Cyanoketenes: Synthesis and Cycloadditions

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1 Introduction

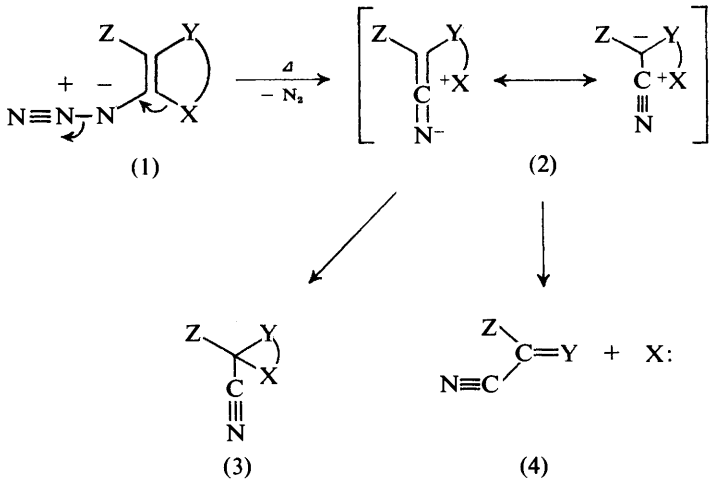
In 1970 it was reported that cyanoketenes could be conveniently prepared by the thermolysis of 2,5-diazido-1,4-quinones.[1] Since that time a great deal of work has appeared concerning the synthesis and chemistry of these unusual electron-deficient cumulenes. t-Butylcyanoketene (TBCK) has received the most attention since it provides several experimental advantages; it is unsymmetrical, stable to selfcondensation when kept in solution, and highly reactive towards a large number of keteneophiles. Thus, it is an ideal reagent for investigations of the mechanisms of 2 + 2 cycloaddition reactions as well as a starting material that can be used to prepare a variety of carbocyclic and heterocyclic compounds. To this end, TBCK and some of its analogues have been observed to react with alkenes, alkynes, allenes, ketenes, imidates, imines, aldehydes, isonitriles, amine oxides, azirines, sulphurdi-imides, and a number of heterocyclic substrates. The purpose of this article is to provide a review of cyanoketenes with a focus on their syntheses and cycloaddition reactions.

2 Synthesis of Cyanoketenes

Cyanoketenes are but one class of compounds whose synthesis can be viewed as arising from zwitterionic intermediates formed in the thermolysis of appropriately substituted vinyl azides. The general rationale for their formation is defined as outlined in Scheme 1.[2] Specifically, vinyl azides of structure (1) cleave to zwitterions, (2), when X is a substituent capable of cation stabilization and Y and/or Z are anion stabilizing. The zwitterionic intermediate, (2), can then undergo ring closure to (3) or cleave to (4). Thus, a synthetic route to cyanoketenes can be envisaged for cases in which Y is a carbonyl substituent and X is an appropriate leaving group.

A particularly suitable class of azides that one would predict to give cyanoketenes by the above generalized mechanism is 2,5-diazido-1,4-benzoquinones. The thermal chemistry of such compounds has now been explored in moderate depth,[2] and it has been found that they do give good yields of alkyl- and aryl-

[1] H. W. Moore and W. Weyler, *J. Am. Chem. Soc.*, 1970, **92**, 4132.
[2] H. W. Moore, *Acc. Chem. Res.*, 1979, **12**, 125; H. W. Moore, *Chem. Soc. Rev.*, 1974, **2**, 415.



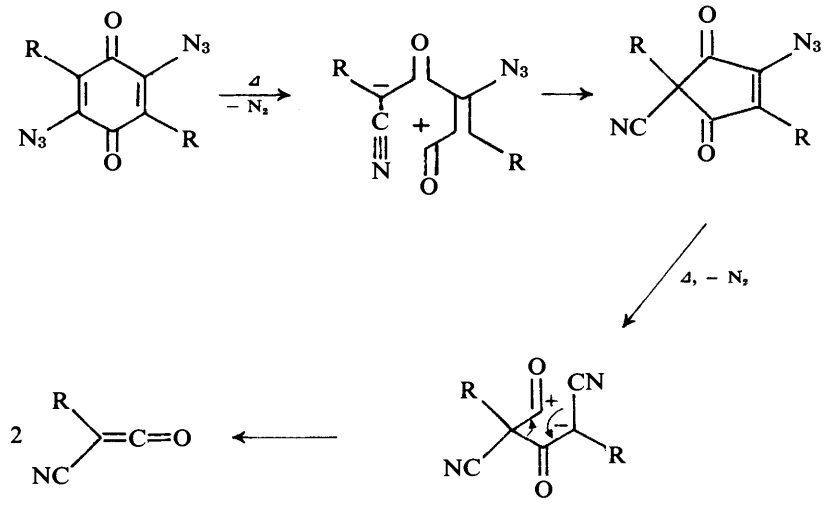
Scheme 1

cyanoketenes[3] as well as dicyanoketene.[4] An interesting example in this series is 2,5-diazido-3,6-di-t-butyl-1,4-benzoquinone which gives a nearly quantitative yield of t-butylcyanoketene (TBCK) when decomposed in refluxing benzene. The mechanism for the generation of this and other cyanoketenes by this method is outlined opposite.

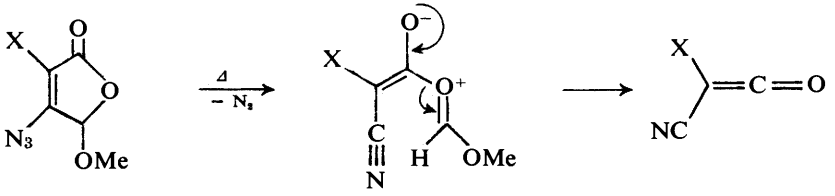
Attempts to utilize the diazidoquinone method for the synthesis of halocyanoketenes met with failure due to the insolubility of the diazidoquinone precursors. However, this problem was circumvented by utilizing 4-azido-3-halo-5-methoxy-(5*H*)-furan-2-ones which were found readily to cleave in refluxing benzene to the corresponding halocyanoketene and methylformate.[5–7] This has now been employed for the synthesis of chloro-, bromo-, and iodo- as well as phenoxycyanoketene (see opposite page).

With the exception of t-pentyl- and t-butylcyanoketene, the other cyanoketenes reported readily undergo self-condensation and thus must be generated *in situ* for their reactions to be studied. This is often an advantage since, under these conditions, the ketene is slowly generated in the presence of the keteneophile. Thus, its concentration is minimized and product yields are often enhanced. The bulky examples mentioned above are stable for days in anhydrous aromatic solvents. However, these, as well as all of the other cyanoketenes studied, are very reactive as electrophilic species in their reactions with a large variety of keteneophiles.

[3] W. Weyler, W. G. Duncan, and H. W. Moore, *J. Am. Chem. Soc.*, 1975, **97**, 6187.
[4] R. Neidlein and E. Bernhard, *Angew. Chem., Int. Ed. Engl.*, 1978, **17**, 369.
[5] H. W. Moore, L. Hernandez, and A. Sing, *J. Am. Chem. Soc.*, 1976, **98**, 3728.
[6] D. M. Kunert, R. Chambers, F. Mercer, L. Hernandez, and H. W. Moore, *Tetrahedron Lett.* 1978, 929.
[7] H. W. Moore, R. Czerniak, G. Hughes, C. C. Yu, F. Mercer, D. Goldish, B. Axon, unpublished result.



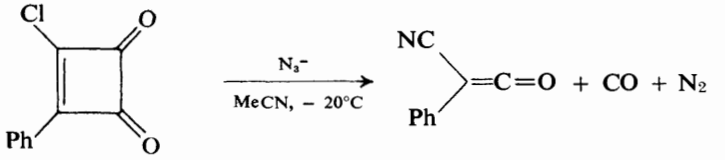
R = Et—C(Me)(Me)—, Me_3C—, Me_2CH—, Me, Ph—, or —C≡N



X = Cl, Br, I, or OPh

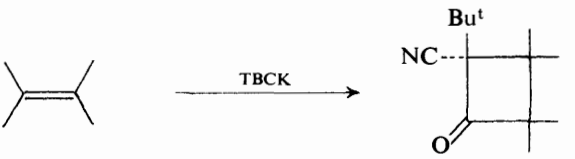
A related route to cyanoketenes was reported for the synthesis of phenylcyanoketene. Treatment of 3-chloro-4-phenylcyclobutene-1,2-dione with azide ion in acetonitrile at ambient temperature or below gave carbon monoxide, nitrogen, and phenylcyanoketene.[8] The synthetic scope of this reaction deserves more attention since it may provide an advantage over the azidoquinone or azidobutenolide methods. That is, the reactive cyanoketenes could conceivably be generated at low temperature.

[8] R. C. DeSelms, *Tetrahedron Lett.*, 1969, 1179.

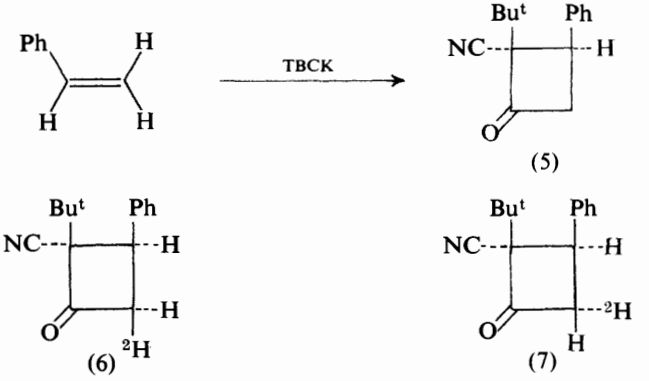


3 Cyanoketene–Alkene Cycloadditions

Monosubstituted, vicinal disubstituted, and trisubstituted alkenes react with TBCK to give cyclobutanones, in a 2 + 2 cycloaddition. Geminal disubstituted alkenes, on the other hand, sometimes also give 'ene' reaction products.



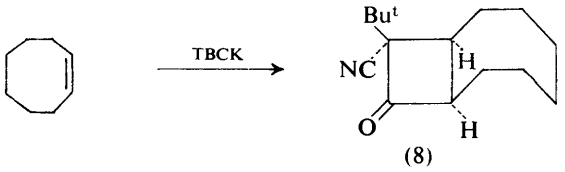
The cycloaddition of TBCK to styrene has been studied in greatest depth.[9–11] The sole reaction product is the cyclobutanone (5) having a *cis* stereochemical relationship between the bulky t-butyl and phenyl substituents. Such a result is best rationalized in terms of a concerted $2\pi_a + 2\pi_s$ reaction mode.[12] This mechanism further demands preservation of the alkene stereochemistry in the cyclobutanone product. Such was observed for the TBCK cycloadditions to the *Z*- and *E*-isomers of monodeuteriostyrenes to give, respectively, the cyclobutanones (6) and (7). The configurations of these cyclobutanones were determined by



[9] M. D. Gheorghiu, F. Kerek, and M. Avram, *Rev. Roum. Chim.*, 1975, **20**, 75.
[10] M. D. Gheorghiu, L. Pârvulescu, C. Drăghici, and M. Elian, *Tetrahedron*, 1981, **37**, 143.
[11] M. D. Gheorghiu, O. Ciobanu, and M. Elian, *J. Magn. Reson.*, 1981, **44**, 330.
[12] R. B. Woodward and R. Hoffmann, 'The Conservation of Orbital Symmetry,' Academic Press, New York, 1970.

theoretical and experimental n.m.r. analyses which included anisotropy effects, as well as solvent and lanthanide induced chemical shift experiments.[9–11]

1,2-Disubstituted alkenes react readily with TBCK to give cyclobutanones. Several of these cycloadditions related to the anticipated *cis*-stereochemical relationship between the bulky t-butyl group and the substitutent at position-3, as well as to the preservation of alkene stereochemistry in the product. For example, treatment of *cis*- and *trans*-cyclo-octene with TBCK gave, respectively, (8) and (9).[13] Cyclohexene has also been observed to form cycloadducts with



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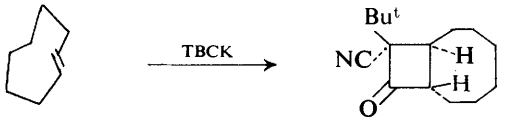

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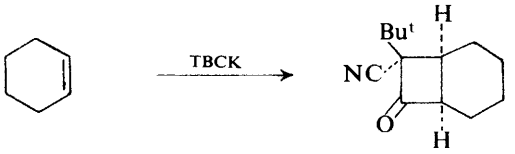

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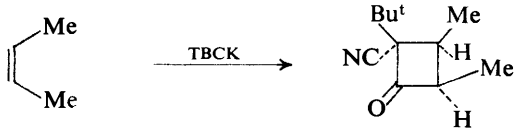
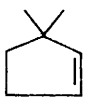


(11)

TBCK to give (10).[3] Although stereochemical evidence for (10) is lacking, one can reasonably assume a relationship analogous to that found in (8) and (9), *i.e.*, t-butyl *cis* to the adjacent CH_2. Analogously, *cis*-but-2-ene gave the cyclo-

[13] W. Weyler, L. B. Bird, M. C. Caserio, and H. W. Moore, *J. Am. Chem. Soc.*, 1972, **94**, 1027.

butanone, (11).[14] Contrathermodynamic cyclobutanones were also observed when the cyclopentene keteneophiles (12)—(20) were treated with TBCK.[9,15–18]



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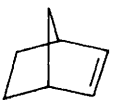

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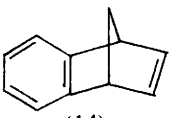

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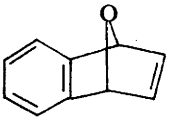

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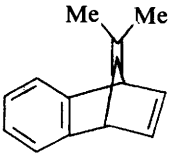

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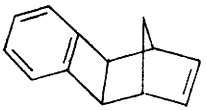

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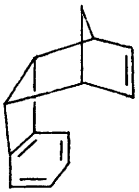

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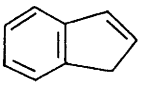

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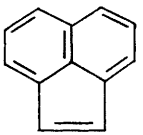
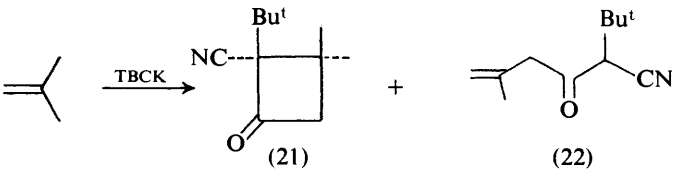


(20)

It is noteworthy that only cyclobutanones and no rearranged products were observed for the bicyclo[2.2.1]heptenes (13)—(18), a result that is again consistent with a concerted mechanism for the cycloadditions.

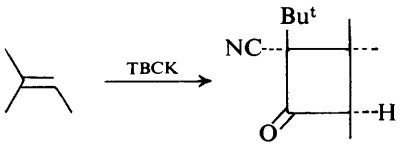
The geminal disubstituted alkene, 2-methylpropene, gave the cyclobutanone (21) and the 'ene' product (22) when treated with TBCK.[15] Interestingly, no 'ene'



(21) (22)

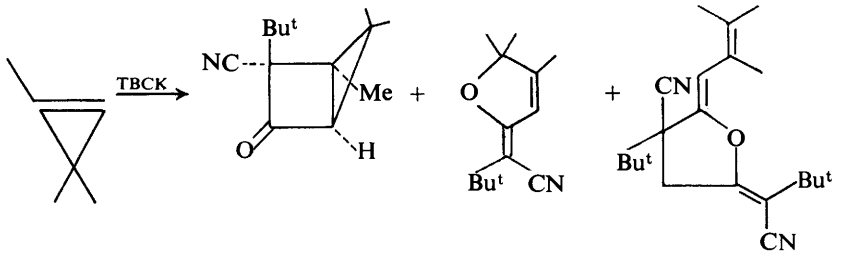
[14] P. R. Brook, A. M. Eldeeb, K. Hunt, and W. S. McDonald, personal communication (1978). We thank Professor Brook for providing these results.
[15] P. R. Brook and K. Hunt, *J. Chem. Soc., Chem. Commun.*, 1974, 989.
[16] M. D. Gheorghiu, P. Filip, C. Drăghici, and L. Pârvulescu, *J. Chem. Soc., Chem. Commun.*, 1975, 635.
[17] M. D. Gheorghiu, C. Drăghici, and L. Pârvulescu, *Tetrahedron*, 1977, **33**, 3295.
[18] M. D. Gheorghiu, L. Pârvulescu, and C. Drăghici, *Rev. Roum. Chim.*, 1979, **24**, 1005.

product was observed in the analogous cycloaddition using the trisubstituted alkene, 2-methylbut-2-ene; only the cyclobutanone (23) was obtained.[19]

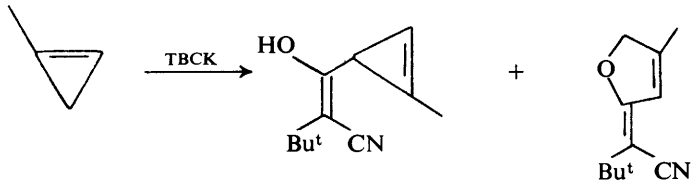


(23)

TBCK cycloaddition to 1,3,3-trimethylcyclopropene gave three products: the cyclobutanone (24; 28%), the furan (25; 7%), and the 2:1 adduct (26; 40%).[20] A similar preference for rearranged products from these strained alkenes was observed when 1-methylcyclopropene was treated with TBCK.[21] Here, the products were (27) and (28), and no cyclobutanone was detected.



(24) (25) (26)



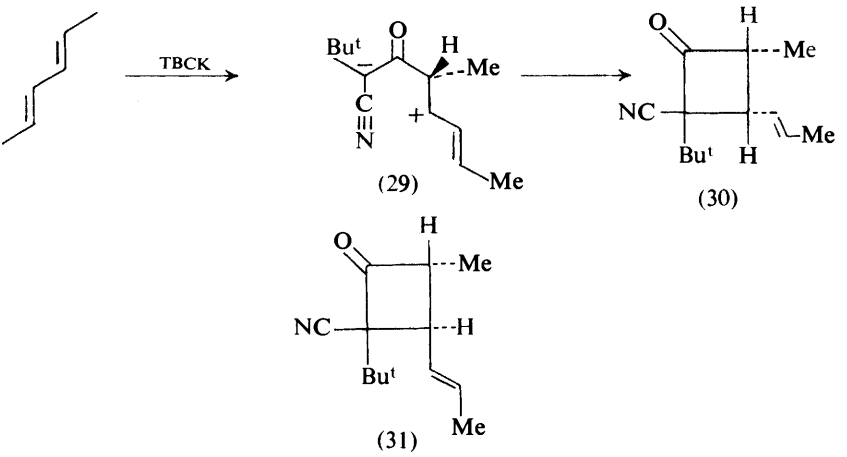
(27) (28)

It appears that no examples of the reactions of TBCK with tetrasubstituted alkenes have been reported.

Only one brief report has appeared in the literature describing the cycloaddition of TBCK to an acyclic conjugated diene.[3] Treatment of the ketene with *trans, trans* hexa-2,4-diene resulted in > 80% yield of the cyclobutanone (30).

[19] P. R. Brook, A. M. Eldeeb, K. Hunt, and W. S. McDonald, *J. Chem. Soc., Chem. Commun.*, 1978, 10.
[20] D. H. Aue, D. F. Shellhamer, and G. S. Helwig, *J. Chem. Soc., Chem. Commun.*, 1975, 603.
[21] D. H. Aue and G. S. Helwig, *J. Chem. Soc., Chem. Commun.*, 1975, 604.

Only tentative stereochemical assignments could be made on the basis of n.m.r. data obtained on (30) and the corresponding cyclobutanols formed upon borohydride reduction. However, it is noteworthy that these data are consistent with (30) rather than (31), and the latter would be expected if the cycloaddition

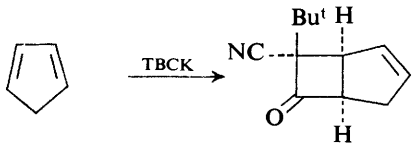


were concerted. Thus, a stepwise mechanism involving a zwitterionic intermediate such as (29) may be involved.

Some cyclic dienes have been reported to give unusual products when treated with TBCK. Cyclopentadiene behaves as expected and gives only the contrathermodynamic cyclobutanone (32).[15,22] More interestingly, cyclohexa-1,3-diene resulted in the cyclobutanone (33; 71%) and the bicyclic enol ether (34; 29%).[22] Furthermore, it was observed that (33) can be converted into (34) upon thermolysis. However, it has not been determined if this transformation is a concerted oxy-Cope rearrangement or a stepwise process.

Anomalous transformations have also been reported for the cycloaddition of TBCK to certain homoconjugated dienes. For example, bicyclo[2.2.1]heptadiene gave the cyclobutanone (35) and the polycyclic ether (36).[15,17] The ratio of these products shows little solvent dependence; in benzene the (35): (36) ratio was 2.08 and in acetonitrile it was 1.48. Thus, both products were suggested to arise *via* a concerted process. Benzobarelene behaved analogously in that the cyclobutanone (38; 33%) and the polycyclic ether (39; 66%) were the observed products.[22] Bicyclo[3.2.1]octa-2,5-diene, on the other hand, gave only the cyclobutanone (40).[22] Other nonconjugated dienes such as cyclohexa-1,4-diene,[15,22] *cis,cis*[15,22] and *cis, trans*-cyclo-octa-1,5-diene[15] gave only cyclobutanones when treated with TBCK.

[22] M. D. Gheorghiu, L. Pârvulescu, C. Drăghici, I. Manolescu, and B. David, unpublished results; presented, in part, at the Chemical Meeting at Timisoara (October, 1979) and at the Meeting of the Chemical Section of the Romanian Academy of Science, Bucharest (March, 1980).



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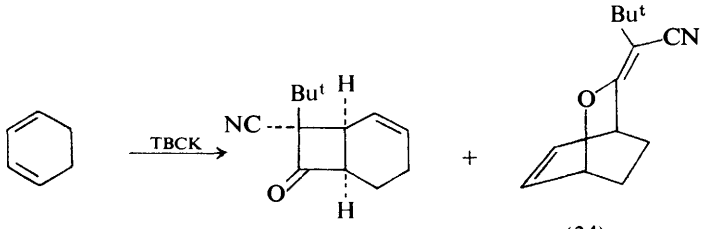

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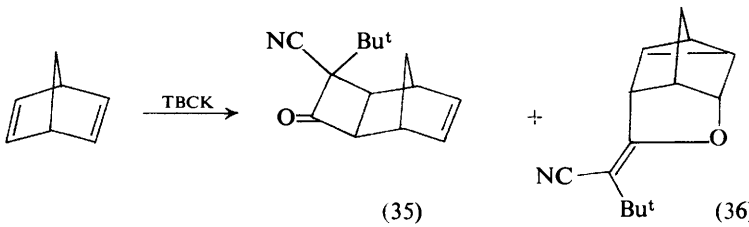

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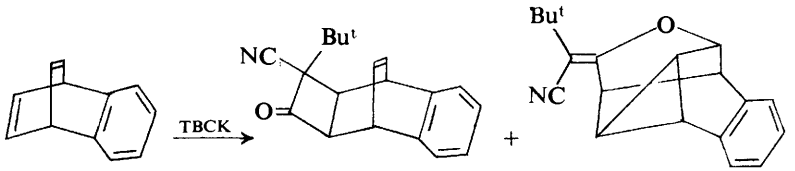

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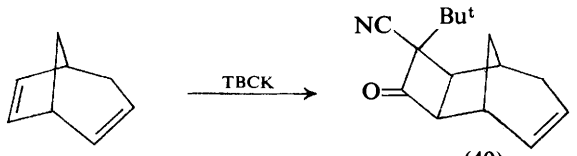


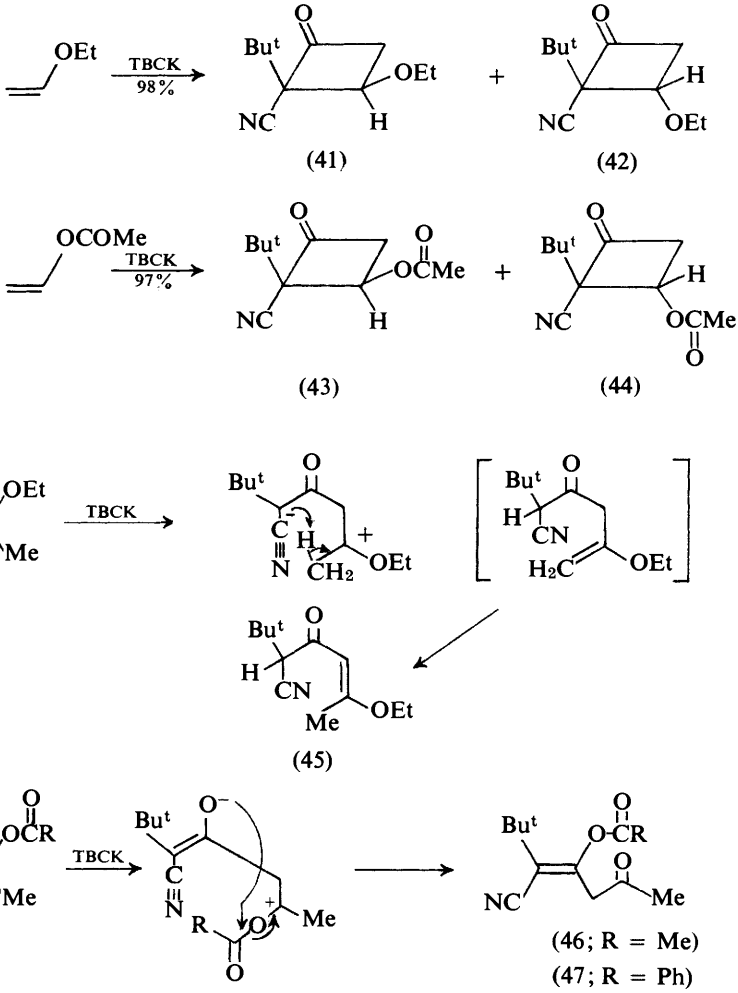
(40)

4 Cyanoketene–Enol Ether Cycloaddition

A zwitterion mechanism is most likely for the cycloadditions of TBCK to enol

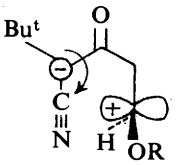
ethers.[23] Ethyl vinyl ether and vinyl acetate gave the corresponding cyclobutanones [(41), (42); 3:1] and [(43), (44); 3.5:1] upon treatment with TBCK. It is significant to note that the stereochemistry of the major isomers [(41) and (43)] is that predicted to arise from a $[2\pi_s + 2\pi_a]$ concerted process. However, this was rejected since the products obtained from the related enol ethers, 1-ethoxypropene, 1-acetoxy- and 1-benzoxypropene, were (45), (46), and (47), respectively, and these could reasonably arise *via* zwitterionic intermediates.

Thus zwitterionic intermediates were also suggested as the precursors to the cyclobutanones (41)—(44). The slight selectivity observed for the formation of



[23] D. Becker and N. C. Brodsky, *J. Chem. Soc., Chem. Comm.*, 1978, 237.

the contrathermodynamic products (41) and (43) was viewed as arising by the favoured rotation sequence indicated in the proposed zwitterion, (48), *i.e.*, small



(48)

cyano-group rotating past small proton. Such a process is consistent with the predictions arising from Orbital Correspondence Analysis in Maximum Symmetry,[24,25] which proposes specifically oriented zwitterions or diradicals in 2 + 2 cycloadditions.

5 Cyanoketene–Alkyne Cycloadditions

Limited reports have appeared concerning the cycloaddition of cyanoketenes to simple alkynes.[26,27] Here again, the ketene was t-butylcyanoketene, and the cycloadditions gave the cyclobutenones (49*a*—*d*) in yield ranging from 40—80%.

(49) *a*; R^1 = Ph, R^2 = H
b; R^1 = Bu^t, R^2 = H
c; R^1 = Bu^t, R^2 = Ph
d; R^1 = R^2 = Ph

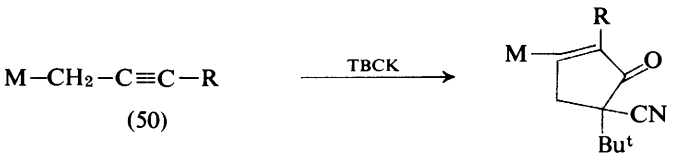
For the unsymmetrical alkynes only a single regioisomer was detected. These data are consistent with a concerted cycloaddition.

An unusual transformation was observed when the acetylenic transition-metal complexes, (50) were treated with TBCK.[28] Rather than cyclobutenones, the cyclopentenones (51) were isolated. Analogous results were obtained with diphenylketene.

6 Cyanoketene–Allene Cycloadditions

A most interesting series of observations has been recorded for studies of the

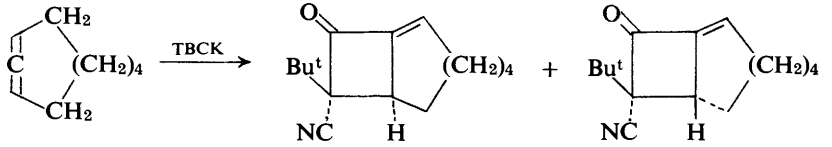
[24] A. Halevi, *Helv. Chim. Acta*, 1975, **58**, 2136.
[25] A. Halevi, *Angew. Chem.*, 1976, **88**, 664.
[26] M. D. Gheorghiu, C. Drăghici, L. Stănescu, and M. Avram, *Tetrahedron Lett.*, 1973, 9.
[27] M. D. Gheorghiu, *Rev. Roum. Chim.*, 1977, **22**, 1069.
[28] L. S. Chen, D. W. Lichtenberg, P. W. Robinson, Y. Yamamoto, and A. Wojcicki, *Inorg. Chim. Acta*, 1977, **25**, 165.



(50) (51)

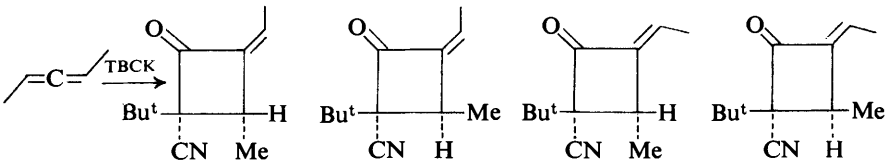
M = η^5-$C_5H_5Fe(CO)_2$, R = Me, Ph, or CH_2—$Fe(CO)_2(\eta^5$-Ph)
M = η^5-$C_5H_5Mo(CO)_3$, R = Ph

cycloaddition of TBCK to allenes. The cyclic and optically enriched allene, cyclonona-1,2-diene, gave the adducts (52) and (53) in a ratio of 3:2, and both showed some optical activity.[13]



(52) (53)

With the optically enriched acyclic allene, penta-2,3-diene, the four possible isomers, (54)—(57), were formed. However, only the minor *E*-isomers, (56) and (57), showed optical activity.[29,30]

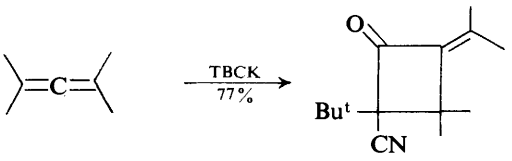


(54; 39%) (55; 36%) (56; 21%) (57; 3%)

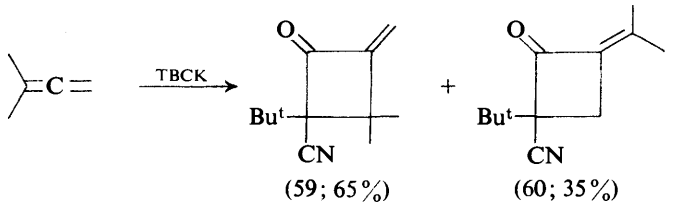
Tetramethylallene gave a 77% yield of (58), and 1,1-dimethylallene gave (59) and (60) in a respective ratio of 65:35. 1-t-Butyl-1-methylallene reacted with TBCK to give four adducts in 27% yield. The major product was (61) and the minor was (62); the other two were (63) and (64).[31]

Optically enriched 1,3-diphenylallene gave the cyclobutanones (65) and (66) having only the *E*-configuration of the benzylidine groups.[32] Both were optically active and (65) was shown to have 53% of the optical purity of that of (66).[33]

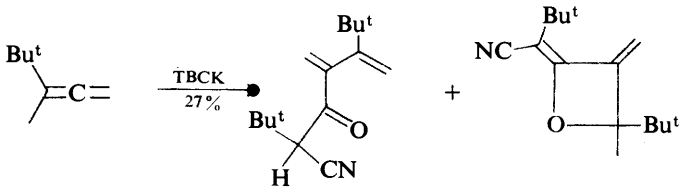
[29] W. G. Duncan, W. Weyler, and H. W. Moore, *Tetrahedron Lett.*, 1973, 4391.
[30] H. A. Bampfield and P. R. Brook, *J. Chem. Soc., Chem. Commun.*, 1974, 171.
[31] H. A. Bampfield and P. R. Brook, *J. Chem. Soc., Chem. Commun.*, 1974, 172.
[32] H. A. Bampfield, P. R. Brook, and W. S. McDonald, *J. Chem. Soc., Chem. Commun.*, 1975, 132.
[33] H. A. Bampfield, P. R. Brook, and K. Hunt, *J. Chem. Soc., Chem. Commun.*, 1976, 146.



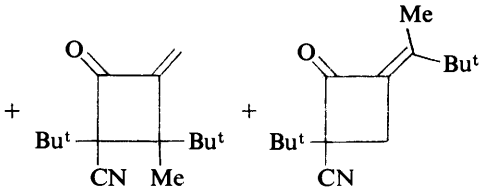
(58)



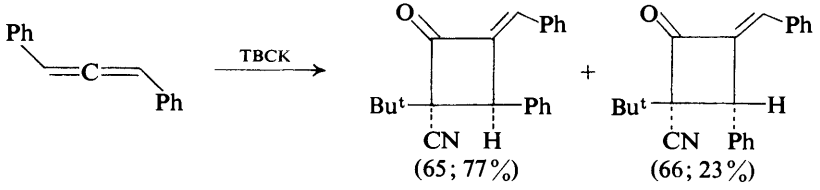
(59; 65%) (60; 35%)



(61; 58%) (62; 3%)



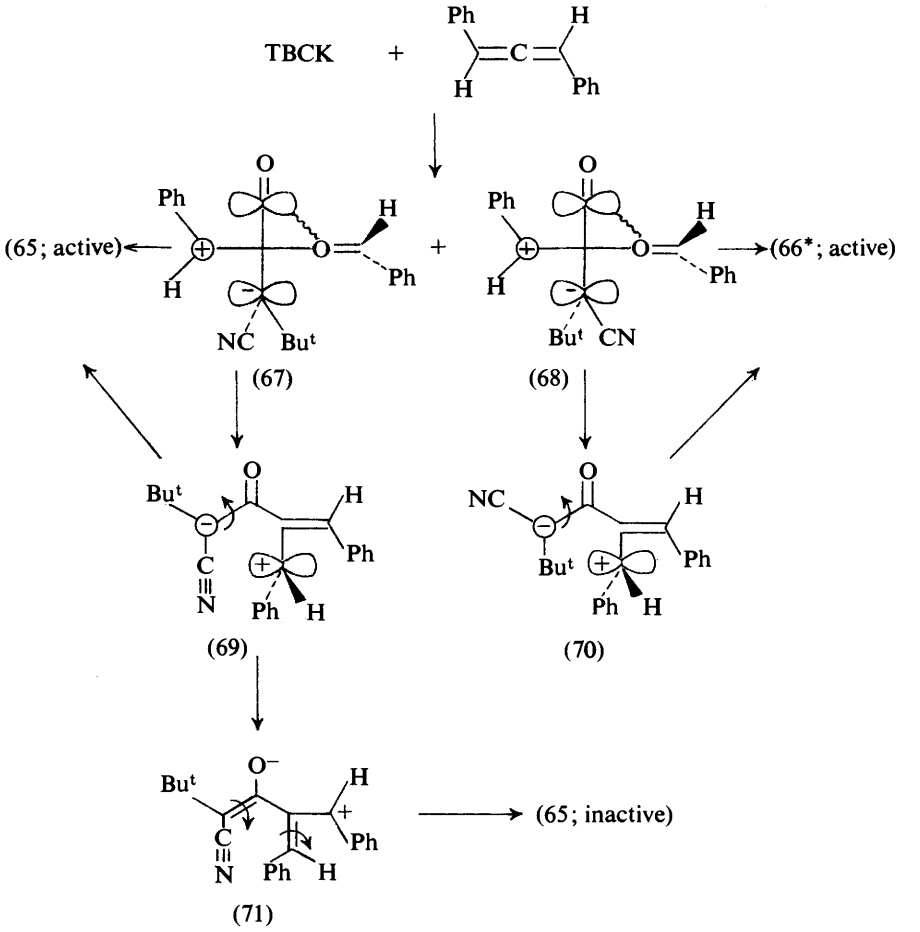
(63; 24%) (64; 15%)



(65; 77%) (66; 23%)

In this last example, any detailed mechanism must account for the following two salient points: (i), the major product is the torsionally strained adduct (65) and it is formed with approximately half the optical purity of (66); (ii), only the *E*-isomers are formed. These data are consistent with the mechanism outlined in

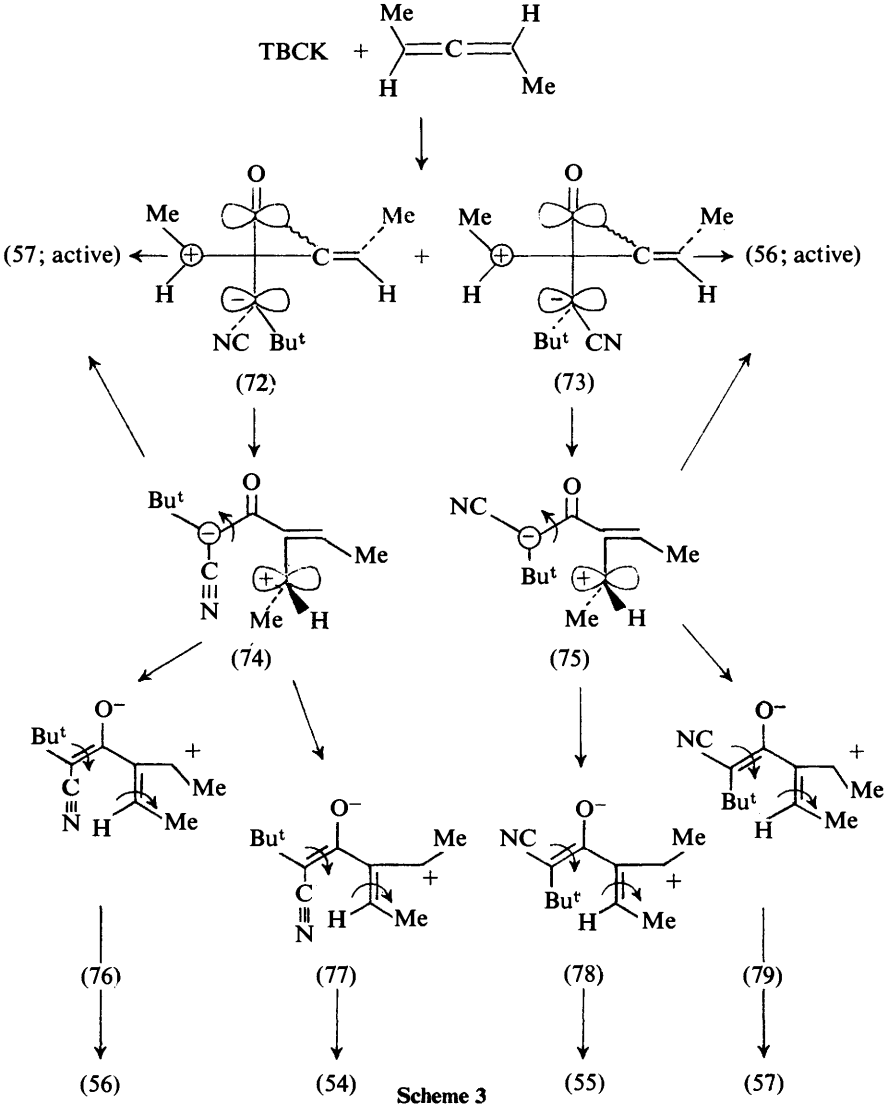
Scheme 2. The cycloaddition resembles a concerted reaction in that the ketene and allene components approach one another in an orthogonal fashion. However, initial bond formation takes place to give the chiral zwitterions (67) and (68). Ring closure of these gives, respectively, the optically active products (65) and (66). Zwitterions (67) and (68) could assume another chiral conformation, *i.e.*, (69) and (70), respectively, and these could also undergo ring closure to give active (65) and (66). Finally, ion (69) could proceed to the achiral (71) and conrotatory ring closure of this would lead to optically inactive (65). On the other hand, a planar achiral ion arising from (70) would be less likely on the basis of steric effects. Thus, even though the total yield of (65) would be expected to



Scheme 2

exceed that of (66), the optical activity of the former should be less than the latter. An analogous mechanism can be envisaged for the conversion of optically enriched cyclonona-1,2-diene into (52) and (53).

The mechanism of TBCK addition to penta-2,3-diene is more complex in that both *E*- and *Z*-isomers are formed. In addition, only the *E*-isomers [(56) and (57)] show optical activity; yet the *Z*-isomers [(54) and (55)] are the major products. These results can be rationalized in somewhat analogous manner to those arguments presented for the diphenylallene case and are outlined in Scheme 3. It can



Scheme 3

be assumed that (72) and (73) are the initially formed chiral zwitterions and that these lead to optically active *E*-isomeric products. However, there is a significant driving force for these to proceed to the achiral zwitterion [(76)—(79)] to gain allylic resonance stabilization. Although several planar zwitterions other than those listed [(76)—(79)] are possible, the ones represented do minimise steric interactions. Indeed, one would predict their stabilization order to be (77) > (76) and (78) > (79). Thus, the predominance of the *Z*-isomers over the corresponding *E*-isomers might be expected.

The formation of [(58)—(64)] can also be viewed as arising *via* dipolar intermediates rather than by concerted processes.

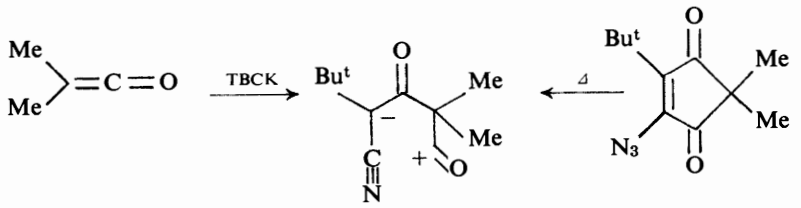
Clearly additional work is needed before a detailed understanding of the mechanism of cyanoketene–allene cycloadditions can be obtained. However, the results thus far reported suggest these cycloadditions to be non-concerted and to involve zwitterionic intermediates.

7 Cyanoketene–Ketene Cycloadditions

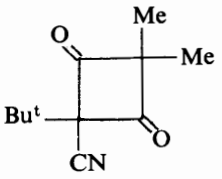
In general, the mechanism of ketene to ketene cycloadditions is fraught with ambiguities concerning their concerted *versus* non-concerted nature. The exception to this concerns the cycloadditions of TBCK to aldo- and ketoketenes since here it is clearly established that these proceed *via* a dipolar process.[34] The key to this interpretation is that the intermediate zwitterionic species has been independently generated and shown to give the same products as the cycloadditions themselves. Specifically, it was shown that TBCK reacts with the ketoketenes, dimethyl-, ethylmethyl-, and benzylmethyl-ketene to give, respectively the cyclobutanediones, (80), [(81), (82); 43: 57], and [(83), (84); 46: 54]. That these cycloadditions involve a zwitterionic intermediate was established by the observation that the thermolysis of the azidocyclopentenones, (85), (86), and (87) gave the same products and isomer ratios. A zwitterion was established by trapping experiments in the thermolysis of (85). In an analogous set of experiments TBCK and methylketene were shown to undergo cycloaddition to give (88), and the same product was formed as the exclusive 1:1 adduct from the thermolysis of (89).

The most consistent interpretation of these results is that the two ketenes undergo initial bond formation in a head-to-tail orientation to give the zwitterion represented by conformer (91) (Scheme 4). Such an interpretation is possible since (91) would be exactly the expected conformer to arise when the zwitterion is independently generated from the azidocyclopentenedione precursors, (90). Direct ring closure of (91; R = Me) to (80) would involve the orthogonal enolate anion and acyl cation orbitals. The product-forming step apparently experiences very little steric influence from the substituents at positions 2 and 4 of the zwitterion since a nearly equal mixture of *cis*- and *trans*-isomers is observed for the ring closure of (91: R = Et and R = Bn). However, there is a pronounced steric effect on conformational equilibration of the zwitterion as a function of the substituents at position 2. Thus, when R = H rapid rotation to (92) is

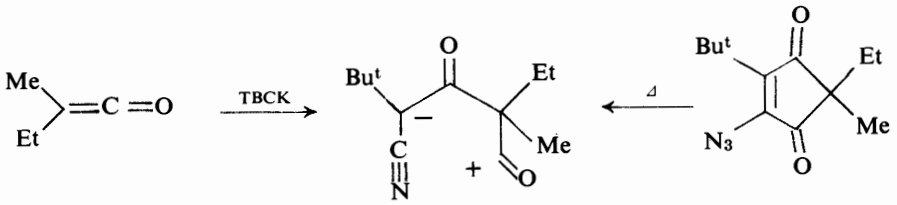
[34] H. W. Moore and D. Scott Wilbur, *J. Org. Chem.*, 1980, **45**, 4483.



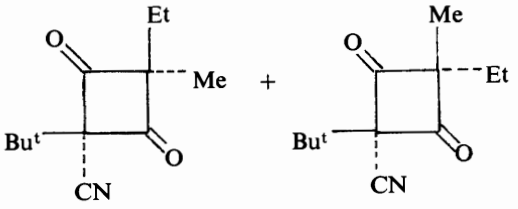
(85)



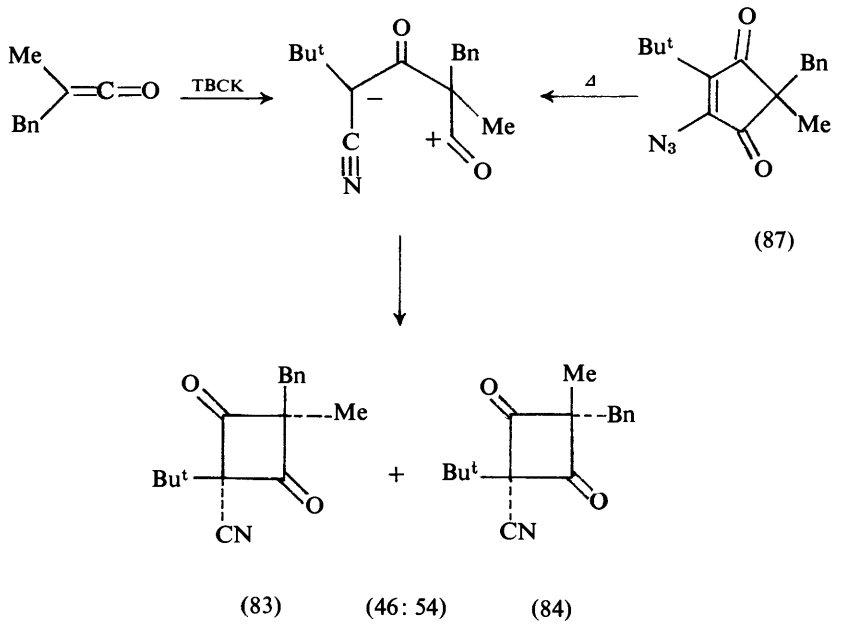
(80)

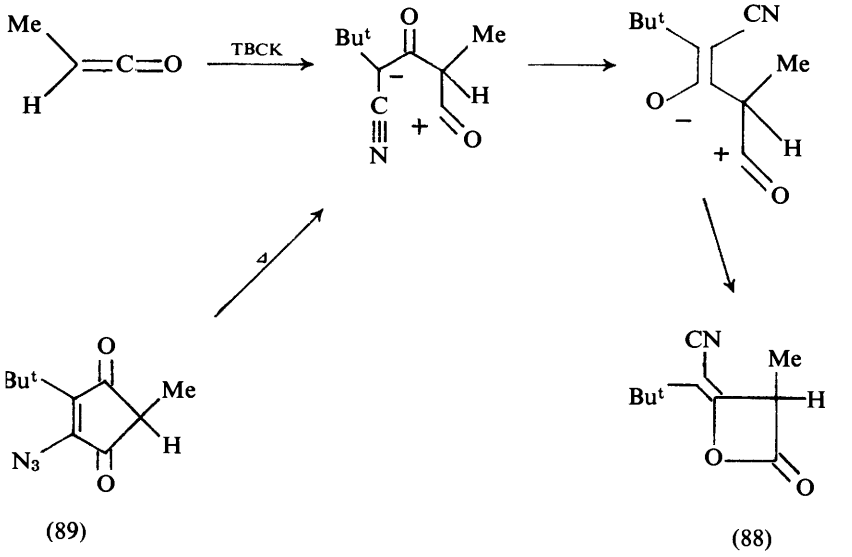


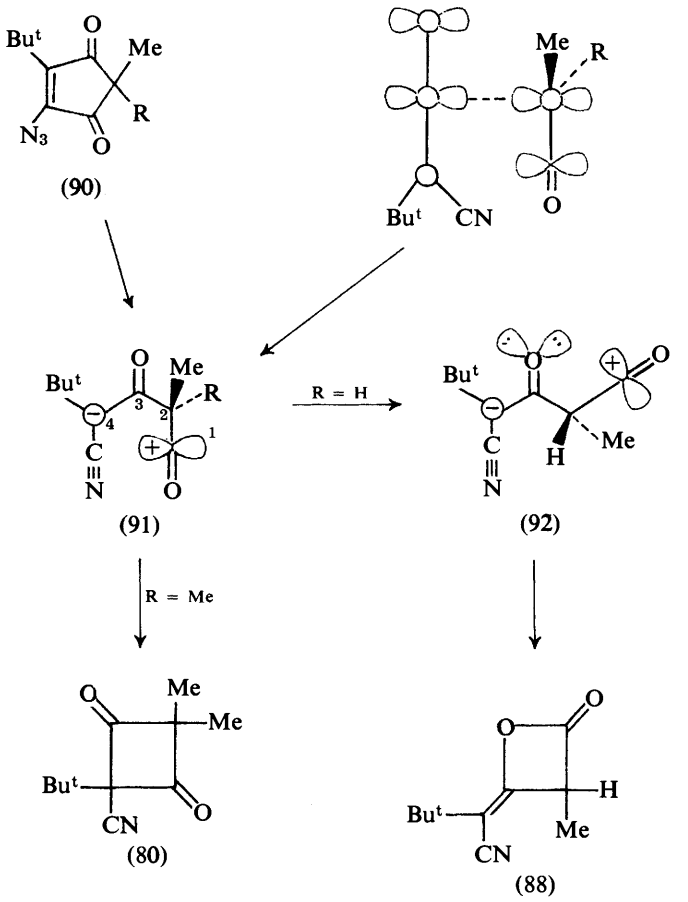
(86)



(81) (43 : 57) (82)


Me
Bn
TBCK
But
Bn
Me
C
N
Δ
(87)
(83)
(46: 54)
(84)


Me
H
TBCK
But
Me
H
CN
Δ
(89)
(88)



Scheme 4

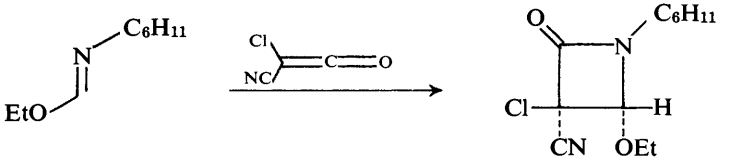
allowed and subsequent ring closure to the oxetan-2-one (88) occurs. Indeed, oxetan-2-one formation would be expected to be the kinetically favoured route on electronic grounds, but can compete sterically with cyclobutanedione formation only when one of the ketene components is an aldoketene.

8 Cyanoketene–Imine Cycloadditions

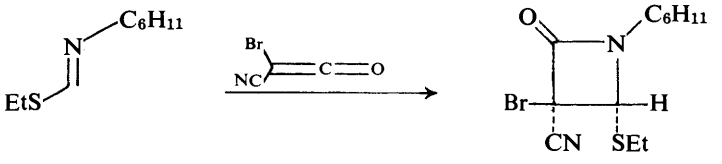
Extensive studies have appeared concerning the cycloadditions of cyanoketenes to formimidates, thioformimidates, and imines. t-Butyl-, methyl-, chloro-, bromo-, and iodocyanoketene were found readily to form cycloadducts with a variety of acyclic formimidates and thioformimidates to give 3-cyano-2-azeti-

dinones (β-lactams) in yields of 46—95%.[6,35] The fact that β-lactams are formed was anticipated since ketene cycloadditions to imidates and imines is one of the oldest synthetic routes to such compounds. However, it was surprising that the cyanoketene cycloadditions proceed in a stereospecific manner to give, in general, those azetidinones having a *trans*-relationship between the 3-cyano- and 4-protio-groups.[35,36] Although over sixty 3-cyano-2-azetidinones have been prepared by this method, the few examples listed below are sufficient to illustrate the transformation.

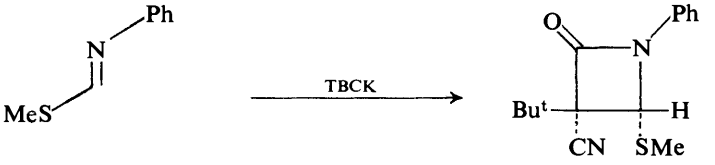
Sufficient data have now been accumulated to establish these cycloadditions



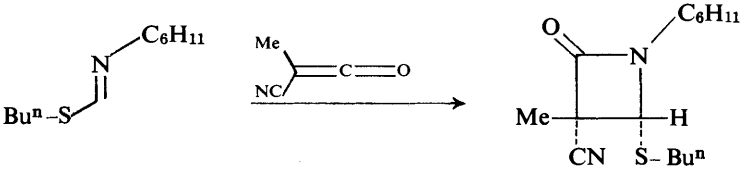
(93; 94%)



(94; 63%)



(95; 40%)

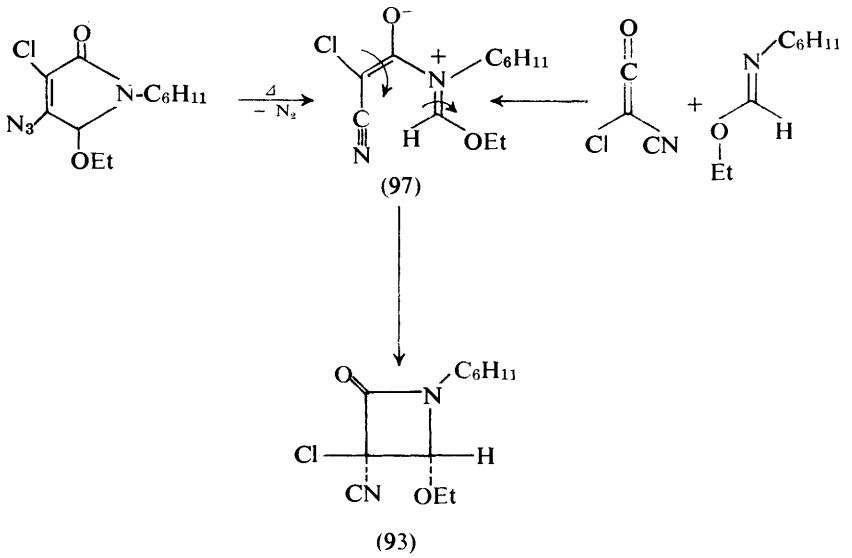


(96; 50%)

[35] H. W. Moore, L. Hernandez, D. M. Kunert, F. Mercer, and A. Sing, *J. Am. Chem. Soc.*, 1981, **103**, 1769.

[36] R. Chambers, D. Kunert, L. Hernandez, F. Mercer, and H. W. Moore, *Tetrahedron Lett.*, 1978, 933.

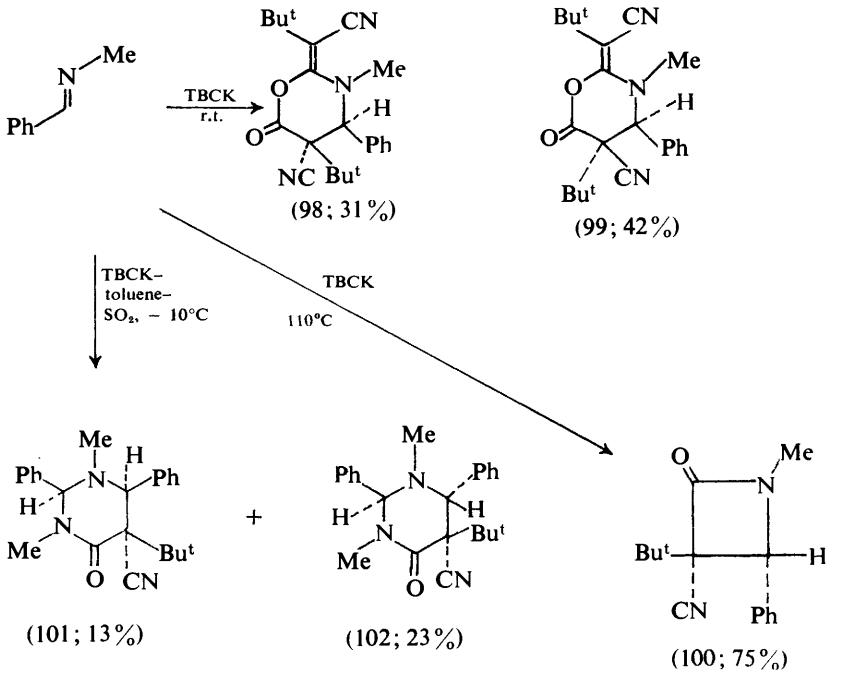
to be dipolar in character. The most significant mechanistic finding is of the independent generation of the zwitterion from the thermolysis of 4-azido-2-pyrrolinones.[2,36,37] For example, chlorocyanoketene forms cycloadducts with *O*-ethyl-*N*-cyclohexylformimidate to give (93). The same product was formed when 4-azido-3-chloro-1-cyclohexyl-5-ethoxy-3-pyrrolin-2-one was thermally decomposed in refluxing benzene (Scheme 5). In this thermolysis the intermediacy of the zwitterion (97) was established by a series of trapping experiments.[38] Thus, it is reasonably assumed that zwitterion (97) is a common intermediate in both the azidopyrrolinone decomposition as well as the ketene cycloaddition.



Scheme 5

A variety of cycloadditions of TBCK to azomethines provides additional support for a stepwise mechanism since often 2:1 adducts are formed. For example, *N*-methylbenzylideneamine and TBCK undergo cycloaddition in toluene at room temperature to give a mixture of (98) and (99).[39] On the other hand, if the reaction is accomplished at reflux temperature, or if (98) and (99) are pyrolysed at 180°C, the β-lactam (100) is formed.[40] In addition, if the reaction conditions are toluene–SO_2 at −10°C, then the adducts (101) and (102) are formed in addition to a small amount of the β-lactam (100; 15%). A particularly unusual result was observed when the reaction was accomplished by adding

[37] H. W. Moore, L. Hernandez, and R. Chambers, *J. Am. Chem. Soc.*, 1978, **100**, 2245.
[38] F. Mercer, L. Hernandez, and H. W. Moore, *Heterocycles*, 1979, **12**, 45.
[39] Z. Lysenko, M. M. Joullé, I. Miura, and R. Rodebaugh, *Tetrahedron Lett.*, 1977, 1705.
[40] E. Schaumann and H. Mrotzek, *Chem. Ber.*, 1978, **111**, 672.



the azomethine to an excess of TBCK containing a catalytic amount of triphenylphosphine.[41] Under these conditions a 45% yield of the 3:1 adduct, (103), was realized; its proposed mechanism is outlined below, but the effect of triphenylphosphine is not understood.

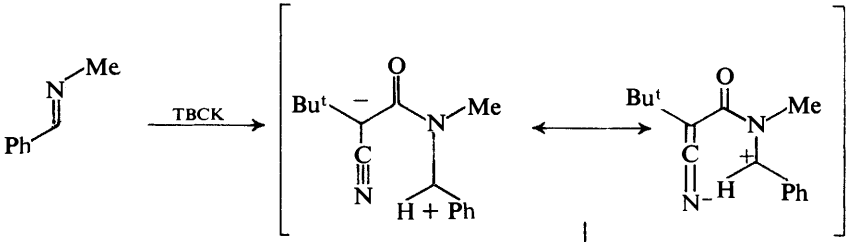
Cycloadditions analogous to the formation of (98) and (99) were also observed for TBCK with *N*-methyl-*p*-methoxy- and *N*-methyl-*p*-nitrobenzylideneamine. However, β-lactam products [(105), (107)] were observed for the cycloaddition to (104) and (106).

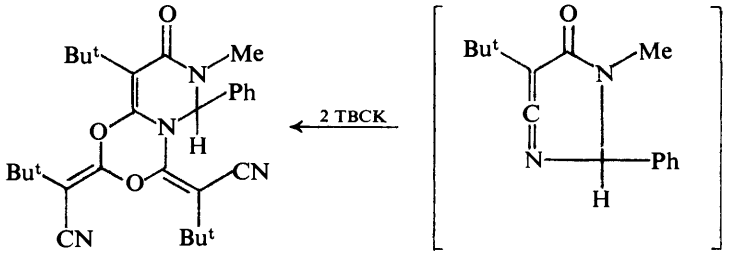
With *N*-t-butylbenzylideneamine the 2:1 adduct, (108) is formed in 45% yield if the amine is added to the ketene. If the addition is reversed, the β-lactams (109; 6%) and (110; 31%) are formed in addition to (108; 10%).

Cyclic imines and TBCK give either β-lactams or 2:1 adducts; the outcome is dependent upon the ring size and substitution pattern of the imine.[42] For example, the β-lactams (111), (112), and (113) result from the corresponding imines. However, (114) and (117) give the respective 2:1 adducts (115), (116) and (118), (119).

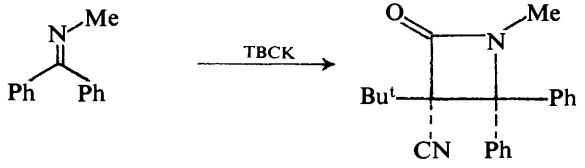
Additional examples resulting in 2:1 adducts were reported for dihydroisoquinoline to give (120) and the conversion of (121) into (122) (ketene added to imine solution).[40] In this latter case it was initially reported that (123) was the

[41] E. Schaumann, H. Mrotzek, and G. Adiwidjaja, *J. Chem. Soc., Chem. Commun.*, 1978, 820.
[42] E. Schaumann, H. Mrotzek, and F. Abmann, *Justus Liebigs Ann. Chem.*, 1979, 334.

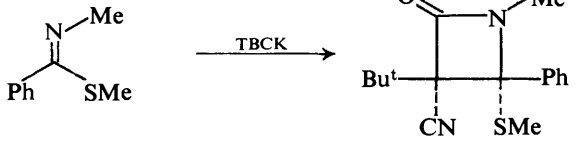




(103)



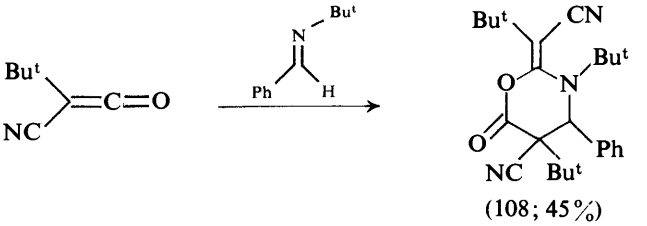
(104) (105)



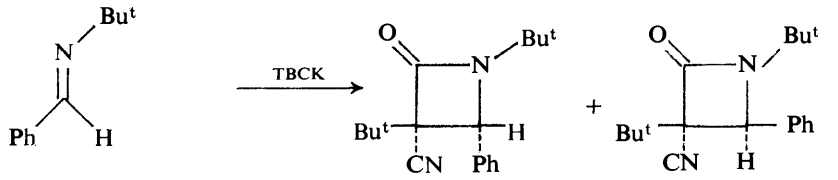
(106) (107)

product when the imine was added to a solution of the ketene.[43] However, the structure has recently been revised to (124) and this arises from the reaction of the ketene dimer with the imine. Finally, one last example of a cyclic imine–

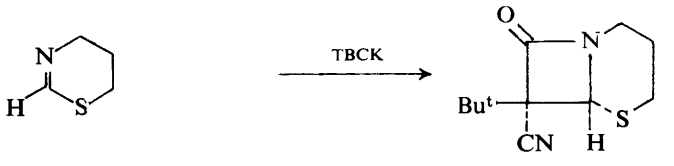
[43] D. H. Aue and D. Thomas, *J. Org. Chem.*, 1975, **40**, 2552.



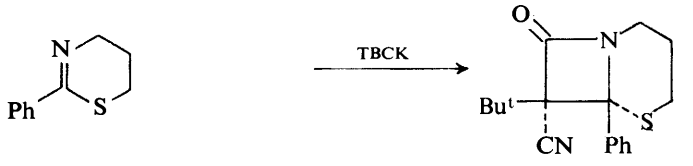
(108; 45%)



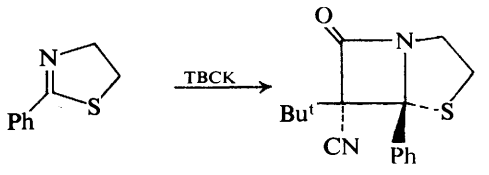
(109; 6%) (110; 31%)



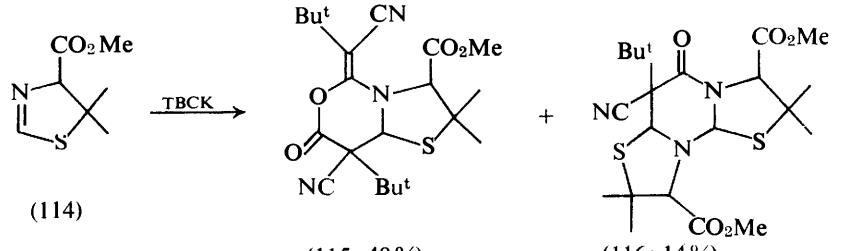
(111; 40%)



(112; 35%)

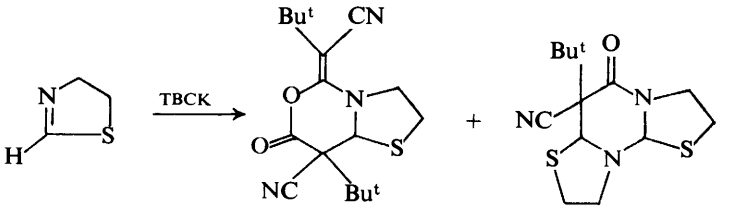


(113; 35%)

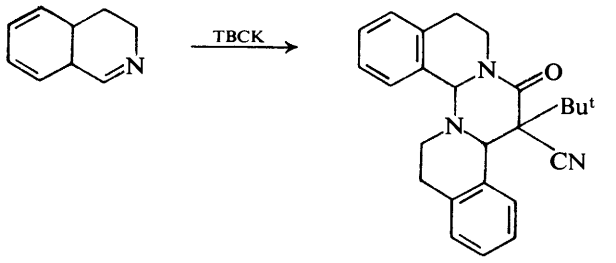


(114)

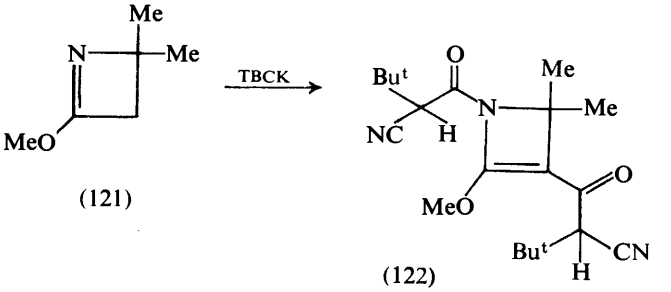
(115; 48%) (116; 14%)



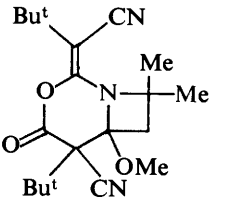
(117) (118; 20%) (119; 31%)



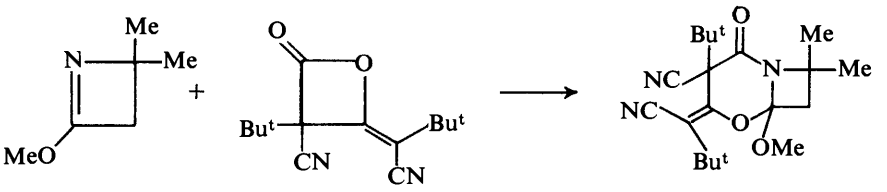
(120; 23%)



(121) (122)

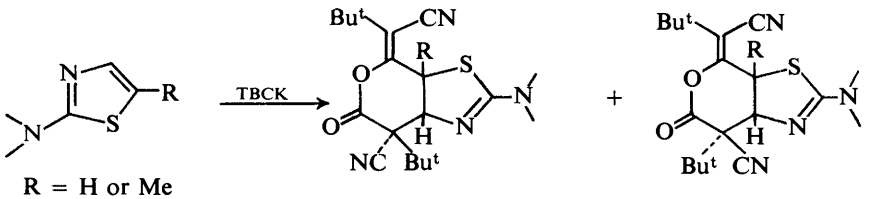


(123)



(124)

TBCK cycloaddition has been reported. This involves the reaction of 2-(dimethylamino)thiazole and its 5-methyl analogue with the ketene.[44] In both cases the 2:1 adducts (125) and (126) were formed.



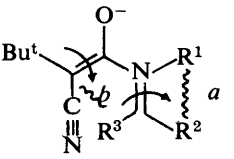
R = H or Me

(125) (126)

The observation of 2:1 adducts along with the work outlining the independent generation of zwitterionic intermediates, provides solid evidence that cyanoketene

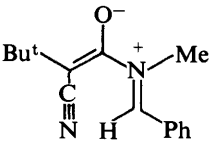
[44] A. Dondoni, A. Medici, C. Venturoli, L. Forlani, and V. Bertolasi, *J. Org. Chem.*, 1980, **45**, 621.

cycloadditions to imines and formimidates is dipolar in character. However, a few additional comments are in order regarding those reactions resulting in the β-lactams (95), (100), (107), and (110)—(113). In general, the stereochemistry of these products is predictable on the basis of zwitterions of structure (127). The

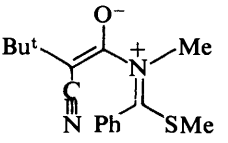


(127)

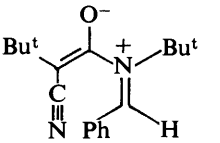
major or exclusive, product would arise *via* a conrotatory ring closure of that zwitterion in which steric interactions (*a*) and (*b*) would be minimized. For example, the penultimate precursors to (100), (107), (110), and (113) would be, respectively, (128), (129), (130), and (131). Particularly noteworthy is the com-



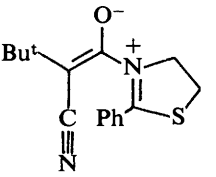
(128)



(129)



(130)

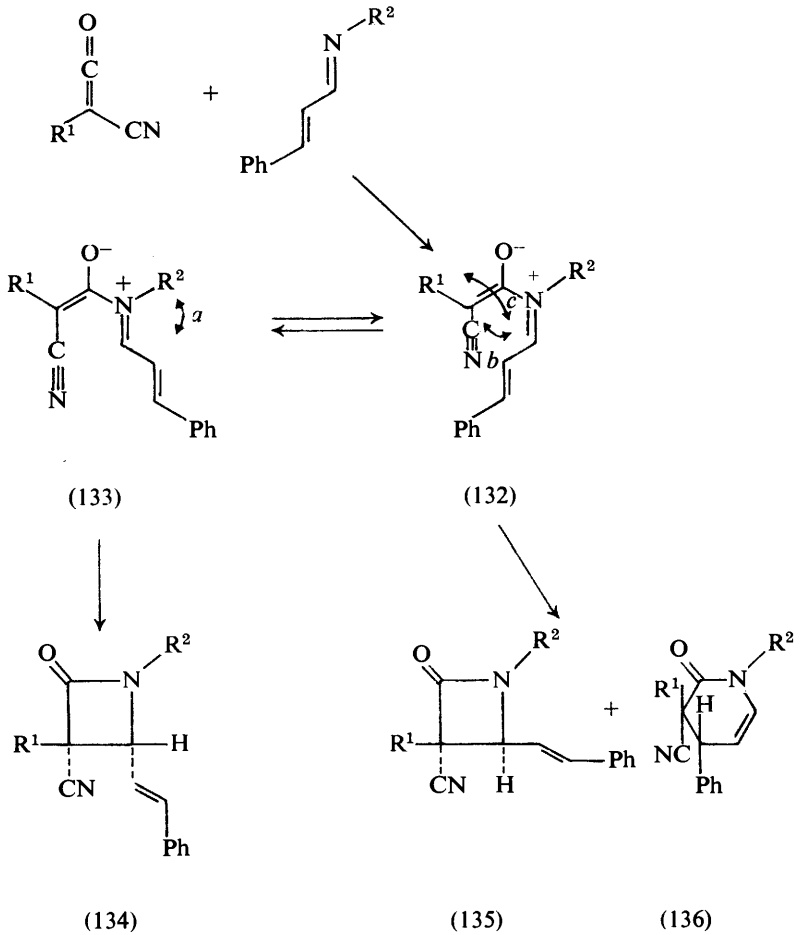


(131)

parison of (128) and (130), which vary in the steric bulk of the *N*-substituent. The former leads to the less hindered β-lactam, (100), and the latter gives the more torsionally strained product, (110).

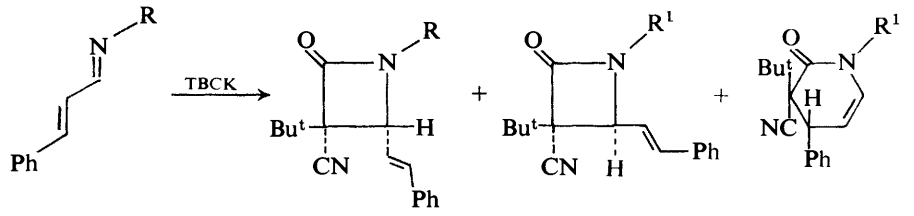
The influence of the above-mentioned steric factors also plays a prime role in dictating the products of the cycloadditions of cyanoketenes to α,β-unsaturated imines.[7] Specifically, steric interactions (*a*), (*b*), and (*c*) (Scheme 6) are of impor-

tance in determining the relative population of zwitterionic intermediates and thus products that arise from such. For example, when using TBCK and when steric interaction (*a*) is minimized, zwitterion (133) is favoured; this leads to 3-cyano-azetidin-2-ones (134) having a *trans*-relationship between the 3-cyano- and 4-protio-groups. As steric interaction (*a*) increases, zwitterion (132) becomes important, which results in increased amounts of *cis*-3-cyano-azetidin-2-ones (135) and the δ-lactam (136). Thus, TBCK reacts with the *N*-*p*-methoxyphenylimine of cinnamaldehyde to give the β-lactam (137*a*) in 85% yield. When the steric bulk on nitrogen is increased by utilizing the *N*-cyclohexylimine, the δ-lactam (139*b*) is formed in 23% yield and the β-lactams (137*b*) and (138*b*) in, respectively, 64% and 10% yield. The δ-lactam (139*b*) and β-lactam (138*b*) can be viewed as arising from zwitterion (132; R^1 = Bu^t, R^2 = C_6H_{11}) and the β-lactam (137*b*) from



Scheme 6

(133). Finally, with the *N*-t-butylimine, the products are the β-lactam (137*c*; 17%), its torsionally strained diasteriomer (138*c*; 29%), and the δ-lactam (139*c*; 52%).

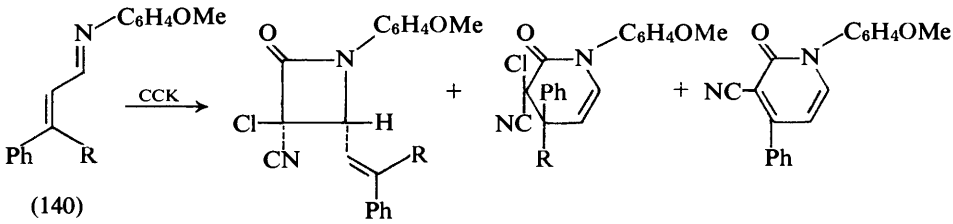


(137) (138) (139)

R		% *Yield*	
(*a*) C_6H_4OMe	85	–	–
(*b*) C_6H_{11}	64	10	23
(*c*) Bu^t	17	29	52

As expected from the above arguments, the steric bulk of the ketene also has a pronounced influence on the zwitterionic intermediates and thus on product formation. For example, chlorocyanoketene (CCK) undergoes cycloaddition with the *N*-*p*-methoxyphenylimine of cinnamaldehyde to give the β-lactam (141*a*; 17%), the δ-lactam (142*a*; 42%), and the pyridone (143*a*; 22%), whereas, as already mentioned, TBCK gave only the β-lactam (137*a*; 85%). Six-membered ring formation can be minimized by employing (140; R = Ph) since the additional phenyl group at the β-position would be expected to impart enhanced steric crowding in the ring closure of the zwitterion to a δ-lactam. Indeed, treatment of (140*b*) with CCK resulted in a > 90% yield of the β-lactam in (141*b*), and no δ-lactam could be detected.

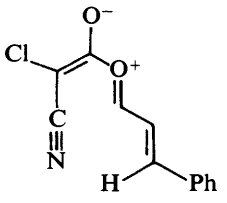
These results and mechanistic interpretations are also consistent with data obtained in the study of chlorocyanoketene cycloadditions to *trans*-cinnam-



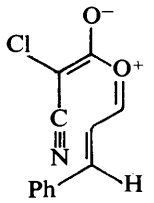
(140) (141) (142) (143)

R		% *Yield*	
(*a*) H	17	42	22
(*b*) Ph	>90	—	—

aldehydes. The aldehydes, unlike their *anti*-imine derivatives, could give zwitterions (144) or (145) in their initial interactions with the ketene. The former

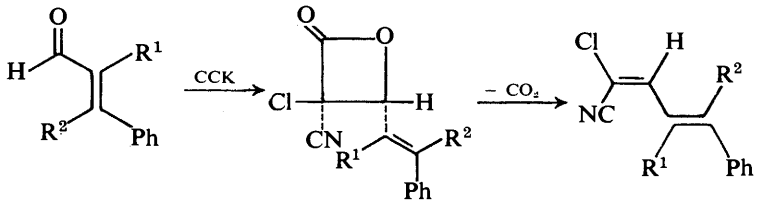


(144)



(145)

should give *E*-β-lactones and the latter should give the *Z*-isomers as well as δ-lactones. Certainly, on the basis of steric arguments, zwitterion (144) would be favoured. It was observed that CCK, but not TBCK, readily undergoes cycloaddition with (146*a–c*) to give the dienes (148*a–c*).[7] Although undetected, the *E*-β-lactones (147*a–c*) are most likely the precursors to the dienes and give such upon stereospecific decarboxylation under the reaction conditions. Thus, the products of the reaction come exclusively from zwitterion (144).



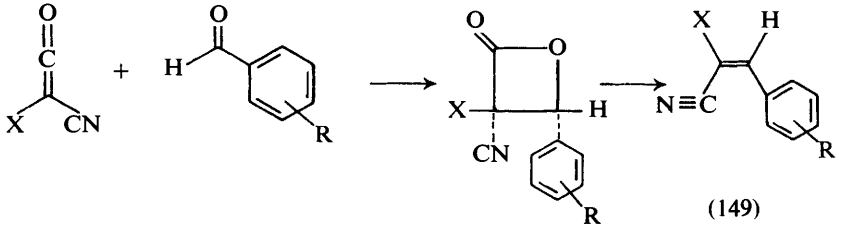
(146) (147) (148)

	R^1	R^2	% *Yield*
(*a*)	H	H	85
(*b*)	Me	H	79
(*c*)	H	Ph	82

9 Cyanoketene–Benzaldehyde Cycloadditions

Chloro- and bromocyanoketene, but not TBCK, undergo cycloaddition with a variety of substituted benzaldehydes in analogy to the above-mentioned reaction of cinnamaldehydes.[45] That is, the corresponding β-lactones are formed and suffer stereospecific decarboxylation to give the alkenes (149). It was observed that the relative rates as well as the product yields decreased as the benzaldehyde was substituted with increasingly stronger electron-withdrawing groups. Such observations are consistent with a dipolar mechanism in which the ketene functions as the electrophile and the aldehyde as the nucleophile. This was

[45] H. W. Moore, F. Mercer, D. Kunert, and P. Albaugh, *J. Am. Chem. Soc.*, 1979, **101**, 5435.



(149)

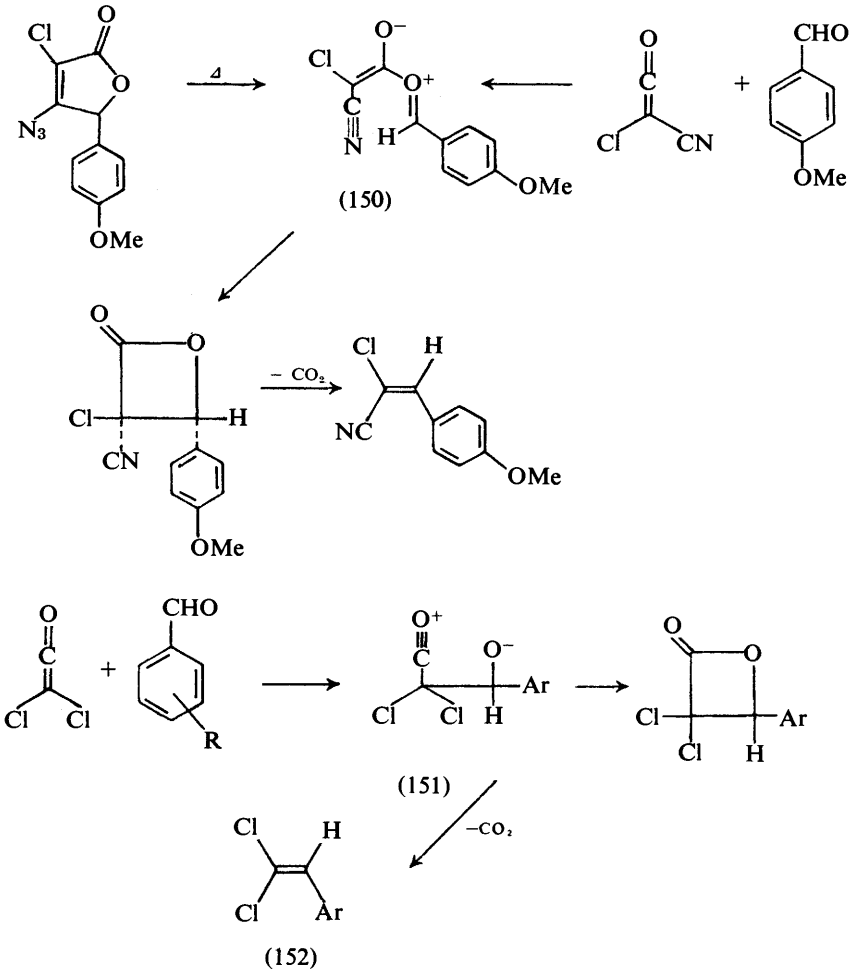
X	R	% *Yield*
Cl	2,4-$(OMe)_2$	92
Cl	4-NMe_2	78
Cl	4-OMe	73
Br	4-OMe	79
Cl	4-OCOMe	61
Br	4-OCOMe	51
Cl	H	61
Br	H	48
Cl	4-Me	54
Cl	4-Cl	32
Br	4-Cl	17
Cl	4-NO_2	8
Br	4-NO_2	< 5

further substantiated by the independent generation of the zwitterionic intermediate. That is, thermolysis of 4-azido-2-chloro-5-(4-methoxyphenyl)-(5*H*)-furan-2-one cleaved to zwitterion (150) which subsequently gave the same product as the cycloaddition of chlorocyanoketene to 4-methoxybenzaldehyde (Scheme 7).

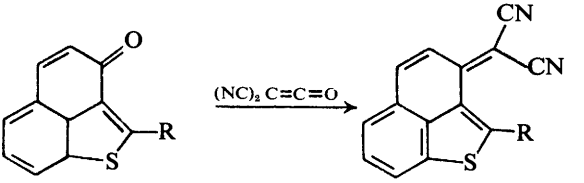
It is particularly noteworthy that dichloroketene gives analogous products, (152), when treated with substituted benzaldehydes.[46] However, the relative rates and product yields are reversed from those observed with chlorocyanoketene. Thus, whereas chlorocyanoketene functions as the electrophile in these reactions, the dichloro-derivative behaves as a nucleophile. As a result, dipolar character represented by zwitterion (150) controls product formation for the former and (151) for the latter.

In another series of studies, dicyanoketene was shown to give (153), (154), and (155) *via* a cycloaddition–decarboxylation mechanism.[4,47–49] Products analogous to (153) and (154) were also observed when the ketenes employed were t-butyl-cyano-, cyanomethyl-, and cyanophenyl-ketene. Dicyanoketene was also used to prepare the fulvenes (156), (157), and (158) from the corresponding ketones.

[46] H. O. Krabbenhoft, *J. Org. Chem.*, 1978, **43**, 1305.
[47] R. Neidlein and K. F. Cepera, *Chem. Ber.*, 1978, **111**, 1824.
[48] R. Neidlein and G. Humburg, *Justus Liebigs Ann. Chem.*, 1978, 1974.
[49] R. Neidlein and E. Bernhard, *Justus Liebigs Ann. Chem.*, 1979, 959.

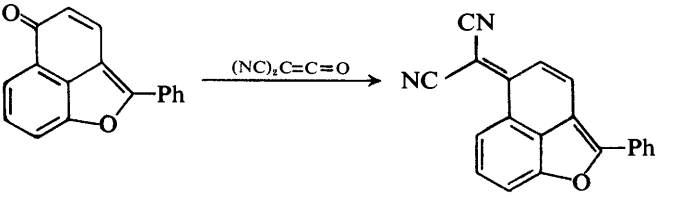

Cl
O
N3
OMe
Δ
O−
Cl
O+
C
N
H
OMe
(150)
O
C
Cl
CN
+
CHO
OMe
O
O
Cl
H
CN
OMe
− CO2
Cl
H
NC
OMe
O
C
Cl
Cl
+
CHO
R
O+
C
O−
Ar
Cl
Cl
H
O
O
Cl
Ar
Cl
H
(151)
−CO2
Cl
H
Cl
Ar
(152)

Scheme 7

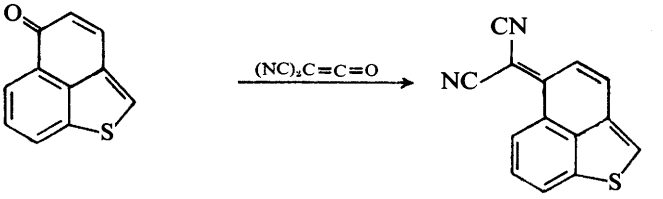


R = H or Me

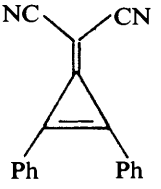
(153)



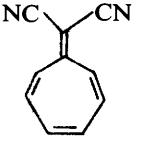
(154)



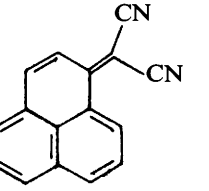
(155)



(156)



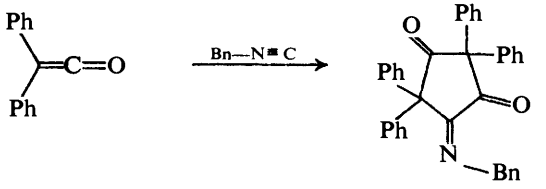
(157)



(158)

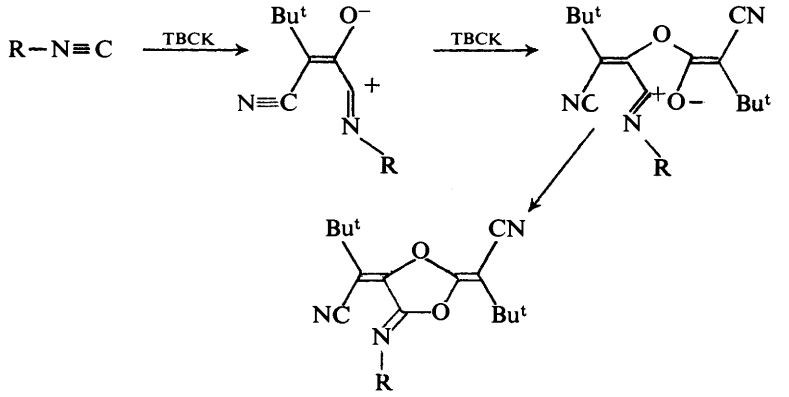
10 Cyanoketene–Isonitrile Cycloadditions

Little work has appeared concerning the addition of ketenes to isonitriles, but that which has documents the products to be 2:1 adducts having the 1-imino-cyclopentane-2,4-dione ring system. For example, diphenylketene and benzyl-isonitrile give a 90% yield of (159).[50] Cyanoketene–isonitrile cycloadditions have



(159)

been shown to be anomalous to the above. For example, TBCK has been shown to give the 2:1 adducts (160) when treated with isonitriles at ambient temperature.[7] Again zwitterions are reasonable intermediates to these products.

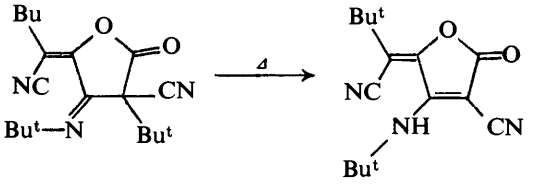


(160)

R	% *Yield*
Bu^t	97
Bu^n	70
C_6H_{11}	82
Bn	73
$CH_2SO_2C_6H_4Me$	68

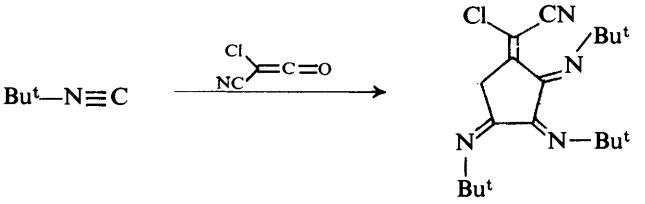
[50] I. Ugi and K. Rosendahl, *Chem Ber.*, 1961, **94**, 2233.

The adducts, (160), were shown to be the kinetic products of these reactions since thermolysis of the *N*-t-butyl analogue in refluxing benzene caused its rearrangement to (161). Further thermolysis of (161) at 130°C in *o*-dichlorobenzene resulted in the butenolide, (162).



(161) (162)

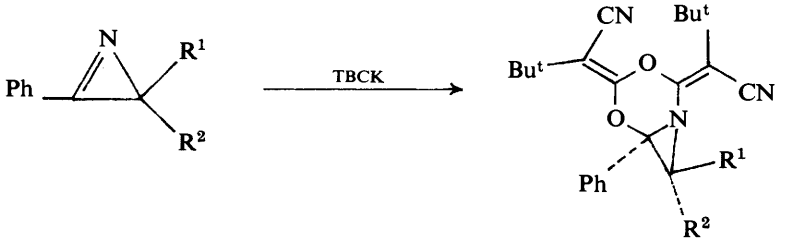
The cycloaddition of chlorocyanoketene to isonitriles appears to follow a completely different course. For example, when this ketene was generated in the presence of excess t-butylisonitrile, the unusual 3:1 adduct, (163), was obtained.[7]



(163)

11 Cyanoketene–1-Azirine, Oxaziridine, and Thiaziridinimine Cycloadditions

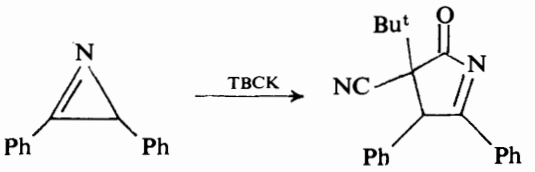
TBCK was shown to react with a variety of 1-azirines to give the 2:1 adducts



(164)

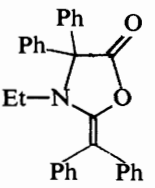
R^1	R^2
H	H
H	Me
Me	Me

(164).[51] Analogous adducts were observed when diphenylketene was employed. A 1:1 adduct, (165), was observed when TBCK was treated with 2,3-diphenyl-1-azirine.

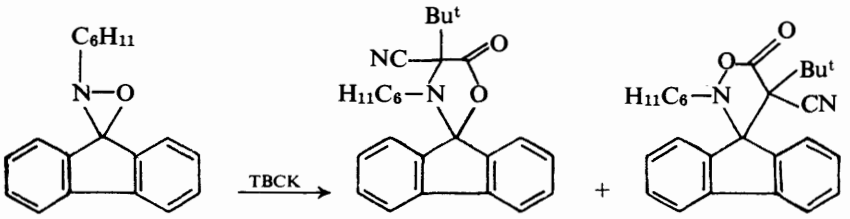


(165)

Very limited work has appeared describing the reaction of ketenes with heterocyclic compounds containing two adjacent heteroatoms. Diphenylketene and 2-ethyl-3-phenyloxaziridine combine to give an oxazolidinone (166; 38%) and benzaldehyde (50%).[52] TBCK reacts with 2′-cyclohexylspiro[fluorene-9,3′-oxaziridine] to give the spiro-oxazolidinone (167) and a spiroisoxazolidinone (168) in respective yields of 48% and 22%.[53]



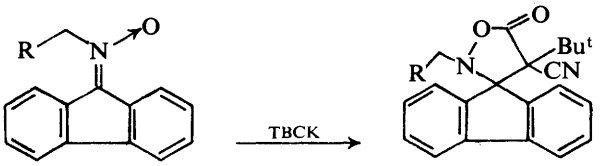
(166)



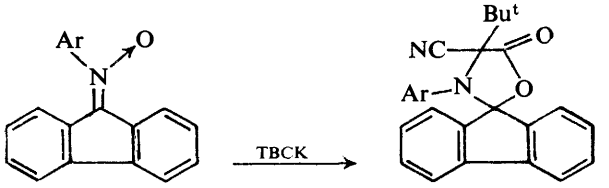
(167; 48%) (168; 22%)

[51] A. Hassner, A. S. Miller, and M. J. Haddadin, *Tetrahedron Lett.*, 1972, 1353.
[52] M. Komatsu, Y. Oshhiro, H. Holta, M. Sato, and T. Agawa, *J. Org. Chem.*, 1974, **39**, 3198.
[53] M. A. Abou-Gharbia and M. M. Joullé, *Synth. Commun.*, 1979, **9**, 871.

Spiroisoxazolidinones (169) were also obtained when TBCK and the corresponding *N*-fluorenylidene alkylamine oxides were subjected to refluxing benzene temperature.[54] On the other hand, arylamine analogues give (170). Compounds analogous to (170) were also observed when the ketene was cyclopentamethylene ketene or t-butylcarboethoxyketene.



(169; R = H, Me, or Ph)



(170; Ar = *p*-Me-C_6H_4-,
p-MeO-C_6H_4-, *p*-F-C_6H_4-,
p-CF_3-C_6H_4-)

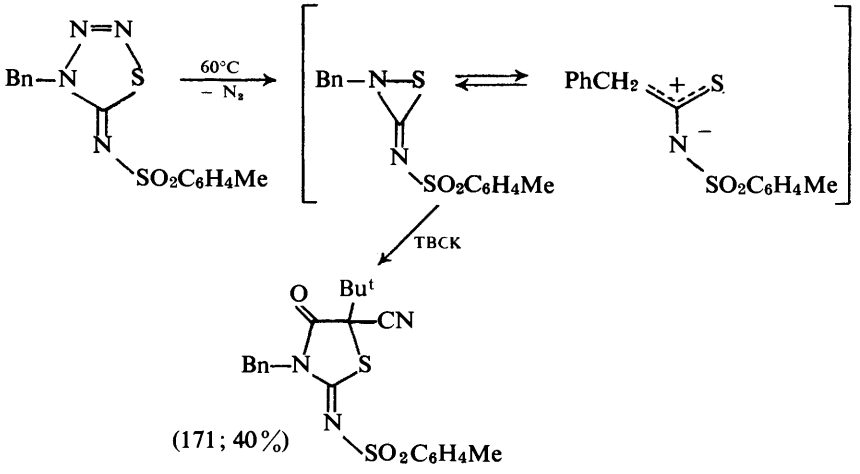
N-Sulphonyliminothiaziridines generated by the thermolysis of 4-alkyl-5-sulphonylimino-1,2,3,4-thiatriazolines react with TBCK to give (171). An analogous product was observed when phenylketene was employed.[55]

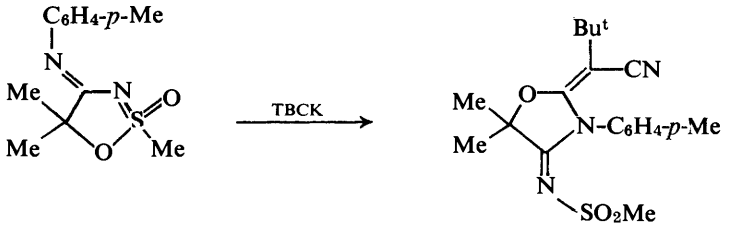
On the last an unusual reaction of TBCK with a heterocyclic compound has been described. Treatment of the ketene with 4-imino-4,5-dihydro-1,2λ^6,3-oxathiazol-2-ones gave a 70% yield of (172).[56] Diphenylketene gave an analogous product.

12 Cyanoketene–Sulphurdi-imide Cycloadditions

Cycloadditions of ketenes to sulphurdi-imides has received only limited attention,[57–60] and no reports have previously appeared where cyanoketenes have

[54] M. A. Abou-Gharbia and M. M. Joullé, *J. Org. Chem.*, 1979, **44**, 2961.
[55] G. L'abbé, G. Verhelst, C. C. Yu, and S. Toppet, *J. Org. Chem.*, 1975, **40**, 1728.
[56] G. L'abbé, C. C. Yu, and S. Toppet, *J. Org. Chem.*, 1979, **44**, 3991.
[57] H. Grill and G. Kresze, *Tetrahedron Lett.*, 1970, 1427.
[58] H. H. Horhold and H. Eibisch, *Tetrahedron*, 1969, **25**, 4277.
[59] T. Minami, K. Yamataka, Y. Ohshiro, T. Agawa, N. Yasuoka, and N. Kasai, *J. Org. Chem.*, 1972, **37**, 3810.
[60] T. Minami and T. Agawa, *J. Org. Chem.*, 1974, **39**, 1210.



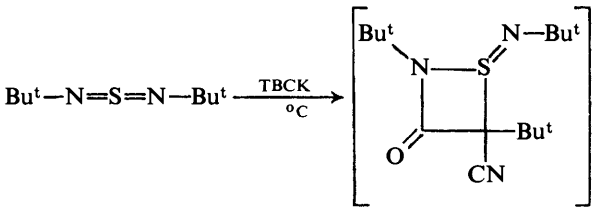


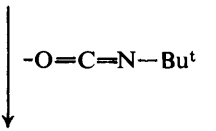
(172)

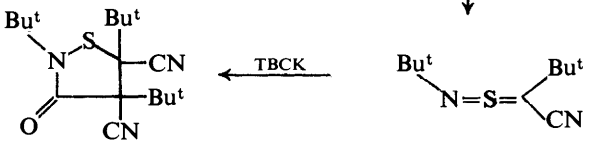
been utilized. Such a study has now been accomplished,[7] and the results are unusual in that the observed products are generally different from those reported for less electrophilic ketenes such as phenyl-, diphenyl-, and chlorophenylketene. Selected examples employing TBCK and chlorocyanoketene (CCK) are given below. The transformations leading to (174) and (179) are unique in that the thione-*S*-imides (173) and (178) are formed as intermediates. The former is trapped by an additional molecule of TBCK to give the isothiazolidin-3-one, (174), and the latter undergoes ring closure with loss of HCl to give (179). The formation of (176) and (177) is also without precedent. The formation of (175) is the only example anticipated on the basis of previously reported work employing other ketenes.

13 Conclusion

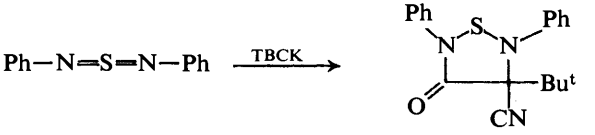
Cyanoketenes are a readily accessible class of electron-deficient cumulenes. They are prepared from the thermolysis of appropriately substituted vinyl azides; the substituent on the cyanoketene moiety can be varied to include t-pentyl, t-butyl, isopropyl, methyl, cyano-, bromo-, chloro-, iodo-, and phenoxy-groups. All of these function as potent electrophiles in their cycloadditions to alkenes, alkynes,



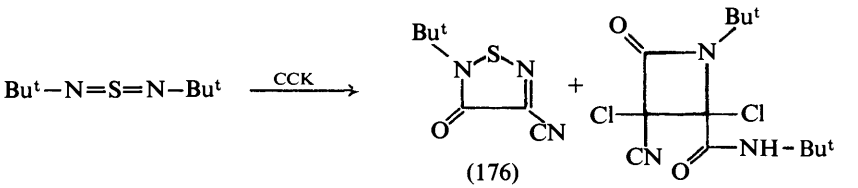




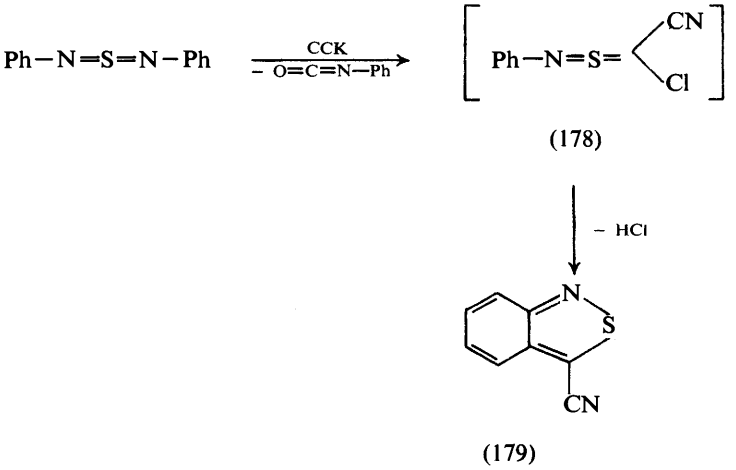
(174) (173)



(175)



(176) (177)



allenes, ketenes, imidates, imines, aldehydes, isonitriles, amine oxides, sulphurdiimides, and azirines. With the exceptions of the alkene and alkyne cycloadditions the reactions appear to be non-concerted and proceed *via* zwitterionic intermediates. In many cases the reactions are unique in that products result which have not been previously observed to arise from analogous reactions using less electrophilic ketenes. Clearly, a variety of carbocyclic and heterocyclic compounds are available from the reactions outlined in this review.