZO KETONES

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CONTENTS

DIAZO KETONES

General perspectives

In 1927 Arndt *et al.*,[1] and later Robinson and Bradley,[2] demonstrated that α-diazo ketones can be prepared in near quantitative yield by reaction of an acid chloride with excess diazomethane. Since that time, α-diazo ketones have received considerable attention, enjoying wide application as useful synthetic intermediates.[3,4] Undoubtedly, the most important example of their preparative significance is the Arndt–Eistert procedure[5] for converting a carboxylic acid to its homologous acid or acid derivative. In addition, diazo ketones can be induced to undergo a variety of related reactions such as addition to olefins and insertion into C–H bonds.[6,7]

Two principal reactive intermediates are available from α-diazo ketones, they are: α-ketocarbenes (or carbenoids) and α-diazonium ketones. Loss of nitrogen from α-diazo ketones by thermal, photolytic, or metal ion catalysis affords the α-ketocarbene and/or carbenoid intermediate which can, depending upon the substrate structure and reaction conditions, undergo: (a) the Wolff rearrangement, (b) insertion reactions, (c) addition to multiple bonds, (d) 1,3-dipolar additions and (e) dimerization reactions.

Second, reaction of α-diazo ketones with electrophilic reagents affords the highly reactive diazonium ketone. Nucleophilic substitution with displacement of nitrogen is the major reaction pathway here. Thus, treatment of α-diazo ketones with hydrohalic acid in polar solvents such as glacial acetic acid affords the α-halo ketone.[4] Similarly, reaction of diazo ketones with bromine[4] gives α-dibromoketones, while reaction with water in dilute mineral acids affords α-hydroxymethyl ketones. Ester derivatives of hydroxymethyl ketones can be prepared by reaction of an organic acid with the appropriate α-diazo ketone.

Collectively, these observations suggested that acid promoted decomposition of diazo ketones, containing a suitable internal nucleophile, could undergo a reaction leading to intramolecular cyclization. That is, if an appropriate nucleophilic olefin or aromatic ring were to participate efficiently in this cyclization process, a reaction of considerable synthetic utility would be available. Prior to the work of

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Dahn, Mander, and that of our laboratory, no systematic study of the acid promoted cyclization of aromatic and olefinic α-diazo ketones had been undertaken.

Intramolecular cyclization (i.e. alkylation) of α-diazo ketones initiated by acid can be conveniently classified according to the nature of the participating nucleophile. Consequently, in this review the intramolecular cyclization of α-diazo ketones will be discussed in terms of the participating nucleophile (i.e. heteroatom, aryl, olefinic or single bond). We note in advance that this presentation is merely a formal classification and does not necessarily imply that participation of the internal nucleophile is concerted with nitrogen loss.

In an extension of the simple or mono-cyclization process, we have recently demonstrated that the α-diazo ketone functionality is a moderately effective initiator of polyolefinic cationic cyclization. Accordingly, a brief discussion of polyolefinic cationic cyclization is presented in this review in order that our more recent results are placed in perspective.

Mechanistic considerations

Kinetic studies have revealed that acid catalyzed decomposition of primary α-diazo ketones[8,9] occur via rapid protonation in a pre-equilibrium step followed by nucleophilic substitution in a rate determining step (eqn 1), whereas secondary diazo ketones[10,11] and a few primary diazo ketones[12] undergo protonation in a rate determining step followed by rapid nucleophilic substitution (eq. 2). This latter pathway

$$R\overset{O}{C}CHN_2 \xrightleftharpoons{H^+} R\overset{O}{C}CH_2N_2^+ \xrightarrow[r.d.s.]{X^-} R\overset{O}{C}CH_2X + N_2 \qquad \text{eq 1}$$

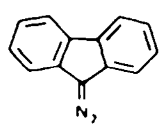
$$R\overset{O}{C}CHN_2 \xrightarrow[r.d.s.]{H^+} R\overset{O}{C}CH_2N_2^+ \xrightarrow[fast]{X^-} R\overset{O}{C}CH_2X + N_2 \qquad \text{eq 2}$$

(A-S_E2 mechanism) is characterized by a solvent kinetic isotope effect $k_{H_2O}/k_{D_2O} > 1.0$; the former pathway, on the other hand, has a kinetic isotope effect of $k_{H_2O}/k_{D_2O} = 0.3$–0.5.

The substitution step in eq. (1) can in principle occur either by a step wise (S_N1) or concerted (S_N2) pathway. Evidence for both reaction pathways can be found in the literature. For example, Lane and Feller,[13] on the basis of activation entropies (−18 to −23 cal deg^{-1}) and the direct dependence of rate upon concentration of added nucleophiles, proposed an S_N2 mechanism for the acetolysis of several diazoacetophenones. Later, Dahn[14] and Gold investigated the decomposition of a series of diazo ketones at various concentrations of perchloric acid in aqueous dioxane. The small negative entropies of activation (−6 to −2 cal deg^{-1}) and the correlation with Hammett's acidity function were interpreted as supporting an A-1 (S_N1cA) mechanism. More O'Ferrall,[9] however, has pointed out that neither of these criteria is definitive.

Later investigations by Dahn,[10] Tillett,[15] and Thomas[16] demonstrated that primary diazo ketones in general undergo a rapid pre-equilibrium protonation and subsequent substitution requiring participation of the nucleophile in the transition state. The S_N2 character of this substitution reaction has been observed for nucleophiles as weak as water.[10,15] These investigations, coupled with the well studied decomposition of ethyl diazoacetate[8,9] which undergoes S_N2 displacement of nitrogen, suggest that most primary diazo ketones undergo S_N2 reaction in the substitution step. The possibility remains, however, that the pathway for decomposition of a particular diazo ketone may be altered by substrate structure, concentration, reactivity of the nucleophiles,[16] and/or choice of solvent.

Similarly, the substitution step in eq. (2) can occur either by a stepwise or concerted pathway. Since this step occurs after the rate determining step, kinetic data does not reveal which pathway is operative. Warren,[17] in a study of the acid catalyzed solvolysis of 9-diazofluorene 1, found rate determining protonation and general acid catalysis for the solvolysis reaction characteristic of the A-S_E2 mechanism. Since the solvolysis products were formed independently of the nucleophilicity of the nucleophiles examined, the loss of nitrogen was believed to occur in a unimolecular fashion to yield an intermediate



(1)

$CH_3\overset{O}{C}CRN_2$

(2)

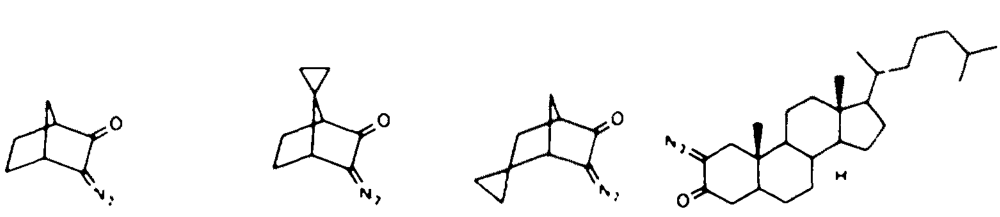
(a) R = CH_3
(b) R = CH_2CH_3
(c) R = C_6H_5

carbonium ion. Similarly, in an investigation of solvolysis of secondary diazo ketones, Dahn[10,11] observed general acid catalysis and solvent kinetic isotope effects of $k_{H_2O}/k_{D_2O} > 1.0$ for methyl ketones 2a–c as well as 2-diazocyclohexanone, diazocamphor and 2-diazoindanone. In particular the product determining step for methyl ketones 2a–c, which affords both alcohols and olefins, is independent of added nucleophiles. These observations were interpreted in terms of free α-ketocarbonium ions.[10,11] As More O'Ferrall[9] has pointed out, competition between proton loss and nitrogen loss may be critical in determining the reaction pathway. That is, rate determining protonation can apparently occur under two very different circumstances. In the first case, illustrated by secondary diazo ketones[10,11] and 9-diazofluorene,[17] the resulting carbonium ion is sufficiently stabilized so that unimolecular loss of nitrogen is faster then deprotonation. In the second case, illustrated by the cyclization of diazo ketone[18] 3, loss of nitrogen is enhanced by anchimeric assistance of the participating olefin to such an extent that protonation becomes rate determining. This is an example of the substitution step in eq (2) occurring by a S_N2 or concerted pathway. In addition, the relative basicity of the diazo ketone[10] should have some influence on the rate of deprotonation.

The specific site of protonation or Lewis acid complexation on the diazo ketone framework has important mechanistic implications. The most likely sites of protonation are carbon and oxygen although, in principle, protonation on nitrogen is a possibility. In this regard, EHMO calculations[19] indicate that the oxygen atom is the most negative site in the diazo ketone functionality. This view is also supported by NMR[20] and IR spectra[21] which suggest that the canonical form 4 makes a major

(3) (4) (5) (6)

contribution to the diazo ketone structure. Moreover, Dahn and Wentrep[22] and Allard and Levisalles[23] have shown, by NMR studies, that protonation of diazo ketones in magic acid occurs exclusively on oxygen. The observation of two diazonium ions (corresponding to the *syn* and *anti* isomers 5 and 6) and the failure of the methine proton to undergo H–D exchange is strong evidence for exclusive O-protonation. In this strong acid medium the diazo ketone is completely protonated and there is no equilibrium with C-protonated intermediates. In contrast, Dahn *et al.*[24] have reported acid catalyzed deuterium incorporation at the α-diazo carbon atom in heavy water/dioxane mixtures. This H–D exchange occurs in a rapid pre-equilibrium step prior to nitrogen loss and suggests that carbon protonated intermediates may exist in an equilibrium process. In this regard, the products formed from decomposition of diazo ketones 7–10 are best explained[8,25] by protonation on carbon followed by concerted



(7) (8) (9) (10)

rearrangement and displacement of nitrogen. It has been noted, however, that the aqueous acid decomposition of diazo ketones 7–10 may proceed through the hydrated diazonium ion.[9] In addition, the cyclization of a γ,δ-unsaturated diazo ketone (3)[18] proceeds with anchimeric assistance by the olefin to such an extent that protonation is rate determining and irreversible. Protonation on oxygen would require, therefore, the unattractive occurrence of an S_N2 displacement at an sp^2 center. The possibility remains, however, that the oxygen protonated intermediate does not undergo reaction[26] and must equilibrate to the carbon or nitrogen protonated intermediate for concerted cyclization to occur. Finally, the ability of α-diazo ketones to participate in intermolecular H-bonding[27] raises the possibility that the site of protonation may be solvent dependent. In this regard, protonation could occur on carbon in an aqueous medium capable of H-bonding and on oxygen in non-aqueous solvents.

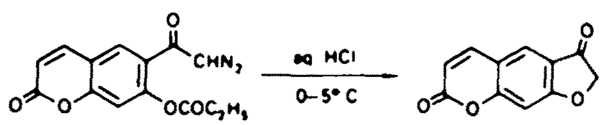
The site of complexation of Lewis acids with diazo ketones is equally unclear. The alkylation of α-diazoketones with alkylboranes[28] has been postulated to involve β-ketoboranes resulting from complexation at carbon. Subsequent alkyl migration from boron to carbon with prior or concurrent loss of nitrogen would yield the observed alkylated ketones. Attempted isolation of the reactive intermediates, however, yielded only vinyloxyboranes.[29] As is noted, these results do not exclude the possibility of an initially formed α-boryl derivative undergoing rapid rearrangement to the vinyloxyborane.

It appears firmly established that the acid catalyzed decomposition of α-diazo ketones involves formation of a highly electrophilic diazonium ion which undergoes facile nucleophilic substitution with loss of nitrogen. There is, however, good kinetic data only for the hydrolysis of simple α-diazo ketones and several mechanistic pathways (A-1, A-2 and A-S_E2) have been observed. This mechanistic information provides a conceptual framework for the subsequent discussion of acid catalyzed intramolecular cyclization of α-diazo ketones. The actual nature of the reactive intermediates in these cyclizations is, however, merely speculative.

2. HETEROATOM PARTICIPATION

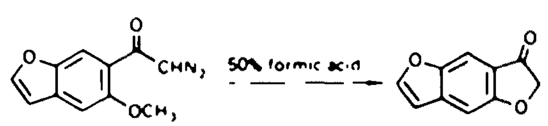
The first example of heteroatom participation in the intramolecular cyclization of an α-diazo ketone was reported in 1935 by Eistert and Krzikalla.[30] These investigators found that o-hydroxy diazo ketone **11**, when treated with mineral acid, affords furanone **12**. Three years later, Haberland and Siegert[31] demonstrated in a similar substrate that the cyclization process was unaffected by methylation of the phenolic hydroxy group. Similarly, Bruchhausen and Hoffman[32] reported the cyclization of diazo ketone **13** in cold aqueous hydrochloric acid, while Seetharamiah[33] prepared furanone **15** by treatment of diazo

(11) (12) (64%)

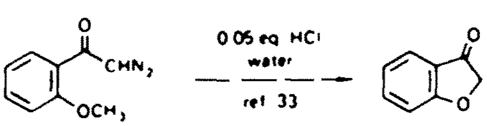


(13) (62%)

ketone **14** with 50% formic acid. More recently several groups[34a-d] have investigated diazo ketone **16**. In this case the cyclization could be induced via acetic acid,[34a] hydrochloric acid,[34d] or silver oxide.[34c] The



(14) (15) (35%)

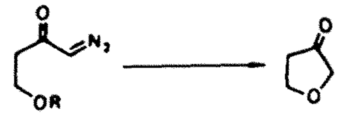


(16) (87%)

parent furanone **18** has been prepared by the acid catalyzed cyclization of diazo ketones **17(a-d)**.[35] The yield of **18** was dependent upon the ability of R to leave the intermediate oxonium ion as a positively charged species. Finally, diazo ketone **19** undergoes a facile conversion[36] to lactone **20** when treated with hydroiodic acid.

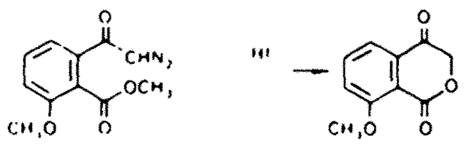
The ready formation of 4-membered rings can also be accomplished via the acid catalyzed decomposition of α-diazo ketones. For example, decomposition of **21** with acetic acid[37] afforded oxetanone **22** while reaction of diazo ketone **23** with phosphoric acid in dioxane[38] gave oxetanone **24**. Finally, the parent compound, oxetan-3-one, has been prepared from the diazo ketone derived from glycolic acid.

That nitrogen nucleophiles effectively participate in this cyclization process was demonstrated by Moore *et al.* For example, treatment of **25** with glacial acetic acid[39] gave **26** while **27** or **28** afforded **29** and **30**,



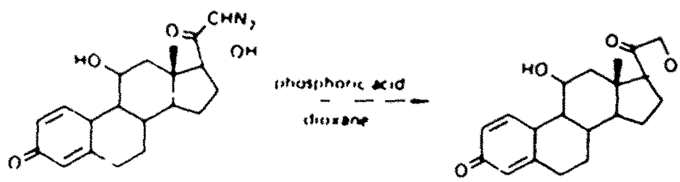
(17) (18)

(a) R = CH_3 (5%)
(b) R = i-C_3H_7 (17%)
(c) R = t-Bu (47%)
(d) R = CH_2Ph (42%)



(19) (20)

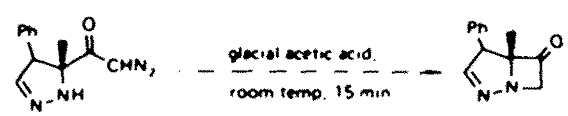
(21) (22)



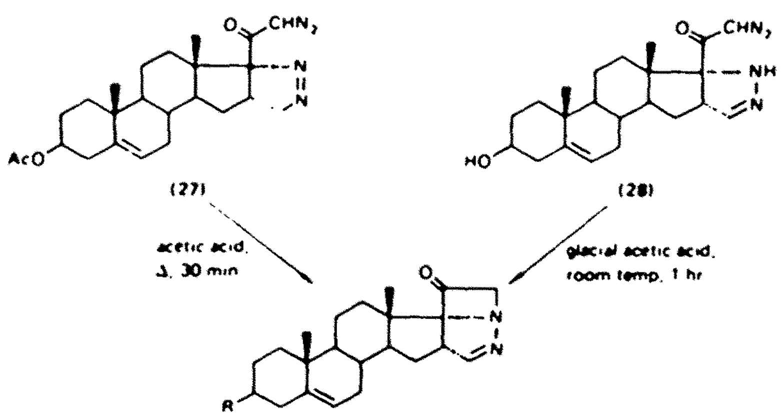
(23) (24)

respectively, in excellent yield when treated with acetic acid. These observations are in sharp contrast to the normally unfavorable formation of 4-membered rings in solvolytic processes.[41]

The first indication that formation of 6- or 7-membered cyclic systems was less favorable than formation of 4- or 5-membered ring systems was obtained by Moore *et al.* For example, chromanones



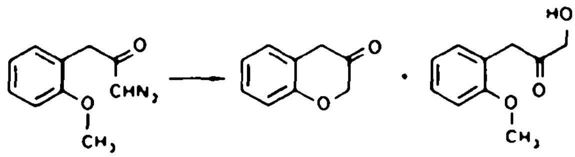
(25) (26)



(27) (28)

(29) R = OAc (86%)
(30) R = OH (78%)

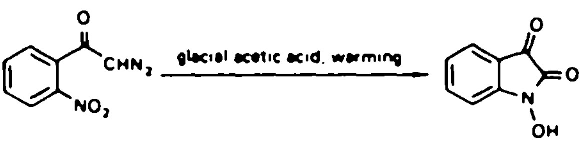
are reported to be produced from the appropriate diazo ketones in only poor yield. This observation must be contrasted with the ready preparation of furanones and oxetanones as described above. In particular, Sheffer and Moore[42] examined a variety of acid catalysts, solvents, and catalyst-diazo ketone ratios in the decomposition of diazo ketone **31**. While most of the conditions explored led predominantly to the uncyclized α-hydroxymethyl ketone **33**, 1.5 equivalents of BF_3 in ether was found to give chromanone **32** in 35% yield. No cyclization products were observed from the next higher homologue of **31**. The poor yield of cyclization products in the case of **31** and its homologue was attributed both to ring size (i.e. the entropy of cyclization) and the formation of a tight ion pair between the diazonium ion and the gagen ion in solvents of low dielectric constant. Interestingly, the reaction was not examined in non-nucleophilic solvents of high dielectric constant.



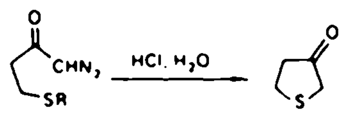
(31) (32) (33)

Solvent	Acid	Acid eq	Yield (percent)	
			(32)	(33)
Ether	Acetic	3.4	--	42
Ether	Sulfuric	1.0	4	19
Aq dioxane	Sulfuric	0.04	15	45
Ether	BF_3	1.5	35	—

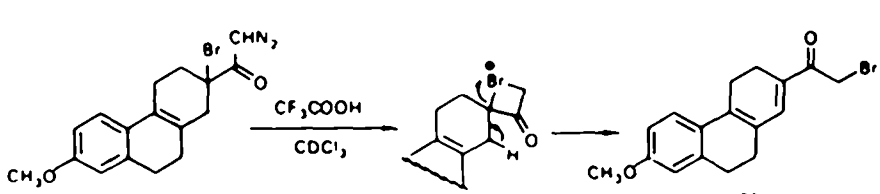
Participation of nitro groups,[43a–b] as well as sulfur[35] and bromine[44] substituents has been reported. In particular, nitro diazo ketone **34** affords N-hydroixyisatin **35** while diazo ketones **36** and **38** afford **37** and **39**, respectively.



(34) (35)



(36) (37)

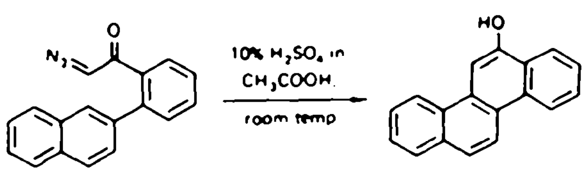


(38) (39)

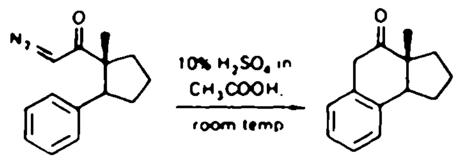
3. ARYL PARTICIPATION

In 1945 Cook and Schoental[45] provided the first example of aryl participation in the acid promoted decomposition of a diazo ketone. Interested in the preparation of polynuclear hydrocarbons, they obtained 2-chrysenol **41** by reaction of diazo ketone **40** with 10% sulfuric acid in acetic acid. Several years later, this procedure was employed by Newman[46] for the preparation of **43** from diazo ketone **42**.

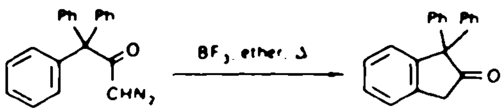
Later still, Wilds *et al.*[47] reported the quantitative preparation of indanone **45** when diazo ketone **44** was treated with $BF_3 \cdot Et_2O$ in ether heated at reflux. These reactions may be viewed as intramolecular alkylation of the aromatic nucleus by the diazo ketone functionality.



(40) (41)

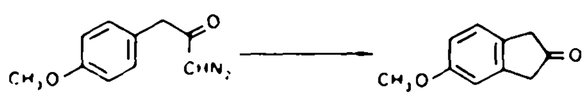


(42) (43)

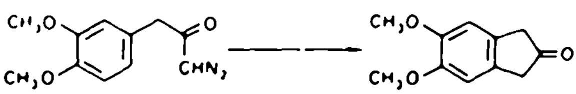


(44) (45)

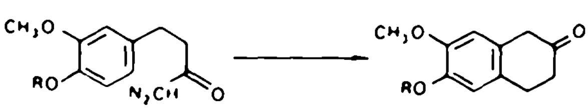
Although unrecognized at the time, formation of **45** can occur by either of two reaction pathways depending upon the initial site of aryl participation (Ar_1-4 or Ar_2-5 according to the notation of Winstein[48]). That is, recent unpublished results of Mander,[49] employing diazo ketones **46**–**48**, demonstrated that the favored mode of cyclization is Ar_1-4 > Ar_2-5, and Ar_1-5 > Ar_2-6. For example, cyclization or **48b** involves 40% Ar_1-5 and 20% Ar_2-6 participation.



(46) (27%)



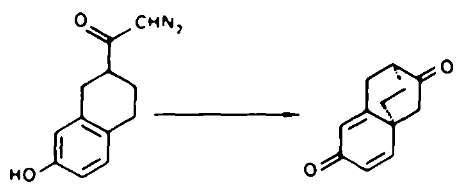
(47) (30%)



(48) (60%)
(a) R = OCH_3
(b) R = OCD_3

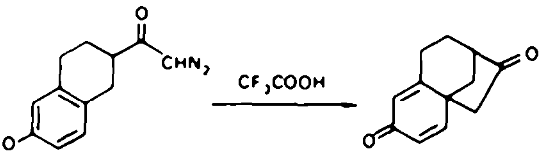
In searching for a suitable functionality that would undergo intramolecular alkylation of the anisole nucleus, Mander initiated in 1971 the first of what was to prove to be a series of elegant and systematic investigations of the acid promoted decomposition of aromatic diazo ketones. Of special interest here was the generation of fused polycyclic compounds bearing, as a result of the intramolecular alkylation, an angular substituent. These compounds were required as synthetic intermediates for the total synthesis of diterpenes. The first system examined by Mander, namely diazo ketone **49**,[50] was subjected to a wide variety of acid catalysts chosen for the non-nucleophilic character of their respective conjugate base. Initially, $BF_3 \cdot Et_2O$ in nitromethane gave the highest yield (35%) of cyclized product (**50**), although later experimentation demonstrated that trifluoroacetic acid was more effective (48%).

In order to assess the generality of this cyclization, Manders' laboratory investigated the decomposition of diazo ketones **51**, **53**, **57**, **60** and **63**. This series of experiments demonstrated that[51,52] the



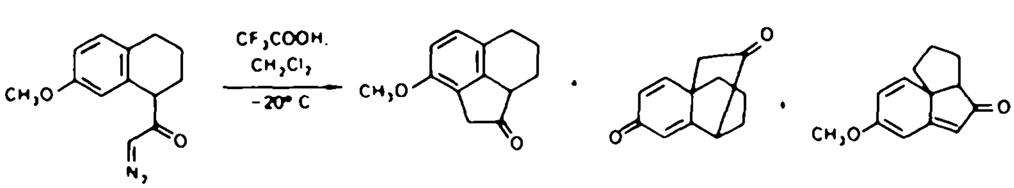
(49) (50)

bicyclo[3.2.1]octane carbon skeleton was readily available from the appropriate diazo ketone. For example, reaction of **51a–b** with trifluoroacetic acid afforded the dienedione **52** in 96% and 86% yield, respectively. Similarly, cyclization of **51a** and **51b** with $BF_3 \cdot Et_2O$ or HBF_4 in nitromethane gave



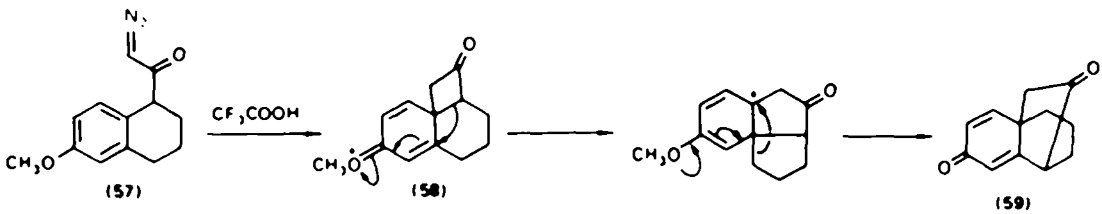
(51) (52)
(a) R = H
(b) R = CH_3

dienedione **52** in 74 and 10–20% yield, respectively. The only additional volatile by-product was the α-hydroxymethyl ketone resulting from solvent participation and subsequent hydrolysis. Similar decomposition of diazo ketone **53** afforded the *ortho* and *para* alkylated products, **54** and **55** in 62 and 3% yield, respectively, as well as **56** in 11% yield.



(53) (54) (62%) (55) (3%) (56) (11%)

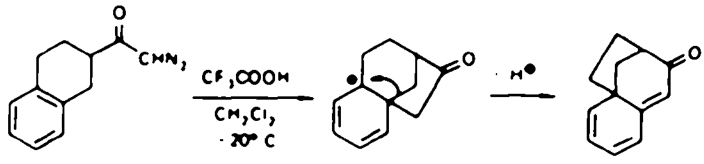
A somewhat more complex rearrangement, presumably involving the above cyclization process, is the decomposition of diazo ketone **57** with trifluoroacetic acid. In this case dione **59** was obtained in 58% yield. Presumably, the initial cyclization leads to cyclobutanone **58** which subsequently undergoes



(57) (58) (59)

rearrangement to **59**. This example again demonstrated the facile formation of four-membered ring derivatives upon acid catalyzed decomposition of appropriately substituted diazo ketones. In addition the results from diazo ketones **51**, **53**, **57**, **60** and **63** are consistent with the earlier observations of Moore[42] indicating that formation of four-and five-membered rings is a more efficient process than formation of large ring systems.

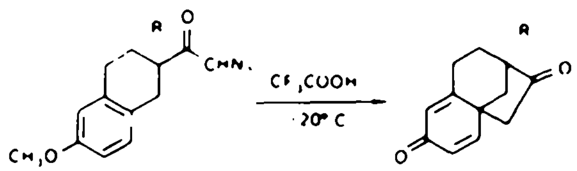
Mander also explored the minimum nucleophilic character required for aryl participation. In particular he demonstrated that a methoxy substituent was not required for successful cyclization. The system chosen for this study was that of diazo ketone **60**. In this case decomposition with trifluoroacetic acid gave enone **62** in moderate yield (56%). Enone **62** presumably arises via rearrangement of the initially formed carbonium ion (**61**). The fact that this yield is significantly lower than observed for the



(60) (61) (62) (56%)

corresponding OMe derivative reveals the importance that the nucleophilicity of the participating π-system and the stability of the initially formed carbonium ion play in these cyclization reactions.

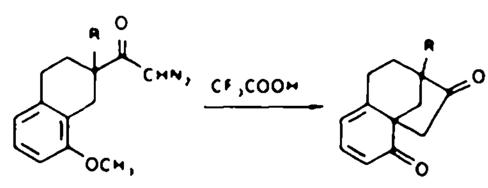
Mander next turned his attention towards the acid catalyzed decomposition of diazo ketone **63** as a potential entré to the C-13 hydroxy giberellins. Initial attempts to effect cyclization of **63b** or the free



(63) (64)

(a) R = OH (0%)
(b) R = $OCOCH_3$ (16%)
(c) R = $OCOCF_3$ (70%)
(d) R = $OCOCCl_3$ (88%)
(e) R = $OCOCHCl_2$ (85%)

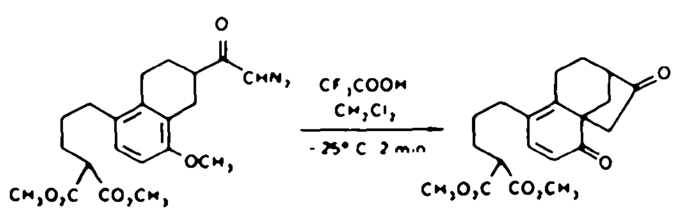
hydroxy species **63a** yielded only β-oxetanones with little (16%) or no aryl participation. However, reaction of the trifluoroacetate derivative **63c** in trifluoroacetic acid afforded hydroxy dione **64a** in good yield (70%). Similarly diazo ketones **63d–e** gave excellent yields of dienediones **64–e**.[33] More recently, this methodology has been extended to the preparation of cyclohexa-2,4-dienones **66a–d** from diazo ketones **65a–d**.[49,33]



(65) (66)

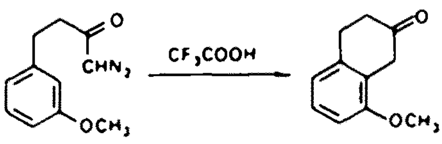
(a) R = $OCOCCl_3$ (82%)
(b) R = $OCOCHCl_2$ (73%)
(c) R = CH_3 (100%)
(d) R = H (68%)

The latter cyclization (i.e. **65a** to **66a**) was exploited as the cornerstone in Mander's elegant total synthesis of (±)-gibberellin A_1 and gibberellic acid.[34] In a closely related strategy for the gibberellins, the cyclization of diazo ketone **67** to **68** proved to be the pivotal transformation.[35]



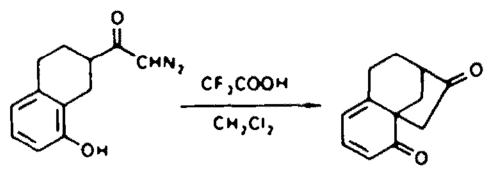
(67) (68) (74%)

In a companion study, Mander and Johnson[56] investigated the *ortho* alkylation of phenolic diazo ketones 71 and 73. The interest, here, was again the construction of intermediates useful in a synthetic approach to gibberellins. The cyclization of diazo ketone 69 was examined as a possible route to tetralone 70 from which diazo ketones 71 and 73 could be prepared. Reaction of 69 with trifluoroacetic acid afforded tetralone 70 in low yield (20%) and, interestingly, gave no products arising from closure *para* to the OMe group.



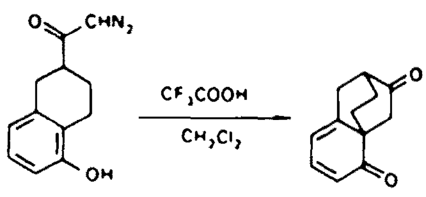
(69) (70) (20%)

On the other hand, reaction of phenolic diazo ketones 71 and 73 with trifluoroacetic acid gave the desired cyclohexa-2,4-dienones 72 and 74, respectively in excellent yields.



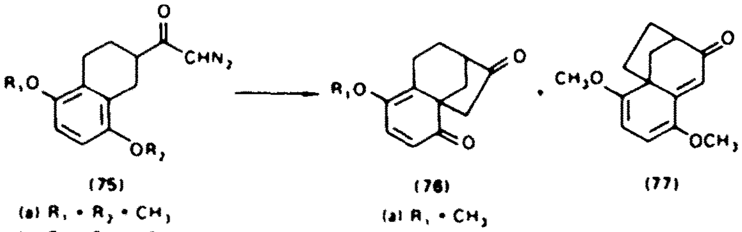
(71) (72) (96%)

Interestingly, formation of the bycyclo[3.2.1]octane system (72) is more efficient than formation of the bicyclo[2.2.2]octane system (74), a result consistent with earlier observations. This tendency was confirmed by more recent studies[57] in which only products containing the bicyclo[3.2.1]octane ring



(73) (74) (76%)

system were observed in the decomposition of diazo ketones 75a–c. More specifically, treatment of diazo ketone 75a gave dienedione 76a in 61% yield and varying amounts of the rearranged product 77, while diazo ketones 75b–c gave only 76b in 100 and 63% yield, respectively. These results, however, were attributed to steric interactions in the transition state leading to the bicyclo[2.2.2]octane ring system rather than the normal preference for 5-membered ring formation in kinetically mediated reactions.[57]

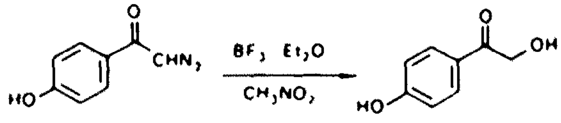


(75)
(a) $R_1 = R_2 = CH_3$
(b) $R_1 = C_2H_5$, $R_2 = H$
(c) $R_1 = C_2H_5$, $R_2 = CH_3$

(76)
(a) $R_1 = CH_3$
(b) $R_1 = C_2H_5$

(77)

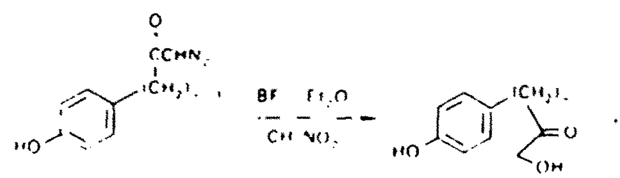
To explore further the mechanistic details of intramolecular alkylations of α-diazo ketones, Beames and Mander[58] investigated the possible preparation of spirodienediones from simple phenolic derivatives. For example, decomposition of diazo ketone 78 with $BF_3 \cdot Et_2O$ in nitromethane gave hydroxy methyl ketone 79 in 81% yield.



(78) (79) (81%)

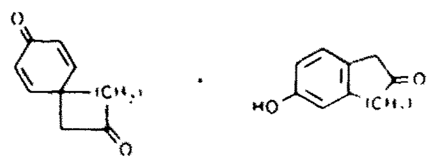
Since the reaction was conducted under stringently anhydrous conditions, **79** most likely results from hydrolysis of an intermediate nitro species, as suggested by Mander. This nitro species could arise via the displacement of nitrogen by the oxygen atom of nitromethane. However, a rate enhancement for this decomposition compared to diazoacetophenone and diazoacetone was taken as evidence for aryl participation. That is, Mander attributed this rate enhancement to the formation of a spirocyclopropanone, which subsequently undergoes nucleophilic ring opening by solvent (CH_3NO_2) to generate the intermediate nitro species.

Similar treatment of **80a** gave **81a**, **82a** and **83a** with dienedione **82a** and indianone **83a** accounting for 56% of the reaction mixture. Under these reaction conditions, dienedione **82a** was observed to undergo a facile dienedione-phenol rearrangement to yield indanone **83a**. Continuing this study, Beames and Mander demonstrated that diazo ketone **80b** gave dienedione **82b** (67%) and hydroxymethyl ketone **81b**



(80) (81)

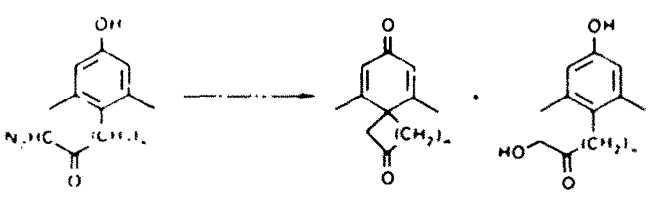
(a) n = 4
(b) n = 5
(c) n = 6
(d) n = 7



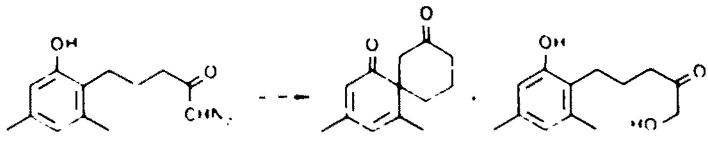
(82) (83)

(13%). Here also, the spiro ketone **82b** underwent, albeit more slowly than **82a**, dienedione-phenol rearrangement to **83b**. Diazo ketones **80c–d** on the other hand, yielded the hydroxymethyl ketones **81c–d** as the major decomposition products. No cyclization products were observed with diazo ketone **80d**, while **82c** and **83c** were obtained in a combined yield of 11%. This study further demonstrates that the cyclization of α-diazo ketones is markedly dependent upon the degree of rotational freedom in the specific system. Only in the case of **80a** and **80b**, each of which contain a relatively short methylene side chain, were the yields of cyclized products synthetically significant.

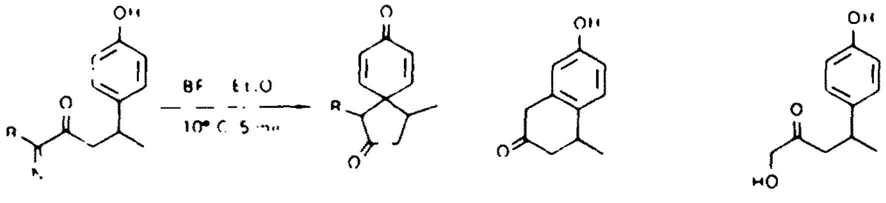
Similar results have been reported by Sen *et al.*[59] for the decomposition of diazo ketones **84–86a–b**. Significantly, the formation of **87b** from diazo ketone **86b** represents the first reported successful cyclization of a secondary α-diazo ketone.



(84)
(a) n = 1 (a) (30%) (18%)
(b) n = 3 (b) (20%) (25%)



(85) (19%) (27%)

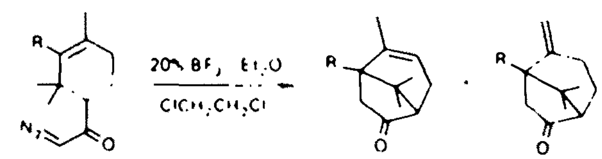


(86)
(a) R = H
(b) R = CH₃

(87)
(a) R = H (30%)
(b) R = CH₃

4. OLEFINIC PARTICIPATION

The first examples of intramolecular olefinic participation in the acid promoted decomposition of α-diazo ketones were reported by Mander[51] and Erman[60] in 1971. In particular, Erman exploited the acid catalyzed cyclization of diazo ketones **88a–b** as the key step in an elegant synthetic approach to the α-patchoulane class of sesquiterpenes. More specifically, reaction of **88a** with $BF_3 \cdot Et_2O$ afforded



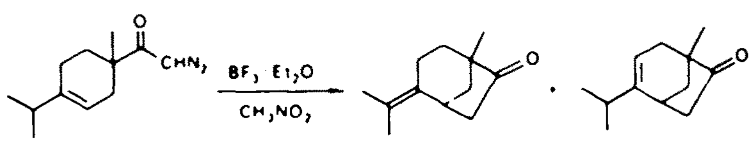
(88)
(a) R = COOEt
(b) R = H

(89)
(a) (30%)
(b) (56%)

(90)
(a) (3%)
(b) (6%)

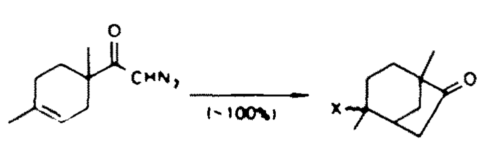
bicyclic ketones **89a** and **90a** while decomposition of **88b** gave **89b** and **90b**. The higher yields obtained from **88b** are undoubtedly a reflection of the greater nucleophilicity of the participating olefin.

Contemporarily with the work of Erman, Mander initiated an extensive research program designed to demonstrate the utility of unsaturated diazo ketones in total synthesis (*vide infra* examples **95** and **97**). Exemplary of this effort is the recent total synthesis of (±)-norhelimthosporic acid and related compounds. In this case, reaction of **91** with $BF_3 \cdot Et_2O$ in nitromethane gave bicyclic ketones **92** and **93**



(91) (92) (93)

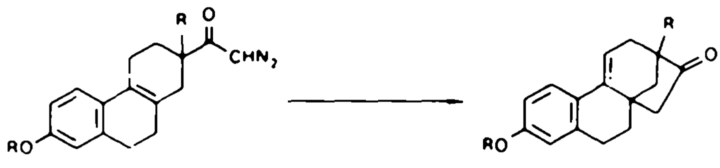
in nearly quantitative yield. Although an initial 4:1 mixture of **92** to **93** was observed, equilibration under the reaction conditions led to a 9:11 mixture. This observation was viewed by Mander as suggestive of a concerted loss of a proton during the cyclization process. In a similar vein, Mander has effected the cyclization of diazo ketone **94** with either hydrochloric acid or trifluoroacetic acid.[62]



(94)

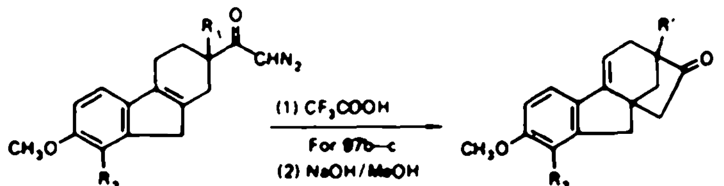
(a) X = Cl
(b) X = OCOCF₃

A number of research groups have examined the synthetic utility of γ,δ-unsaturated diazo ketones, particularly for elaboration of complex bicyclo[3.2.1]-octane derivatives. In each case the objective was the preparation of useful synthetic intermediates for the construction of diterpenes such as the gibberellins. Here Mander *et al.*,[51,63] and more recently Ghatak *et al.*[64] have examined the decomposition of diazo ketones **95a–c**. The yield of cyclized products (**96a–c**) is again indicative of the sensitivity of the reaction toward various acid-solvent couples. Mander *et al.* have also explored the decomposition of diazo ketones **97a–c**[51,65] and **99**[63] which afforded **98a–c** and **100**, respectively in excellent yield. Here, with proper choice of acid catalyst and solvent, high yields of cyclization products can be obtained in



(95) (96)

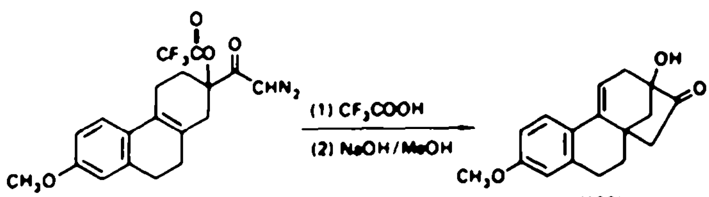
(95)		(96)
(a) R = CH_3, R′ = H	HBF_4/CH_3NO_2, room temp	(a) (90%)
	CF_3COOH/0° C	(a) (100%)
	$BF_3 \cdot Et_2O/CH_2Cl_2$, −5° C	(a) (43%)
(b) R = R′ = CH_3	CF_3COOH, 0° C	(b) (100%)
	$BF_3 \cdot Et_2O/CH_2Cl_2$, −5° C	(b) (41%)
(c) R = R′ = H	HBF_4/CH_3NO_2, room temp	(c) (78%)



(97) (98)

(a) R_1 = R_2 = H
(b) R_1 = $OCOCF_3$, R_2 = H
(c) R_1 = $OCOCH_2Cl$, R_2 = $COOCH_3$

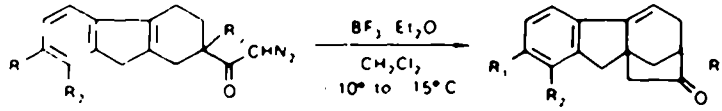
(a) R_1 = R_2 = H (100%)
(b) R_1 = OH, R_2 = H (82%)
(c) R_1 = OH, R_2 = $COOCH_3$ (88%)



(99) (100)

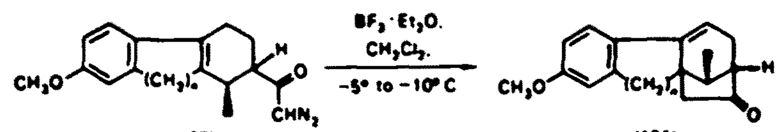
systems wherein the olefin is incorporated in a rigid carbon skeleton, thereby providing the diazo ketone side chain only a few degrees of rotational freedom. Indeed, cyclization of diazo ketone **97c** to **98c** proved to be a key transformation in Mander's recent total synthesis of gibberellic acid.[66]

Exploiting the above favorable characteristics, Ghatak *et al.* examined the decomposition of diazo ketones **101a–d**[64,67] and **103a–b**[68] in studies directed at the synthesis of diterpene derivatives. The observed yields of **102a–d** and **104a–b** were moderate to good (45–80%).



(101) (102)

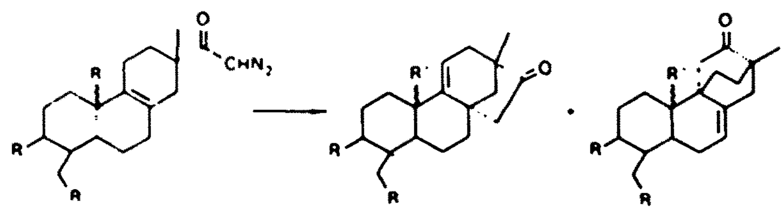
(a) R_1 = OCH_3, R_2 = R_3 = H (a) (45%)
(b) R_1 = R_2 = H, R_3 = CH_3 (b) (60%)
(c) R_1 = OCH_3, R_2 = H, R_3 = CH_3 (c) (48%)
(d) R_1 = H, R_2 = R_3 = CH_3 (d) (80%)



(103) (a) n = 1 (b) n = 2

(104) (a) (71%) (b) (73%)

More recently, Ceccherelli *et al.*[69] have utilized this methodology in a successful attempt to prepare selectively the [3.2.1]octanone skeleton of stachane diterpenes from naturally occurring diterpenes of the pimarane class. Treatment of diazo ketone **105a**, containing a 9-α-angular Me substituent, with 5%



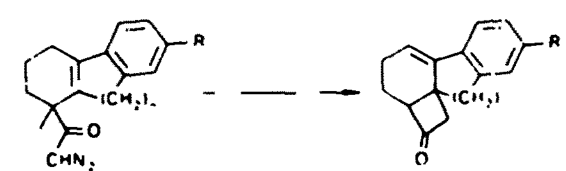
(105) (106) (107)

(a) R = H R' = α CH₃

(b) R = OAc R' = β CH₃

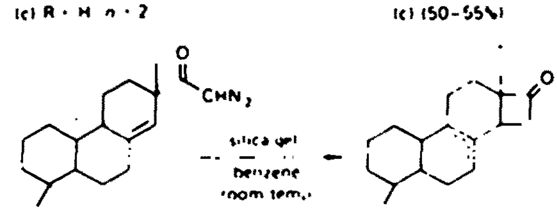
sulfuric acid afforded a mixture of [3.2.1]bicyclic ketone **106a** (42%) and the [3.2.2.]bicyclic ketone **107a** (28%). In contrast, similar treatment of the 9-β-angular methyl derivative **105b** gave exclusively the [3.2.2]bicyclic ketone **107b** in 80% yield.

In related studies, Ghatak and Sanyal[70] employed the acid catalyzed decomposition of diazo ketones for the synthesis of angularly fused cyclobutanones. Here, in the first reported examples of cyclization of β,γ-unsaturated diazo ketones, reaction of **108a** with 2–4 equivalents of 70% aqueous $HClO_4$, 48% HBF_4, or concentrated sulfuric acid in chloroform afforded cyclobutanone **109a** in 80–90% yield. Reaction of diazo ketones **108a–c** with 57% HI, on the other hand, gave the angularly fused cyclobutanones **109a–c** in only moderate (50–60%) yield. This procedure has recently been exploited by Ceccherelli *et al.*[71] for the preparation of the D-norsteroids **111a–b** obtained as a mixture from the cyclization of diazo ketone **110** catalyzed by silica gel.



(108) (a) R = H n = 1 (b) R = OCH₃ n = 1 (c) R = H n = 2

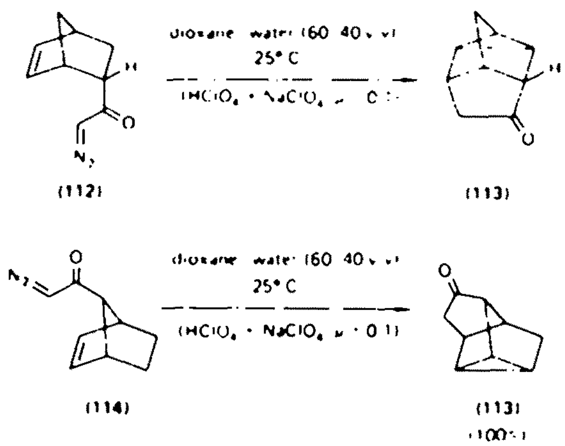
(109) (a) (60%) (b) (50–70%) (c) (50–55%)



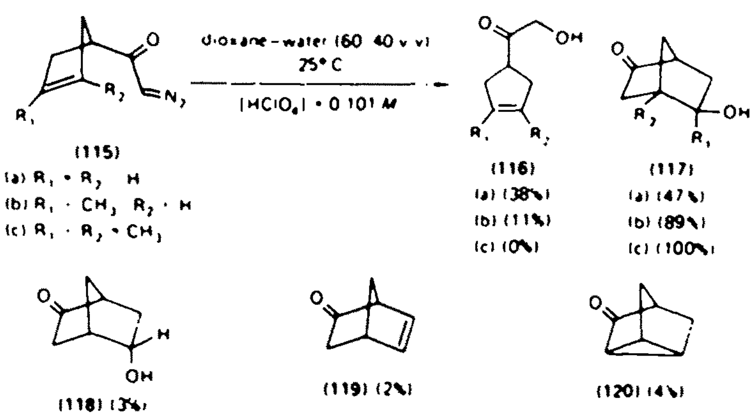
(110)

(111) (a) Δ[5,6] (b) Δ[8,9]

In a very elegant series of experiments, Dahn *et al.*[18,72] investigated several examples of olefin participation in the solvolysis and decomposition of α-diazo ketones. Specifically, they observed that diazo ketone **112** underwent cyclization to **113** in low yield (27%), while diazo ketone **114** also led quantitatively to **113**. In the latter case rate enhancement relative to that of the saturated analogue was observed. The large rate enhancement undoubtedly arises from maximum anchimeric assistance on the

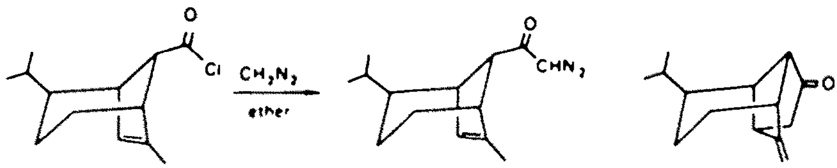


part of the participating olefin as a result of the favorable orientation of the diazomethyl group. The observation of a solvent isotope effect was taken as evidence that the substitution step involving displacement of nitrogen is sufficiently fast that protonation of the diazo ketone becomes the rate determining step. Since this protonation step is a faster process than the substitution step for the saturated analog a rate enhancement is observed for the decomposition of diazo ketone **114**. Smaller rate enhancements were also observed for the solvolysis of diazo ketones **115a–c**. When the cyclization amounted to 50% or greater, the rate was attributed entirely to anchimeric assistance. In addition, the observed yield of cyclization products as well as the rate of reaction were found to be directly



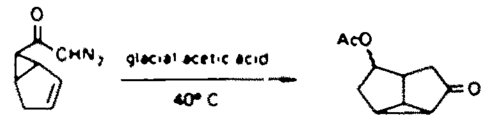
proportional to the degree of olefin substitution. That is, diazo ketones **115b** and **115c** underwent cyclization, respectively, two and four times faster than **115a**. Reaction of **115c** was in fact, ten times greater than that of the saturated analogue. In the case of **115c** cyclization was quantitative. Entropies of activation were measured and competition experiments (i.e. solvolysis in the presence of competing nucleophiles) were performed in order to probe the mechanism of the cyclization reaction. The results suggest an S_N2 mechanism requiring participation of solvent (H_2O) in the transition state. With this in mind, the reaction was described as a concerted cyclization where the loss of nitrogen and bonding of water were not synchronous. In this regard, the formation of products **118–120** from diazo ketone **115a** may reflect the instability of an incipient secondary carbonium ion relative to that of a tertiary carbonium ion.

A similar rate enhanced cyclization was unexpectedly observed by Piers[73] in an attempted preparation of diazo ketone **122**. Reaction of the acid chloride **121** with excess diazomethane yielded cyclopentenone **123** as the major product. Here, the excellent nucleophilicity and proximity of the olefin induces a cyclization process that is faster than deprotonation of the intermediate diazonium ion involved in diazo ketone formation.



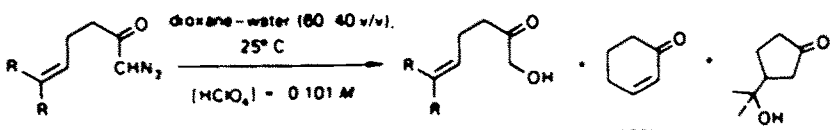
(121) (122) (123)

In an effort to exploit synthetically the above observations, Malherbe[74] has effected the conversion of diazo ketone **124** to **125** (mixture of acetates) in good yield (70–80%). The acetate mixture is a useful precursor of semibulvalene.



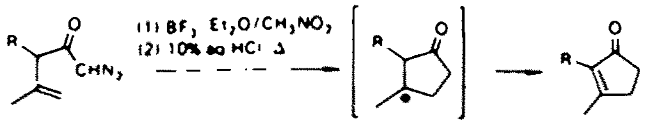
(124) (125)
(70–80%)

These workers have also investigated acyclic analogues **126a–b**. Here, these diazo ketones which possess less favorable geometric constraints (i.e. greater degree of freedom), underwent the cyclization reaction less efficiently yielding instead, a significant amount of hydroxymethyl ketones **127a–b**. Interestingly, formation of cyclization products **128** and **129** was dependent upon the olefin substitution.



(126) (127) (128) (129)
(a) R = H (a) (94%) (4%) (55%)
(b) R = CH_3 (b) (45%)

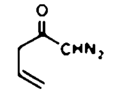
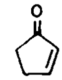
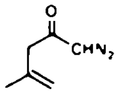
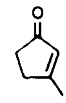
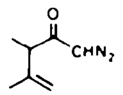
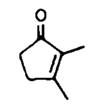
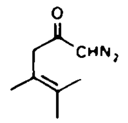
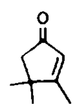
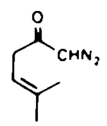
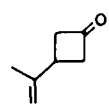
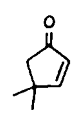
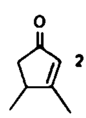
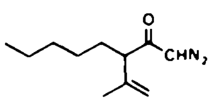
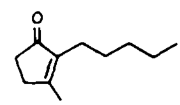
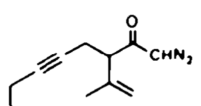
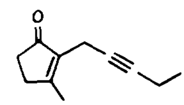
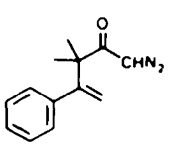
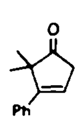
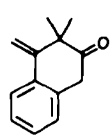
Although by 1975 a great deal of effort had gone into the study of γ,δ-unsaturated diazo ketones, in particular systems possessing a high degree of skeletal rigidity, the question of Lewis acid promoted cyclization of simple acyclic β,γ-unsaturated diazo ketones had not been addressed. In connection with our interest in devising a facile, and hopefully general, cyclopentenone synthesis, we subjected a wide variety of β,γ-unsaturated diazo ketones to such decomposition.[75] Guided in large part by the previous efforts of Erman and Mander, we quickly ascertained that the optimal conditions for cyclization consisted of treatment of the diazo ketone with $BF_3{\cdot}Et_2O$ in freshly distilled nitromethane or methylene chloride at 0°C. In cases where a mixture of α,β- and β,γ-cyclopentenoid derivatives were anticipated, the reaction mixture was subjected to 10% HCl at reflux for 30 min in order to insure equilibration to the thermodynamically more stable α,β-unsaturated system. Our results, illustrated below, are given in Table 1.[75] To demonstrate the synthetic viability of this approach to simple cyclopentenones we completed a short, efficient synthesis of dihydro and *cis*-jasmone.[75]



(130) (131)

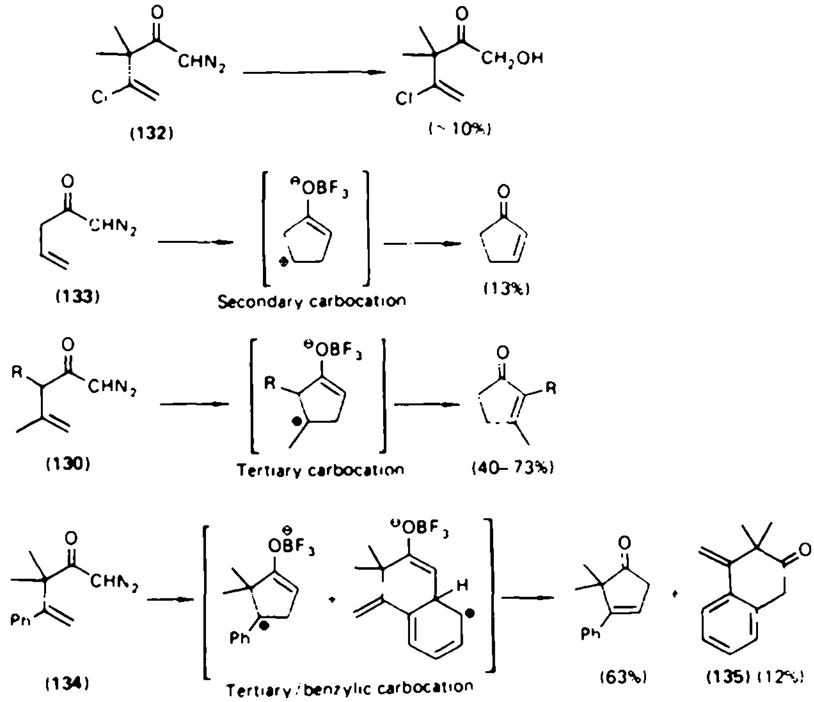
(a) R = H
(b) R = CH_3
(c) R = C_5H_{11}
(d) R = $CH_2C{\equiv}CCH_2CH_3$

Table 1. Acyclic diazo ketones → monocyclic cyclopentenones

Entry	Diazo ketone	Solvent	Product(s)	Yield (percent)
A	 (133)	CH_3NO_2		13
B	 (130a)	CH_2Cl_2 CH_3NO_2		73 64
C	 (130b)	CH_3NO_2		40
D	 (138)	CH_2Cl_2	 (140)	77
E	 (139)	CH_2Cl_2	 (141) 31;  (142) 12.2;  (143) 27.7	
F	 (130c)	CH_3NO_2		65
G	 (130d)	CH_3NO_2		40
H	 (134)	CH_3NO_2	 63;  (136) 12	

A reasonable pathway for the above cyclization involves BF_3 complexation with the diazo ketone at either the oxygen or carbon atom. Cyclization of this intermediate, involving π-bond participation in the displacement of nitrogen, leads to the carbocation **131** which eliminates a proton to yield a mixture of the α,β- and/or β,γ-isomers. Subsequent aqueous acid treatment gives the α,β-unsaturated cyclopentenone as the major product.

Significant here is the fact that even the parent β,γ-unsaturated diazo ketone **133** undergoes the cyclization process, albeit in only 13% yield. Presumably the low yield in this case results both from the reduced nucleophilicity of the participating π-system and from the reduced stability of the intermediate secondary carbocation. That in fact both nucleophilicity of the participating π-system and stability of the postulated intermediate carbonium ion are important parameters in the acid promoted cyclization of unsaturated diazo ketones is further supported by the trend of increasing percent cyclization observed with the diazo ketones illustrated below. Similar results have been observed by Johnson *et al.* in the area of polyolefinic cationic cyclization.[76] In particular, the weakly nucleophilic terminating group, $-CHCl{=}CH_2$ fails to participate in polyene cyclizations, while the vinyl and isopropenyl groups are corresponding more effective.

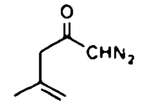
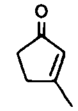
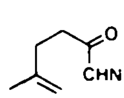
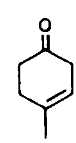
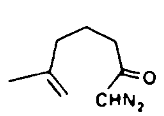
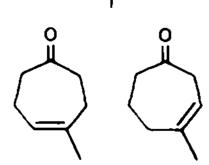


Interestingly, the last diazo ketone in this series (i.e. **134**) also affords a small amount of enone **135**. This result raised several intriguing questions. First, is there a preferred ring size for acid induced cyclization of acyclic unsaturated diazo ketones. Second, what are the relative nucleophilicities of the olefinic partners required for intramolecular alkylations.

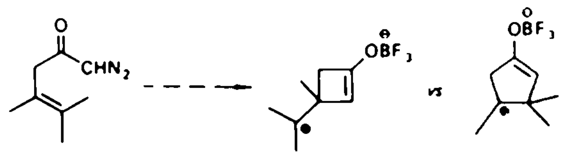
To explore the question of ring size, we subjected acyclic diazo ketones **130a** and **136–137** to $BF_3 \cdot Et_2O$ in CH_2Cl_2. As illustrated in Table 2 cyclization proceeded in each case. However, the yield of cyclized product decreases monotonically as the site of unsaturation from the diazocarbon increases. Significant here is the fact that these examples were designed such that only the number of intervening methylene groups was altered. That is, the nucleophilicity of the participating olefin as well as the stability of the intermediate carbocation (i.e. tertiary) were identical in each case.

To define further the relative importance of ring size (i.e. strain effects) versus stability of the intermediate carbonium ion, we explored the cyclization of diazo ketones **138** and **139**. As illustrated

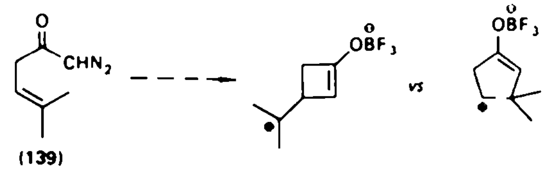
Table 2.

Entry	*Diazo ketone*	*Site of unsaturation*	*Product(s)*	*Yield (percent)*
A	 (130)	β,γ		73
B	 (136)	γ,δ		55
C	 (137)	δ,ε	 (2 : 1)	42

below, there are two possible modes of cyclization available to 138 leading to a stabilized, tertiary carbonium ion while in the case of 139 only cyclization to a 4-membered ring affords the more stable tertiary carbocation.

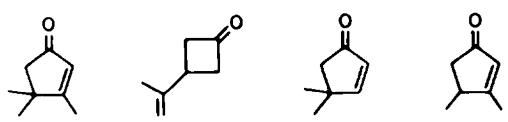


(138)



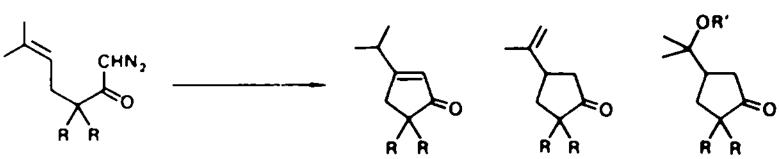
(139)

In the event, a single cyclopentenone (i.e. 140) was obtained in 77% yield from 138, while diazo ketone 139 led to a three component mixture in a combined yield of 71%; the major product being cyclobutanone 141, while the minor products were cyclopentenones 142 and 143. In both cases product formation is consistent with competitive cyclization vs carbonium ion stability. Observation of cyclobutanone 141 as the major product, however, suggests that the overriding feature of this cyclization process is carbonium ion stability. It is of interrest in this regard to note that only the minor cyclopentenone derivative 142 derives via a direct cyclization; the major cyclopentenone 143 requires first a Wagner–Meerwein methyl shift to generate a more stable tertiary carbocation prior to elimination of a proton.



(140) (141) (142) (143)

In a related study, Lorne and Linstrumelle[77] recently demonstrated that closure of 144a–b to 5-membered ring systems possessing an exocyclic tertiary carbonium ion is favored over closure to a 6-membered ring bearing an *endo* cyclic secondary ion. This was the case under a wide range of reaction conditions.

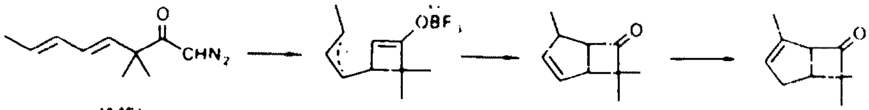


(144)

(a) R = H	$BF_3 \cdot Et_2O/CH_2Cl_2$	(a) (35%)	(a) (7%)	(a) (—)
(b) R = CH_3	$BF_3 \cdot Et_2O/CH_2Cl_2$	(b) (54%)	(b) (6%)	(b) (—)
(b)	CF_3COOH/THF	(b) (17%)	(b) (13%)	(b) (60%)
(b)	HBF_4/CH_3NO_2	(b) (30%)	(b) (—)	(b) (60%)

R' = $OOCCF_3$; OH

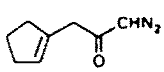
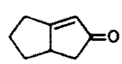
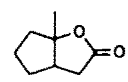
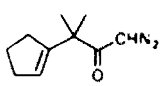
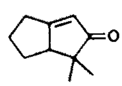
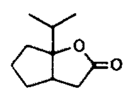
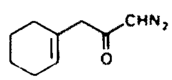
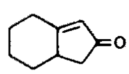
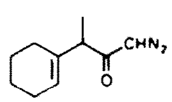
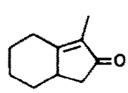
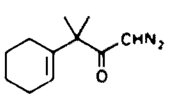
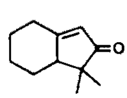
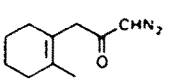
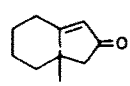
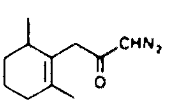
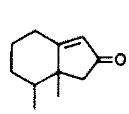
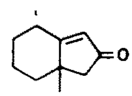
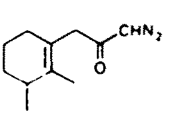
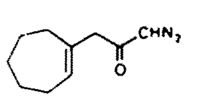
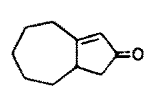
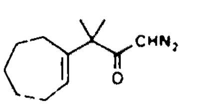
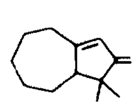
Further demonstration of the synthetic utility of the acid catalyzed cyclization of simple β,γ-unsaturated diazo ketones was recently presented by Hudlicky and Kutchan[78] in their total synthesis of filifolone (147). In this case the intermediate boron enolate derived from 145 was observed to undergo intramolecular capture to afford bicyclic ketone 146.

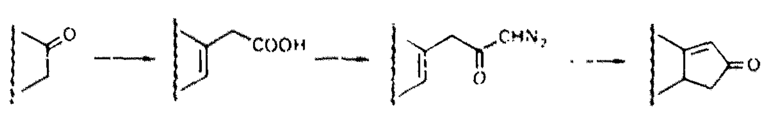


(145) (146) (147) filifolone

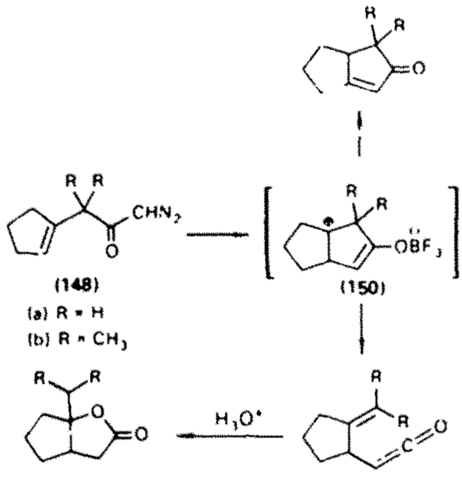
To demonstrate further the synthetic utility of the α-diazo ketone functionality, we developed in 1975 a general cyclopentenone annulation procedure[79] based on the acid catalyzed cyclization of β,γ-unsaturated diazo ketones. As illustrated in Table 3 (also see Table 1), the Lewis acid promoted cyclization of β,γ-unsaturated diazo ketones, in conjunction with the now numerous approaches to β,γ-unsaturated acid derivatives including the improved Reformatsky sequence and the facile ester alkylation–deconjugation procedures introduced by Rathke[80] and Schlessinger,[81] represents a general cyclopentenone annulation strategy. The overall reaction sequence is illustrated below. In general, yields based on ketone (i.e. ketone → β,γ-unsaturated diazo ketone → cyclopentenone) are quite good.

Table 3. Monocyclic diazo ketones → bicyclic cyclopentenones

Entry	Diazo ketone	Solvent	Product(s) and yield (percent)			
A	 (148a)	CH_2Cl_2		50	 (149a)	10
B	 (148b)	CH_2Cl_2		41	 (149b)	30
C		CH_3NO_2		50		
D		CH_3NO_2		63		
E		CH_3NO_2		65		
F		CH_3NO_2		57		
G		CH_3NO_2	 (157)	8	 (158)	46
H		CH_3NO_2	(157)	31.4	(158)	21
I		CH_2Cl_2		60.5		
J		CH_2Cl_2		68		

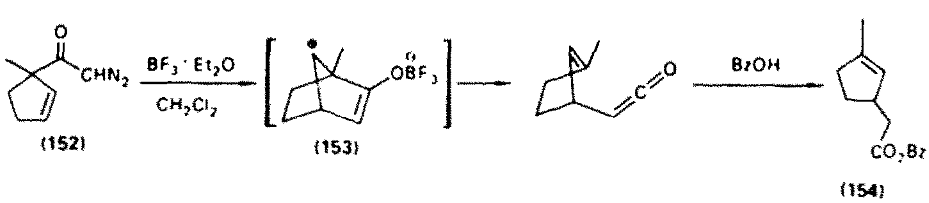


Several additional comments concerning the results in Table 3 are in order. First, cyclization of diazo ketones **148a–b** also affords lactones **149a–b** in low yield. A reasonable pathway for this latter transformation involves fragmentation of the intermediate carbonium ion **150** to unsaturated ketene **151**. Ketene **151**, in turn, upon treatment with aqueous mineral acid, undergoes lactonization to yield **149a–b**. The fragmentation of **150** to **151** is, in effect, an acid catalyzed example of the vinylogous Wolff rearrangement recently explored extensively in our laboratory.[82a,b]



(148) (a) R = H (b) R = CH_3 (150) (149) (151)

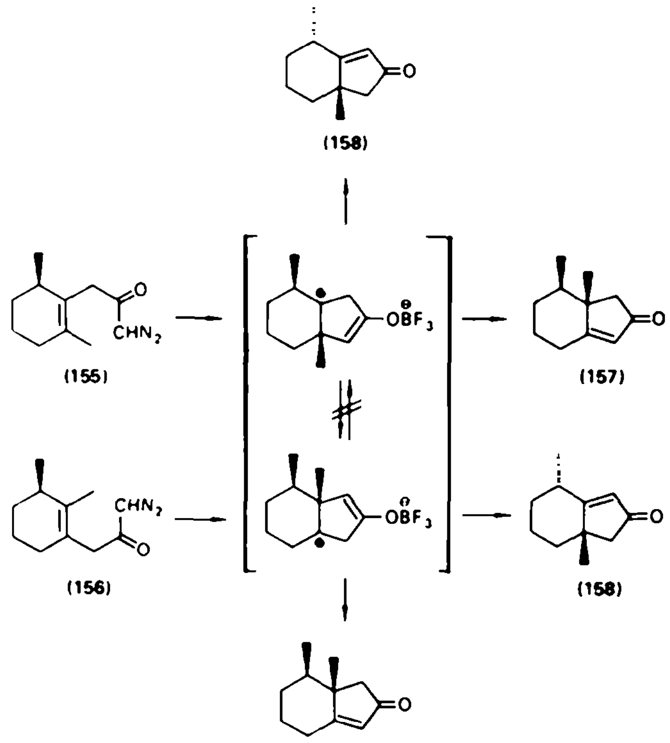
To our knowledge, the only additional example of the acid catalyzed vinylogous Wolff rearrangement occurs upon Lewis acid decomposition of diazo ketone **152**. Presumably ester **154** arises via fragmentation of the initially formed bicycloheptene **153** to afford a ketene which in this case is captured with benzyl alcohol.



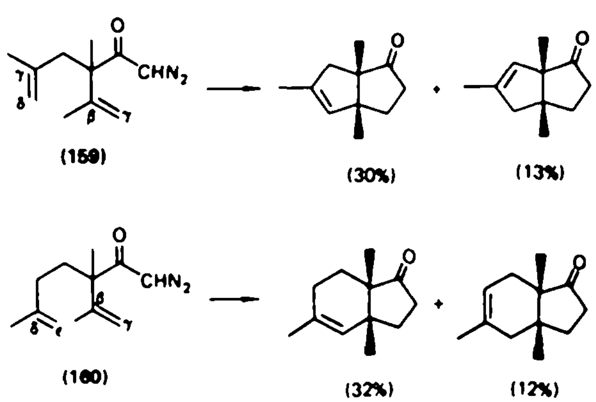
(152) (153) (154) (40%)

Finally, we note that decomposition of diazo ketone **155** and **156** affords the same pair of bicyclic enones (i.e. **157** and **158**). A reasonable pathway for their formation is illustrated below. Although in both cases the combined yield of cyclized material was identical within experimental error (*ca* 52 and 54%), the ratio of **157**:**158** differed significantly. Thus while there is a certain kinship of the pathways leading to product formation (i.e. 1,2-Me migration), a common intermediate can not be involved.

We concluded our study of the acid promoted cyclization of simple unsaturated diazo ketones with an intramolecular competition experiment. In particular we desired to compete cyclization at a β, γ- vs γ,δ-olefinic site and a β,γ- vs δ,ε-olefinic site. For such competition to be valid, of course, the nucleophilicity of both olefinic sites as well as the stability of the derived carbocations would have to be identical.[9] Ideal candidates for this study appeared to be the readily available diazo ketones **159** and **160**. While at the outset it was not our intent to explore polyolefinic cationic cyclization, it soon became evident that this was in fact the overriding process. Our results are illustrated below. Both cases afforded predominantly bicyclic products; the combined yield in each being 43–44%.



(155) (156) (157) (158)



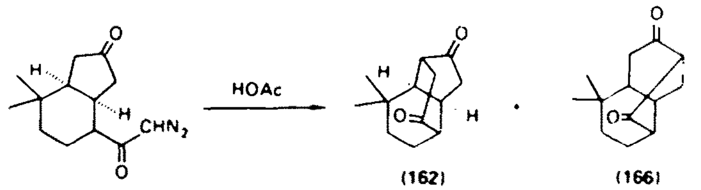
(159) (30%) (13%)

(160) (32%) (12%)

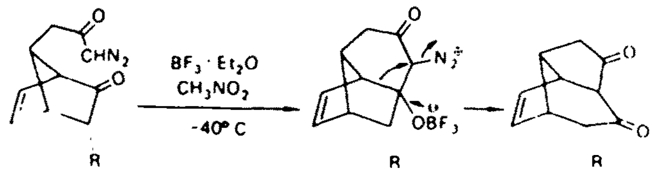
Finally, the question of ketone participation in the acid catalyzed decomposition of diazo ketones requires brief comment. Here, the double bond of an enol tautomer could participate in the displacement of nitrogen from the diazonium ion. Such a process was in fact postulated for the decomposition of diazo ketone 161. However, Lui and Kovacics have critized this mechanism on the grounds of low enol content in saturated ketones.

To explore participation by ketone carbonyl groups Mander and Wilshire subjected diazo ketones 163a–b to $BF_3 \cdot Et_2O$ at $-40°$. The products, 165a–b respectively, were rationalized in terms of nucleophilic addition of the diazocarbon to the electrophilic CO group, in analogy with known reactions of diazo alkanes and diazo esters.[85,86] In conjunction with this study, Mander suggested a revised structure for 162 (i.e. 166); Miyano and Dorn concurred.[85]

Participation of a preformed enol (i.e. enol acetate or ether) would of course obviate the above nucleophilic addition of the diazo carbon to the CO group. Unfortunately, in the case of 163 such a procedure was unsuccessful due to difficulties experienced in attempting to prepare the requisite enol species.[85] Indeed, the general reactivity of enol double bonds with diazo ketones under acidic conditions has not been explored.



(161) (162) (166)



(163) (164) (165)

(a) R = H

(b) R = CH_3

5. POLYOLEFINIC CYCLIZATION-AN OVERVIEW

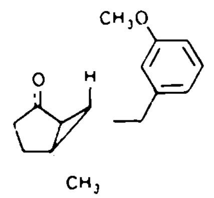
In 1955 Stork[87] and Eschenmoser,[88] independently, proposed a stereoelectronic model to account for the stereospecific conversion of squalene to lanosterol. In this elegant model they pointed out that if the cyclization occurs in a concerted fashion, the stereochemistry of the ring fusion will be the same as the stereochemistry of the olefin. This result arises simply because addition to the olefin (where a cation is the electrophile and another olefin is the nucleophile) occurs stereoelectronically in a trans fashion, similar to the addition of bromine to olefins. This view suggested that an all trans polyene has an intrinsic tendency to undergo an acid catalyzed cyclization process which would generate the natural *trans–anti–trans* ring fusion of the steroids.

The hypothesis immediately spurred the interest of organic chemists to ascertain whether such a reaction could be carried out in the absence of enzymes. These *in vitro* reactions were termed "biogentic like" olefin cyclizations by van Tamelen[89a-b] and later biomimetic polyene cyclizations by Johnson. Several groups, notably those of Johnson, van Tamelen, Stork, Goldsmith, Ireland and Harding have extensively explored the synthetic feasibility of this reaction. While these efforts have been adequately reviewed[89a-h] a few comments are in order here.

Johnson, in a systematic investigation of suitable functional groups, found, in allylic alcohols and acetals, two efficient initiators of cationic polyene cyclization.[89c-f] To this list must be added the terminal epoxide of Goldsmith[89h,90] and van Tamelen[89a-b] and the cyclopropyl ketone of Stork.[91,92] These functionalities by enlarge initiate stereospecific cyclization processes in modest to excellent yields depending upon the specific substrate.

The mechanism of these cyclization reactions has not been clearly established and may, in fact, depend upon the specific nature of the initiating functional group. For example, Johnson has presented evidence strongly pointing to a concerted reaction pathway in the cyclization of an allylic alcohol.[93] On the other hand, the acetal functionality may initiate a cyclization process which proceeds in a stepwise manner through intermediate carbonium ions.[89c-f] This also appears to be the case in the cyclization of several terminal epoxy olefins. In the latter case, Goldsmith[90] demonstrated that the cyclization process proceeds stereospecifically to afford tricyclic hydrocarbons. The stereochemistry of the observed products strongly suggest that the cyclization process proceeds in a stepwise manner through the intermediacy of conformationally stable cyclohexyl cations. Indeed, Harding,[89g] employing the arguments of conformational analysis, has pointed out that the high degree of stereospecificity observed in many biomimetic cyclizations can be rationalized in terms of classical carbonium ions and need not be attributed to concerted processes.

More recently Stork, in an elegant series of papers, demonstrated that cyclopropyl ketones undergo stereospecific cyclization upon acid catalysis.[91,92] For example, reaction of cyclopropyl ketone **167** with $SnCl_4$ in benzene, containing a trace of water, afforded stereospecifically *trans*-phenanthrenones **169** and **170** in 80% yield. Similarly, cyclopropyl ketone **168** gave only *cis*-phenanthrenones **171** and **172** upon acid catalyzed cyclization. The stereospecificity of these reactions was attributed by Stork to be due to a concerted cyclization process. This view is consistent with our observations (*vide infra*) on the cyclization of cyclopropyl ketones **173** and **174**.



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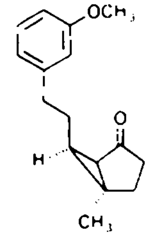
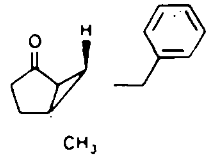
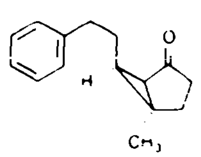


(168)



(173)

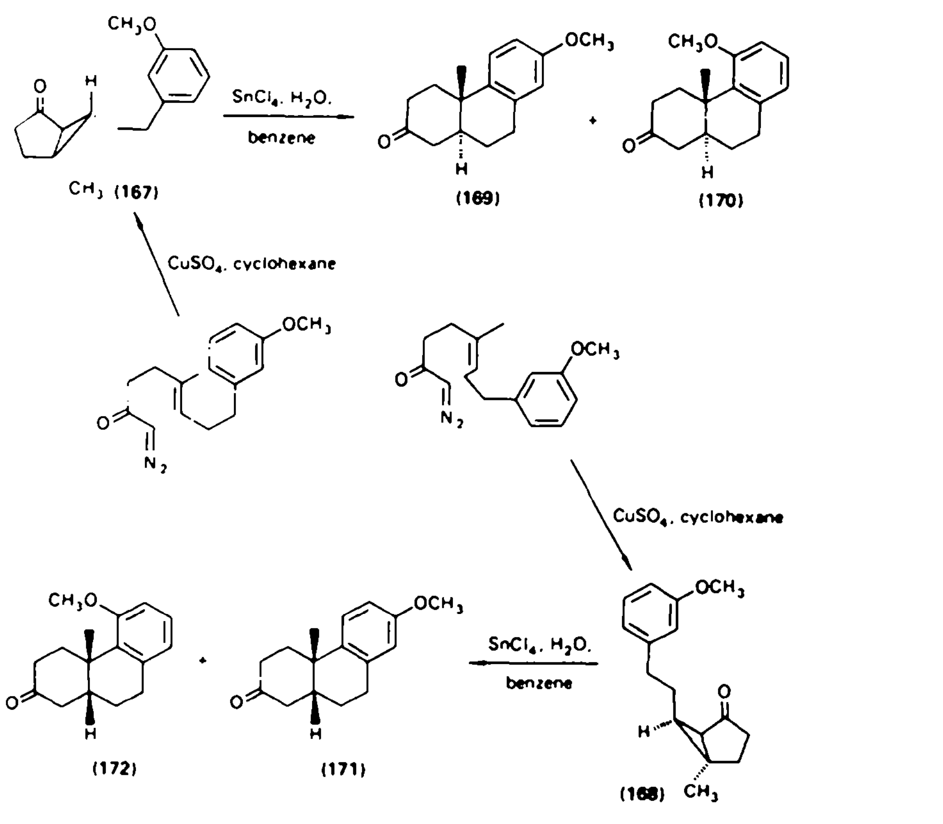


(174)

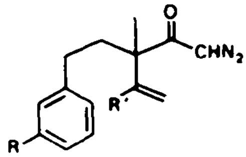
In many instances this two step alkylation procedure (i.e. copper catalyzed cyclopropanation followed by acid catalyzed cyclization or rearrangement) is synthetically equivalent to the direct acid catalyzed cyclization of the diazo ketone. In fact Erman,[60] and Ghatak[63,64] have compared the efficiency of this protocol for several diazo ketones. In general, the cyclopropanation procedure is restricted to γ,δ-unsaturated diazo ketones and occasionally suffers from moderate yields. In addition, non-selective opening of the cyclopropane ring upon acid catalysis can lead to complex mixtures. In the case of monocyclization, the brevity of the direct diazo ketone cyclization as we have demonstrated makes it the procedure of choice.

6. α-DIAZO KETONES: INITIATORS OF POLYOLEFINIC CATIONIC CYCLIZATION

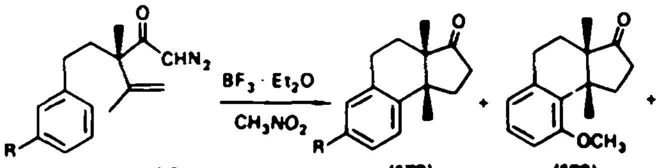
The successful cyclization of diene diazo ketones 159 and 160 to bicyclic ketones suggested the α-diazo ketone functionality as a potential initiator of polyene cationic cyclization. Intrigued by the use of a high energy initiator (i.e. the diazonium ion), we began an extensively investigation[94] of this process



in 1976. Initially, diazo ketones 175–178 were selected since they would not be expected to become involved in complex structural rearrangements.



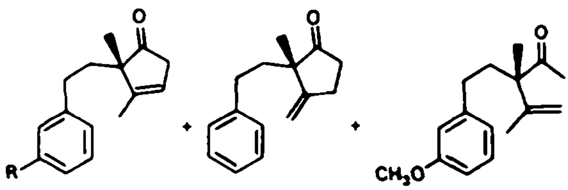
(175) R = OCH_3; R' = CH_3
(176) R = H; R' = CH_3
(177) R = H; R' = H
(178) R = OCH_3; R' = H



(175) R = OCH_3
(176) R = H

(179)
(a) R = OCH_3
(b) R = H

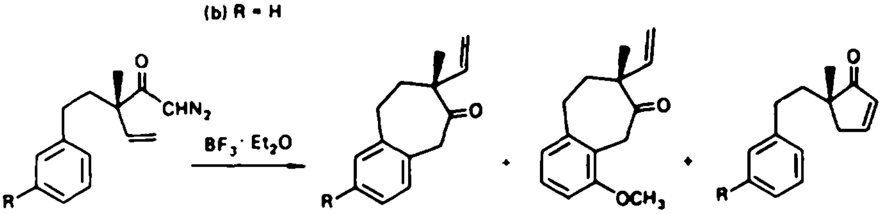
(180)



(181)
(a) R = OCH_3
(b) R = H

(182)

(183)



(177) R = H
(178) R = OCH_3

(184)
(a) R = H
(b) R = OCH_3

(185)

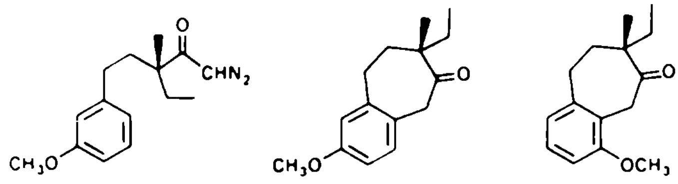
(186)
(a) R = H
(b) R = OCH_3

It was anticipated that the systematic modification of substrate structure would provide some insight into the scope and limitations of this cyclization reaction. In addition, diazo ketone 175 appeared ideally suited for our initial study since two of the four possible tricyclic ketones had been prepared and their stereochemistry rigorously established by Jeger *et al.*[95]

Decomposition of diazo ketones 175–178 with a variety of Lewis or Brønsted acids and complementary solvent systems led to complex mixtures of products.[96] The optimal conditions proved to be 1.1 equivalents of $BF_3{\cdot}Et_2O$ in either nitromethane or methylene chloride. The observed products were the result of either a mono- or polyene cyclization process where significantly, a propensity towards the polyene cyclization was noted only for diazo ketones 175 and 176 containing a nucleophilic disubstituted olefin. More specifically, diazo ketones 175 and 176 gave predominantly tricyclic products (43 and 46% respectively), whereas diazo ketones 177–178 containing the non-nucleophilic vinyl group gave no tricyclic ketones. In addition, diazo ketones 175 and 176 gave comparable yields of tricyclic products [179a (31%), 180 (12%) and 179b (46%) respectively] as well as simple substituted 5-membered ring ketones [181a and 181b(10%), 182(2%), respectively]; the distribution of these products was markedly unaffected by choice of solvent (i.e. methylene chloride or nitromethane). Interestingly, decomposition of diazo ketone 175 in methylene chloride also gave a small amount (2%) of methyl ketone 183 in addition to 179a, 180 and 181. In marked contrast, the distribution of cycloheptanones [184a and 184b, 185 respectively] and cyclopentenones [186a and 186b respectively] from diazo ketones

177 and 178 was affected by the nucleophilicity of the aromatic ring as well as by choice of solvent. These results are summarized in Table 4.

The facile, high yield formation of cycloheptanones 184b and 185 from diazo ketone 178 is particularly noteworthy. Similar treatment ($BF_3 \cdot Et_2O$; CH_2Cl_2) likewise converted the saturated analog diazo ketone 187 into a mixture of cycloheptanones (188 and 189) in good yield. This ready formation of cycloheptanones contrasts with earlier observations on the difficulty of forming 6- and 7- membered

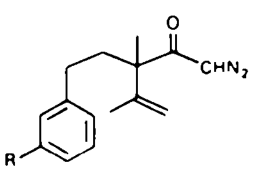
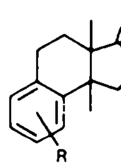
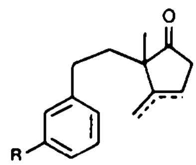
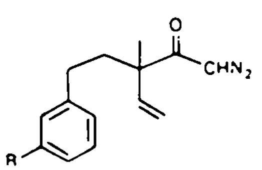
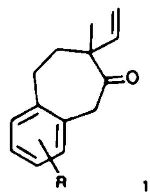
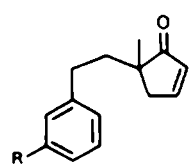
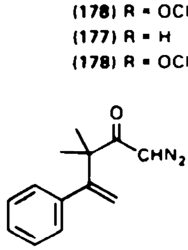
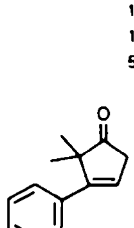
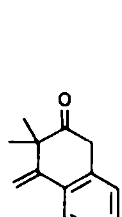


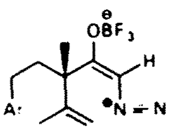
(187) (188) (189)

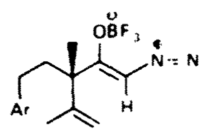
rings by the decomposition of unsaturated diazo ketones possessing long alkyl side chains. In particular, our results contrast sharply with the low yields of chromanones obtained by Moore[42] in solvents of low dielectric constant and with the low yield of tetralone 70 (20%)[56] obtained from diazo ketone 69. These examples reveal the acute sensitivity of the diazo ketone cyclization process to the acid catalyst-solvent couple. Indeed, choice of the optimal acid/solvent conditions for a particular cyclization remains an experimental problem.

A reasonable reaction pathway for the above cyclizations involves initial complexation of boron trifluoride with either the oxygen or carbon atom of the diazo ketone functionality to yield 190, 191 and/or 192; subsequent loss of nitrogen and cyclization then leads, in the case of diazo ketones 175 and 176, to a tertiary carbonium ion 193. The resultant tertiary carbonium ion is, in most instances, sufficiently long lived to suffer capture by the π-system of the aromatic ring before the cation can be removed from the reaction coordinate by proton loss. In the decomposition of diazo ketones 177 and 178, however, the initial cyclization leads to a less stable (by approx. 11 kcal/mole),[97] short-lived

Table 4. Product composition as a function of substrate substitution and solvent

Diazo ketone	Solvent	Product(s) and yield (percent)	
			
(176) R = H	CH_3NO_2	46	12
(175) R = OCH_3	CH_3NO_2	43	10
			
(177) R = H	CH_3NO_2	1	22
(178) R = OCH_3	CH_3NO_2	13	24
(177) R = H	CH_2Cl_2	17	11
(178) R = OCH_3	CH_2Cl_2	58	12
			
(134)	CH_3NO_2	63	12
	CH_2Cl_2	27	23


(190)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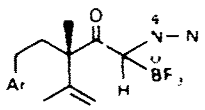
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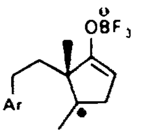
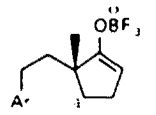

(193)


(194)

secondary carbonium ion **194** which rapidly loses a proton before capture by the aromatic system can take place. Consistent with a stepwise mechanism, the yields of tricyclic ketones (Table 4) obtained from diazo ketones **175** and **176** are independent of the nucleophilicity of the aromatic ring. In addition, partially cyclized products (e.g. **181**) have been shown not to be intermediates in the cyclization process leading to tricyclic ketones. Finally, the exclusive formation of the *cis* C/D ring fusion in the tricyclic ketones is due primarily to the tetrahedral geometry of the α'-carbon center.

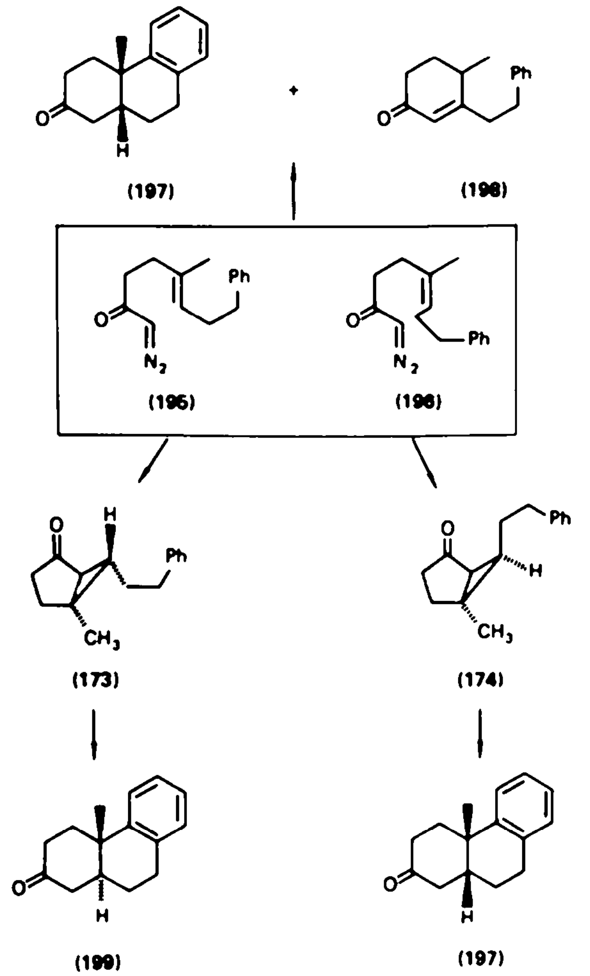
The question of whether nitrogen loss is synchronous with or precedes σ bond formation is more complex and may depend upon the solvent and nature of the participating nucleophile. For example, decomposition of diazo ketones **177**, **178** and **134** led to identical products in either nitromethane or methylene chloride. The distribution of products (Table 4) was, however, strongly dependent upon the choice of solvent and the strength of competing nucleophiles (e.g. the aromatic ring and the olefin). These results suggest that competing S_N1 and S_N2 pathways are responsible for the observed product distribution.

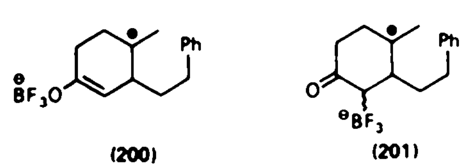
In this regard, the formation of cycloheptanones in either solvent is strongly dependent upon the nucleophilicity of the aromatic ring, a fact consistent with an S_N2 mechanism. Accordingly, the yields of cycloheptanones are increased in dichloromethane, a solvent apparently favoring the concerted pathway. In contrast, formation of cyclopentenones in either solvent is independent of the nucleophilic character of the aromatic ring, which in effect is a competing nucleophile. This observation suggests an S_N1 reaction pathway for the formation of cyclopentenones. Significantly, this solvent effect is manifest only when the nucleophilicity of the β,γ-olefin is sufficiently decreased so that it does not assist in the displacement of nitrogen. Thus, these observations appear to offer an explanation for the extreme sensitivity of the diazo ketone cyclization reaction to acid-solvent couples.

While the preceding examples demonstrate that the α-diazo ketone functionality can in fact initiate biomimetic polyene cyclization, the terminal nature of the participating olefin precluded any information concerning the role of olefin geometry in determining the stereochemistry of the cyclization process. Of particular interest here was whether a diazo ketone possessing a *trans* olefin would undergo a stereospecific cyclization to *trans* fused products.

To explore this question, we examined the Lewis acid catalyzed decomposition of diazo ketones **195** and **196**.[98] Our results are illustrated below. In both cases a single tricyclic ketone **197** was obtained in 44 and 38% yield, respectively, accompanied by minor amounts (*ca* 17 and 15%) of the partially cyclized cyclohexenone **198**. The stereochemistry of **197** was demonstrated to be *cis* by preparation of both the *cis*-**197** and *trans*-**199** ketones as shown below. The cyclopropyl ketones **173** and **174** did in fact undergo a stereospecific acid catalyzed cyclization (15 and 42% respectively) although the major product in each case proved to be cyclohexenone **198** (85 and 43% respectively). This is in marked contrast to the results of Stork[91-92] where the more nucleophilic anisole derivative gave only tricyclic products. That the resultant tricyclic products were obtained stereospecifically from **173** and **174** is consistent with the concerted cyclization originally postulated by Stork.

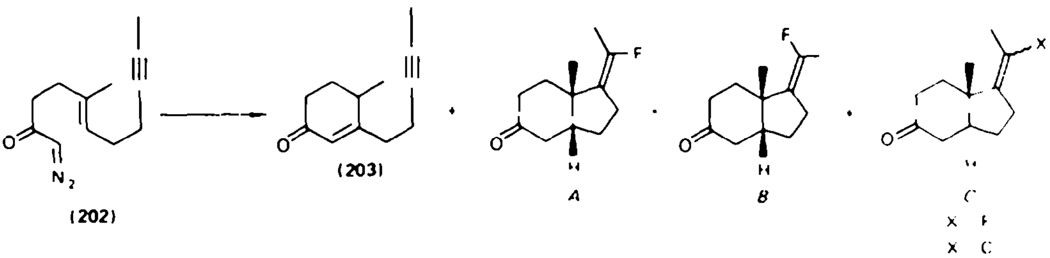
The cyclization of diazo ketones **195** and **196**, however, cannot proceed by a concerted reaction pathway since *cis*-phenanthrenone **197** is formed with equal facility from either the *cis* or *trans* olefinic diazo ketones. Indeed, the almost identical yield of tricyclic ketone **197** is suggestive of a common intermediate. A likely intermediate is the nearly planar species **200** since carbonium ion **201** is expected to yield a mixture of *cis* and *trans* fused tricyclic ketones in view of Harding's[89a] conformational



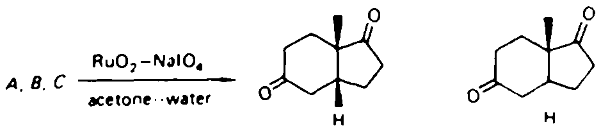


arguments and Goldsmith's[90] experimental observations on olefinic epoxides. Finally, the results obtained from cyclization of cyclopropyl ketones 173 and 174 are vastly different than those obtained from cyclization of diazo ketones 195 and 196. **This observation is significant in that it effectively eliminates from consideration an acid catalyzed cyclopropanation mechanism for cyclizations initiated by the α-diazo ketone functionality.**[99]

Finally, since the acetylenic functional group has been described as an excellent terminator[89c] of the polyene cyclization process, decomposition of diazo ketone **202** was investigated.[98] Under the majority of conditions examined, cyclohexenone **203** proved to be the major product. Eventually, it was discovered that decomposition of **202** in freshly distilled dichloromethane at high dilution (*ca* 1 mg diazo ketone/ml solvent) with greater then five equivalents of $BF_3 \cdot Et_2O$ constituted the optimal conditions to effect cyclization. Combined gc/mass spectrometric analysis revealed a complex mixture of products, many of which contained a fluorine or chlorine substituent. To define the stereochemistry of the ring fusion in the cyclized material, the crude reaction mixture was oxidated with $RuO_2/NaIO_4$. The result was a 5.6:1 mixture respectively of the known *cis* and *trans* diones **204** and **205**. The small yield of trans fused products in this cyclization may merely reflect the smaller steric demands of this linear terminator as opposed to the bulky phenyl group.



(202) (203)

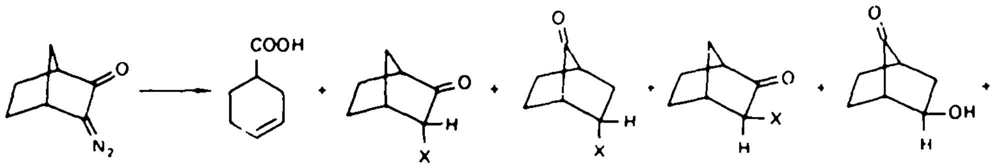


(204) (205)

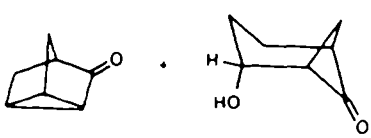
7. SINGLE BOND PARTICIPATION

Several reports have appeared in which C–C and C–H σ-bonds appear to participate in the displacement of nitrogen upon treatment of α-diazo ketones with either Brønsted or Lewis acids. Although many of these examples involve rearrangement rather than cyclization, they formally complete our survey on the participation of nucleophilic bonds in the acid promoted reaction of diazo ketones, and will therefore be included here.

Considerable attention in this regard has been paid to the acid promoted decomposition of diazo norcamphor **206**. For example, Yates and Crawford[100] reported the formation of **207** (17%), **208a** (33%)



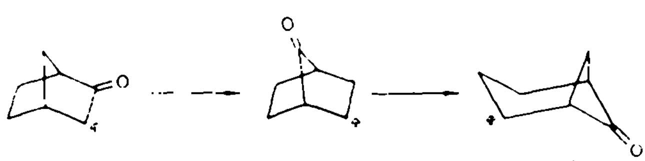
(206) (a) X = OH (207) (208) (209) (210) (211)
(b) X = Cl



(212) (213)

and **213** (29%) from **204** in aqueous THF at pH5, while Hanack and Dolde[101] observed formation of **207** (31%), **208a** (33%), **209a** (17%), **211** (9%), **210a** (3%) and **212** (trace) upon treatment with aqueous acetic acid. Decomposition of **206** in non-polar aprotic media, on the other hand, gave entirely different results.[101] In particular, reaction of **206** with dry HCl in dichloromethane affords **210b** (34%), **212** (22%), **209b** (5%) and **208b** (40%).

These results have been interpreted in several ways. Hanack[101] has suggested that the results can be accounted for in terms of the classical carbonium ions **214**, **215** and **216**. Yates[100] and More O'Ferrall[9] have suggested that the ring opened acid **207** could also arise from the hydrated diazonium ion **217** under



(214) (215) (216)

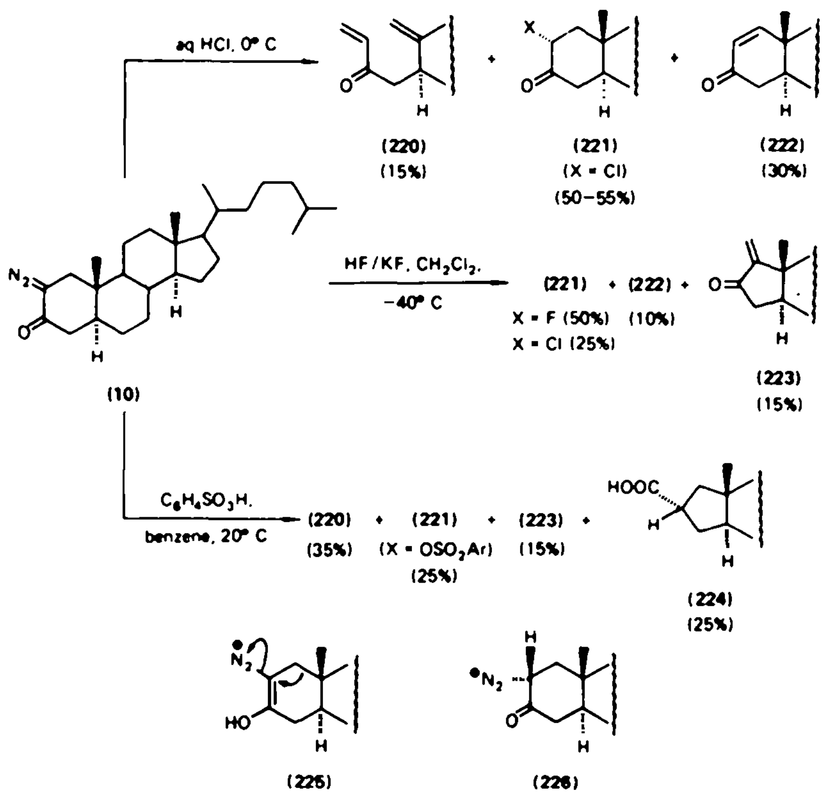
(217) (207)

the aqueous acid conditions. Finally, Friedman[8] has reported similar results for the acid catalyzed decomposition of 3-diazocamphor and has suggested that the distribution of products can be understood

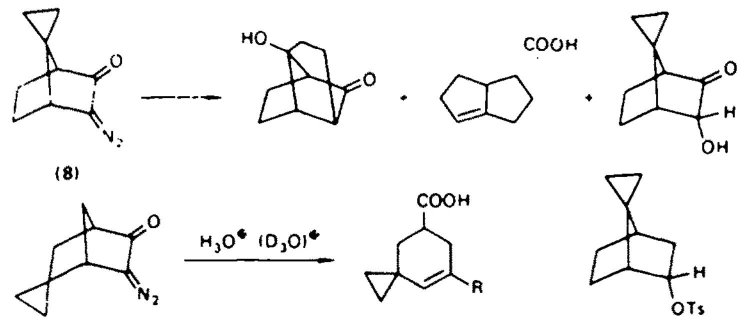
(218) (219)

in terms of the diazonium ion epimers **218** and **219** whose relative ratio, in turn, is solvent dependent. In this view **207**, **208a–b**, **210a–b** and **213** arise from the *endo* isomer **218** while **209**, **211** **212** and **208** arise from the *exo* isomer **219**. The distribution of products is, therefore, a reflection of the relative ratio of diazonium ion epimers (**218** and **219**) present in the reaction medium. It is noteworthy that these results strongly suggest that the diazonium ions undergoing reaction are protonated on carbon and not on oxygen.

In related experiments Avaro and Levisalles[102] examined the decomposition of 2-diazo-5α-cholestan-3-one (**10**). As previously observed, the nature of the products was critically dependent upon the acid-solvent couple employed. Although NMR studies in magic acid demonstrate that protonation occurs predominantly on oxygen in strongly acidic medium, the results of Avaro and Levisalles are best explained, as suggested by Avaro[102] and Friedman,[8] as arising via carbon protonation followed by concerted rearrangement. That is, in non-polar dichloromethane decomposition is anticipated to afford the epimer with an equatorial diazonium ion, thereby facilitating rearrangement to **223**. In benzene the epimer with an axial diazonium ion is suggested to form at a sufficient rate so that a moderate yield of **224** is obtained. Thus, the observed products appear to be highly dependent upon both the relative rates of rearrangement and the predominate diazonium ion epimer present under a given set of conditions. Avarao, however, raised the possibility that **223** arises from **225** by bond migration as shown. It was pointed out that initial rearrangement of **226** would generate an energetically disfavored primary carbonium ion, whereas rearrangement of **225** affords a primary allylic carbonium ion.



Yates[25] extended his earlier observations by an investigation of the acid catalyzed decomposition of the closely related diazo ketones **8** and **9**. The products derived are illustrated below.



(8) (9) (227) (a) R = H (b) R = D (228)

Participation of the cyclopropyl bond in **8** is interesting in light of the fact that Wilcox and Jesaitis[103] found no cyclopropane participation in the solvolysis of **228**. Thus the former reaction demonstrates that the diazonium ion is such a high energy species that rearrangements not normally observed under solvolytic conditions can occur. That in fact both protonation of the diazo ketone on carbon and participation of the C(4,7) carbon carbon σ-bond were occurring was demonstrated by the exclusive formation of **227b** labeled at C(3) when the decomposition of **9** was carried out in D_3O^+.

8. SUMMARY

The acid promoted reactions of α-diazo ketones have been investigated for over 50 years. During that period, they have progressed from an annoying side reaction in the preparation of α-diazo ketones to a number of useful synthetic methods. More specifically, the acid catalyzed solvolysis of simple α-diazo ketones has been studied extensively, and the mechanistic pathways operating are fairly well understood. Reactions involving participation of aromatic and olefinic nucleophiles have only been explored in detail during the past decade and then, primarily in connection with synthetic applications. Although patterns of reactivity have emerged during this period, very little is in fact known about the nature of the cyclization process and the intermediates involved. The reaction is clearly very sensitive to the nature of the diazo ketone substrate and the acid-solvent couple; choice of the latter remains an often difficult experimental problem. Although the powerful synthetic potential of this annulation procedure has been utilized in a synthesis of gibberellic acid, the unpredictable reliability of the reaction places certain tactical and strategic limitations on its general application. Clearly, additional mechanistic and synthetic investigations are required to enhance the utility of these reactions.

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