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Azides: Their Preparation and Synthetic Uses

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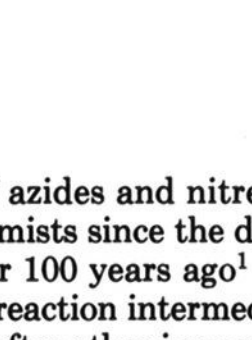
I. Introduction

The chemistry of azides and nitrenes has attracted the attention of chemists since the discovery of phenyl azide by Griess over 100 years ago[1] and the first proposal of nitrenes as reaction intermediates by Tiemann in 1891.[2] However, after other important contributions, especially by Curtius and Bertho, interest waned until about 1950, when reviews by Smith (acyl azides)[3] and Boyer (aryl and alkyl azides)[4] stimulated further work, much of which is described in major reviews by Kirmse (1959),[5] Horner and Christmann (1963),[6] Abramovitch and Davis (1964),[7] and L'abbé (1969).[8] A comprehensive treatment of the literature up to 1969 is contained in two books. One, edited by Lwowski, deals with nitrenes[9] and the other, on azides, is edited by Patai.[10] Work on azides and nitrenes that appeared between 1969 and 1982 has been reviewed in another book[11] and in the supplement to Patai's book.[12] A list of reviews that have appeared since 1970 on azides and related topics is given in Table 1. An ideal supplement to the present review is the excellent short treatment of azide chemistry by Smith.[13]

The aim here is to present applications of azides in synthesis, and it is hoped that this will reflect the current rapid increase in interest in the area. Our emphasis has been the recent literature (1983 to June 1986 inclusive) but important linking references and some mechanistic discussion are provided. In so doing, we are aware that scant recognition is given to the discoverers of the key reactions of azide and nitrene chemistry. Therefore we dedicate this review to that select band whose discoveries have made the synthetic work discussed herein possible. Many of their names appear in the first paragraph.



AZT, R = Me
CS-85, R = Et

Eric Scriven was born in Pembrokeshire, Wales, in 1941. He graduated (Grad. R.I.C.) at the University of Salford (1965) after part-time study while working for BISRA and ESSO. He obtained his M.Sc. (1967) from the University of Guelph (with M. J. Nye) and Ph.D. (1969) from the University of East Anglia (with A. R. Katritzky). After postdoctoral years at the University of Alabama (with R. A. Abramovitch) and University College London (with J. H. Ridd), he returned to the University of Salford. He was a faculty member until he joined Reilly Tar & Chemical Corp. in 1979. He is an adjunct professor at Purdue University School of Science in Indianapolis (since 1983), and he has been a visiting professor at the University of Florida (1983) and the University of Benin, Nigeria (1975–1976). His current research interests include synthetic and mechanistic aspects of azide and nitrene chemistry, heterocyclic chemistry, and the applications of polymers in organic synthesis. He is currently coeditor (with K. Turnbull) of *Annual Reports in Organic Synthesis*.

Kenneth Turnbull was born in Edinburgh, Scotland, in 1951. He received his B.Sc., and Ph.D. (1976, with P. N. Preston) degrees from Heriot-Watt University, Edinburgh. After 2 years as a postdoctoral research associate at the University of Toronto (with I. W. J. Still), he joined the chemistry faculty at Grinnell College, Iowa. Since 1980 he has been at Wright State University, where he is presently an Associate Professor. His research interests include synthetic aspects of azide chemistry, heterocyclic synthesis (mainly mesoionic), and the preparation of compounds containing N=S or S=S functionalities. He is currently coeditor (with E. F. V. Scriven) of *Annual Reports in Organic Synthesis*.

Of topical interest, azidonucleosides (viz., AZT (3′-azido-3′-deoxythymidine) and CS-85) have received international attention for the treatment of AIDS (acquired immune deficiency syndrome) and ARC (AIDS-related complex).[14]

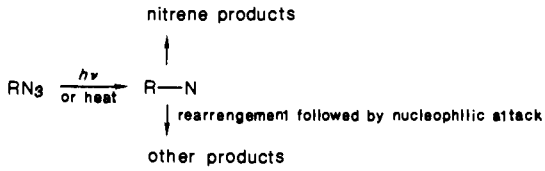
It should be noted that while most azides can be handled without incident, some members of this class are explosive. Accordingly, prudent practice should be scrupulously adhered to in the laboratory.

The most common types of reaction that will be encountered in the following sections are outlined in general form below. These are classified according to the number of nitrogen atoms from the starting azide that end up in the final product and they are subdi-

vided by reaction type. The mechanisms given are illustrative rather than precise; for more detail the reader should consult the references quoted.

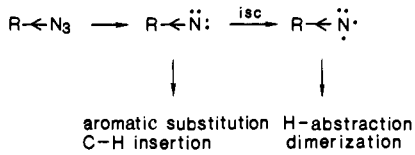
A. One Azide Nitrogen Retained in the Final Product

1. Unimolecular Decomposition by Light or Heat

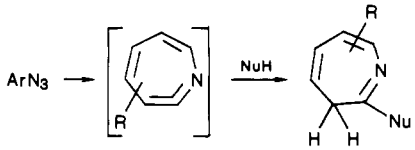


a. Nitrene-Derived Products (Section VI.A.3,5)

The more electron-attracting is R, the more electrophilic will be the singlet nitrene, so promoting its reactions relative to those of the triplet nitrene. The latter are not usually as synthetically useful.

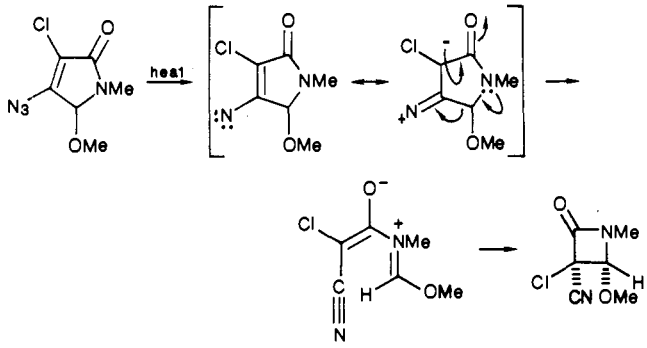


b. Rearrangement Followed by Nucleophilic Attack (Section VI.C.6)

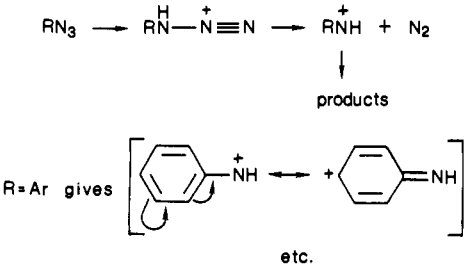


c. Zwittazido Cleavage

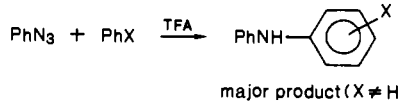
Applications of this reaction are not described herein since a review by Moore has just appeared.[15]



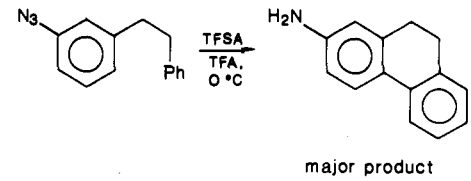
2. Acid-Catalyzed Decomposition (Sections IV.A. and VI.A.3)



Arylnitrenium ions may react at N- or C- thus:



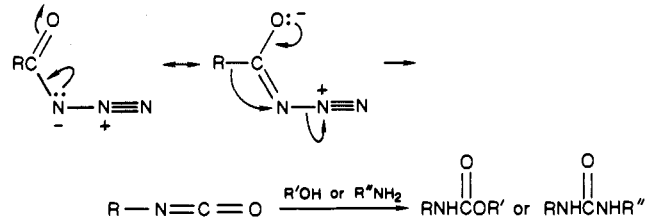
However



3. Staudinger Reaction (Sections III.F and VI.A.7)

$$RN_3 + PR'_3 \rightarrow RN{=}PR'_3$$

4. Curtius Rearrangement (Sections III.D, VI.A.4, and VI.C.4)

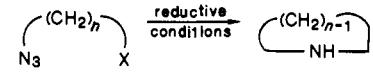


5. Schmidt Rearrangement (Sections III.E and VI.C.1)

$$RCO_2H \xrightarrow[\text{or equivalent}]{HN_3} RNH_2$$

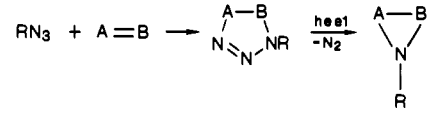
6. Reduction (Sections III.A,B,C and V.C)

$$RN_3 \rightarrow RNH_2$$

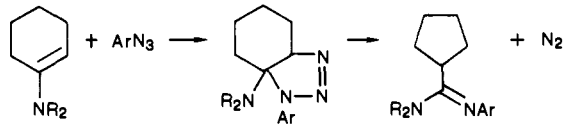


B. One, Two, or Three Nitrogens Retained in Final Product

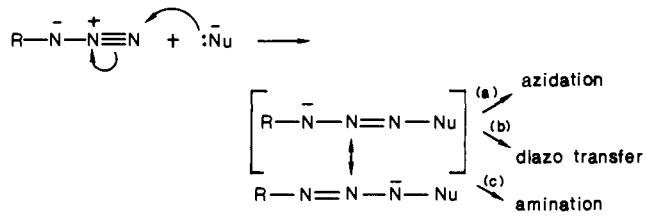
1. Cycloadditions (Sections IV.B,C and VI.B)



The above sequence offers a general synthetic approach to triazolines and related heterocycles; loss of nitrogen gives aziridines (see section VI.B). When A–B is part of a ring system, a Favorskii-like ring contraction can take place.



2. Nucleophilic Attack at the Azide Terminus



a. Azidation (Section II.J)

$$RLi + TsN_3 \rightarrow R{-}N{=}N{-}\bar{N}{-}TsLi^+ \xrightarrow[\text{(or similar)}]{\text{sodium pyrophosphate}} RN_3$$

b. Diazo Transfer (Section III.I)

TABLE 1. Azide Reviews

topic	ref
1,2,3-triazoles	Gilchrist, T. L.; Gymer, G. E. *Adv. Heterocycl. Chem.* **1974**, *16*, 33
acyl azides	Lwowski, W. Ref 11, p 205
acylnitrene cyclizations	Edwards, O. E. Ref 9, p 225
alkyl azides	Kyba, E. P. Ref 11, p 2
alkylnitrenes	Lewis, F. D.; Saunders, W. H. Ref 9, p 47
aminonitrenes	Lemal, D. M. Ref 9, p 345
aminonitrenes in organic synthesis	Chow, T. J. *Hua Hsueh* **1984**, *42*, 139
analysis of azides for assay	Kramer, H. In *Energetic Materials*; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 2, p 55
aryl and heteroaryl azides	Smith, P. A. S. Ref 11, p 95
aryl- and heteroarylnitrenes in heterocyclic synthesis	Suschitzky, H. *Lect. Heterocycl. Chem.* **1980**, *5*, 1
aryl azide photoaffinity labels in biochemistry	Staros, J. V. *Trends Biochem. Sci (Pers. Ed.)* **1980**, *5*, 320
aryl azide pyrolysis	Dyall, L. K. In *Chemistry of Halides, Pseudohalides, and Azides*; Patai, S., Ed.; Wiley: Chichester, 1983; Vol. 1, p 287
aryl azides	Scriven, E. F. V. In *Reactive Intermediates*, Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, p 1
arylnitrenes	Smith, P. A. S. Ref 9, p 99
arylnitrenes in synthesis	Iddon, B. I.; Meth-Cohn, O.; Scriven, E. F. V.; Suschitzky, H.; Gallagher, P. T. *Ang. Chem., Int. Ed. Engl.* **1979**, *18*, 900
azide derivatives of carbohydrates	Mester, L.; El Khadem, H. S. In *Carbohydrates: Chemistry and Biochemistry*, 2nd ed.; Pigman, W. W., Horton, D. Eds.; Academic: New York; Vol. 1B, p 929
azide derivatives of cyclodextrins	Croft, A. P.; Bartsch, R. A. *Tetrahedron* **1983**, *39*, 1417
azide derivatives of oligosaccharides	Paulsen, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 155
azide-containing photoresist materials	El'tsov, A. V.; Yurre, T. A. *Zh. Prikl. Khim.* **1979**, *52*, 365
azides as synthetic starting materials	Sheradsky, T. Ref 10, p 331
azides attached to elements other than carbon	Atkinson, R. S. Ref 11, p 247
azides containing two different metal atoms	Krischner, H. *Monatsh. Chem.* **1985**, *116*, 189
azides in organometallic chemistry	Cenini, S.; La Monica, G. *Inorg. Chim. Acta* **1976**, *18*, 279
azidocumulenes	L'abbé, G. *Bull. Soc. Chem. Belg.* **1984**, *93*, 579
azidoquinones	Moore, H. W. *Chem. Soc. Rev.* **1974**, *3*, 415
azidotrimethylsilane	Groutas, W. C.; Felker, D. *Synthesis* **1980**, 861
azirines	Anderson, D. J.; Hassner, A. H. *Synthesis* **1975**, 483. Hassner, A. H. *Heterocycles* **1980**, *14*, 1517. Padwa, A.; Carlsen, P. H. J. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1982; Vol. 2, p 55
azo transfer	Regitz, M. In *The Chemistry of the Diazonium and Diazo Groups*; Patai, S., Ed.; Wiley: London, 1978; p 751. Regitz, M.; Maas, G. *Diazo Compounds: Properties and Synthesis*; Academic: Orlando, 1986
behavior of arylnitrenes in the gas phase	Wentrup, C. In *Reactive Intermediates*; Abramovitch, R. A., Ed.; Plenum: New York, 1980; Vol. 1, Chapter 4
carbonylnitrenes	Lwowski, W. Ref 9, p 185
characterization and determination of organic azides	Gurst, J. E. Ref 10, p 191
conjugated ketones	Moore, H. W.; Decker, O. H. W. *Chem. Rev.* **1986**, *86*, 821
Curtius rearrangement	Reichen, W. *Chem. Rev.* **1978**, *78*, 569
cyanonitrene	Anastassiou, A. G.; Marsh, F. D. Ref 9, p 305
cycloadditions	Lwowski, W. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, p 559
decomposition of organic azides	Abramovitch, R. A.; Kyba, E. P. Ref 10, p 221
deoxygenation of aromatic nitro compounds	Cadogan, J. I. G. In *Organophosphorus Reagents in Organic Synthesis*; Cadogan, J. I. G., Ed.; Academic: London, 1979; p 269
deoxygenations of nitro and nitroso groups	Boyer, J. H. Ref 9, p 163
derivatives of hydrazine and related compounds	Atkinson, R. S. In *Comprehensive Organic Chemistry*; Sutherland, I. O., Ed.; Pergamon: Oxford, 1979; Vol. 2, p 256
diazo transfer	Regitz, M. In *Methods of Preparative Organic Chemistry*; Foerst, W., Ed.; Academic: New York, 1971; Vol. IV
directing and activating effects of organic azides	Biffin, M. E. C.; Miller, J.; Paul, D. B. Ref 10, p 203
ESR of azides	Wasserman, E. *Prog. Phys. Org. Chem.* **1971**, *8*, 319
electronic structure and spectroscopy of nitrenes	Berry, R. S. Ref 9, p 13
electrochemistry	Iverson, P. E. In *Encyclopedia of Electrochemistry of the Elements*; Bard, A. J., Lund, H., Eds.; Marcel Dekker: New York, 1979; Vol. 13, p 209
electronic spectroscopy of azides	McGlynn, S. P.; Rabalais, J. W.; McDonald, J. R.; Scherr, V. M. *Chem. Rev.* **1971**, *71*, 73
gas-phase and matrix studies	Wentrup, C. Ref 11, p 395
general	Abramovitch, R. A. *Chem. Soc. Spec. Publ.* **1970**, *24*, 323
general and theoretical aspects	Trienin, A. Ref 10, p 1
halogen azides	Dehnicke, K. *Adv. Inorg. Chem. Radiochem.* **1983**, *26*, 169
handling, storability, and destruction of azides	Pollock, B. D.; Fisco, W. J.; Kramer, H.; Forsyth, A. C. In *Energetic Materials*; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 2, p 73
heterocycles via nitrenes	Meth-Cohn, O. *Heterocycles* **1980**, *14*, 1497
heterocyclic synthesis	Kametani, T.; Ebetino, E. F.; Yamanaka, T.; Nyu, K. *Heterocycles* **1974**, *2*, 209
(i) synthesis of five-membered rings with one heteroatom	Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. *Chem. Heterocycl. Comp.* **1979**, *15*, 467
(ii) synthesis of heterocycles	Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. *Chem. Heterocycl. Comp.* **1978**, *14*, 233
indoxazenes and anthranils	Smalley, R. K. *Adv. Heterocycl. Chem.* **1981**, *29*, 2
industrial applications	Breslow, D. S. Ref 11, p 491
introduction of the azido group	Biffin, M. E. C.; Miller, J.; Paul, D. B. Ref 10, p 57
iodo azides	Dehnicke, K. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 507

TABLE 1 (Continued)

topic	ref
lead tetraacetate oxidations	Aylward, J. B. *Q. Rev. Chem. Soc.* **1971**, *25*, 420
main group element azides	Bertrand, G.; Majoral, J. P.; Baceiredo, A. *Acc. Chem. Res.* **1986**, *19*, 17
N-nitrenes	Sakai, K.; Tanaka, A.; Koga, G.; Anselme, J. P. *Nippon Kagaku Zasshi* **1971**, *92*, 1065
nitrene-induced aromatic rearrangements	Cadogan, J. I. G. *Acc. Chem. Res.* **1972**, *5*, 303
nitrenes	Abramovitch, R. A. In *Organic Reaction Intermediates*; McManus, S., Ed.; Academic: New York, 1973; p 127. Ioffe, B. V.; Semenov, V. P.; Ogloblin, K. A. *Zh. Vses. Khim. Ova* **1974**, *19*, 314. Jones, W. H. *Rearrangements in the Ground and Excited States*; de Mayo, P., Ed.; Academic: New York, 1980. Lwowski, W. In *Reactive Intermediates*; Jones, M., Moss, R. A., Ed.; Wiley: New York: 1978, Vol. 1, p 197; 1981, Vol. 2, p 315; 1985, Vol. 3, p 305
nitrenes (annual survey)	*Organic Reaction Mechanisms*; Wiley: London, 1965 et seq.
nitrenes in heterocyclic chemistry	Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 231
nitrenes in synthesis of six- and seven-membered nitrogen heterocycles	Semenov, V. P.; Studenikov, A. N.; Potekhin, A. A. *Sovrem. Probl. Org. Khim.* **1982**, *7*, 97
nitrenium ions	Abramovitch, R. A.; Jeyaraman, R. Ref 11, p 297. Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26. Lansbury, P. T. Ref 9, p 405
organic syntheses using lead(IV) acetate azides	Zbiral, E. *Synthesis* **1972**, 285
peptide synthesis	Meienhofer, J. In *Peptides*; Gross, E., Meienhofer, J. Eds., Academic: New York, 1979; p 197
phosphorus acid azides	Gilyarov, V. A. *Usp. Khim.* **1982**, *51*, 1579
phosphorus azides	Cremlyn, R. J. W.; Wakeford, D. H. *Top. Phosphorus Chem.* **1976**, *8*, 1
photoaffinity labeling	Knowles, J. R. *Acc. Chem. Res.* **1972**, *5*, 155. Lwowski, W. *Ann. N.Y. Acad. Sci.* **1980**, *346*, 491. Rilling, H. C. *Methods Enzymol.* **1985**, *110* (Part A), 125
photoaffinity labeling and related techniques	Bayley, H.; Staros, J. V. Ref 11, p 434
photochemistry of azides in argon	Chapman, O. L. *Pure Appl. Chem.* **1979**, *51*, 331
photochemistry of the azido group	Reiser, A.; Wagner, H. M. Ref 10, p 441
photogenerated reagents in biochemistry and molecular biology	Bayley, H. *Photogenerated Reagents in Biochemistry and Molecular Biology*; North-Holland/Elsevier: Amsterdam, 1983
physical and spectrometric methods	Platz, M. S. Ref 11, p 359
polymerization by nitrenes	Imoto, M.; Nakaya, T. *J. Macromol. Sci., Rev. Macromol. Chem.* **1972**, *7*, 1
pyrolytic methods	Brown, R. F. C. *Pyrolytic Methods in Organic Chemistry*; Academic; New York, 1980; Chapter 5
reactions of azides with indoles	Peach, J. M.; Bailey, A. S. In *Studies in Organic Chemistry*; Elsevier: Amsterdam, 1979; Vol. 3, p 56
reduction of azido sugars	Richardson, A. C. *Methods Carbohydr. Chem.* **1972**, *6*, 218
silyl azides	Nishiyama, K. *Yuki Gosei Kagaku Kyokaishi* **1985**, *43*, 176
sulfonyl azides	Abramovitch, R. A.; Sutherland, R. G. *Fortsch. Chem. Forsch.* **1970**, *16*, 1
sulfonylnitrenes	Breslow, D. S. Ref 9, p 245
synthesis and chemical properties of inorganic azides	Richter, T. A. In *Energetic Materials*; Fair, H. D., Walker, R. F., Eds.; Plenum: New York, 1977; Vol. 1, p 15
synthetic aspects	Smalley, R. K.; Suschitzky, H. *Chem. Ind. (London)* **1970**, 1338
tetrazoles	Koldobski, G. I.; Ostrovskii, V. A.; Popavskii, V. S. *Chem. Heterocycl. Comp.* **1982**, 965
triplet states of azides	Duer, H.; Kober, H. *Top. Curr. Chem.* **1976**, *66*, 89
vapor-phase pyrolysis of aryl azides	Wentrup, C. *Top. Curr. Chem.* **1976**, *62*, 1973
vinyl azides	Fowler, F. W. *Adv. Heterocycl. Chem.* **1971**, *13*, 45. Hassner, A. Ref 11, p 35. L'abbé, G. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 775. L'abbé, G. *Newer Synthetic Methods* **1979**, *5*, 1. L'abbē, G.; Hassner, A. *Angew. Chem., Int Ed. Engl.* **1971**, *10*, 98. Smolinsky, G.; Pride, C. A. Ref 10, p 555
vinyl, aryl, and acyl azides	Moore, H. W.; Goldish, D. M. *The Chemistry of Halides, Pseudohalides, and Azides*; Patai, S., Ed.; Wiley: Chichester, 1983; Vol. 1, p 361
zwittazido cleavage	Moore, H. W. *Acc. Chem. Res.* **1979**, *12*, 125

An exhaustive review of this topic has just appeared.[16]

$$Z\text{-}\bar{C}H\text{-}Z' \xrightarrow[\text{or similar}]{ArSO_2N_3} Z\text{-}C(=N_2)\text{-}Z'$$

Z, Z′ = COR, NO_2, CN, SO_2R, etc.

c. Amination (Section III.G)

$$ArLi + RN_3 \rightarrow \xrightarrow[\text{workup}]{\text{reductive}} ArNH_2$$

R = vinyl, Ts, $PhSCH_2$, $(PhO)_2P(O)$, $TMSCH_2$

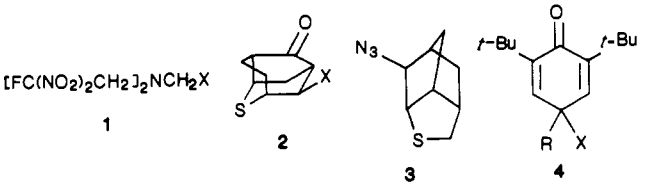
II. Preparations

A. From Halides

1. By Displacement at Saturated Sites

The most commonly applied route, especially to alkyl azides, is halide displacement by azide ion or a congeneric species. The reaction has been routinely used for the preparation of acyl azides (usually as intermediates for the Curtius reaction; see Section III.D) from the corresponding acyl chlorides and NaN_3[17-22] or HN_3/pyridine.[23] The former approach has been improved by utilization of a phase-transfer catalyst (PTC).[24] The same products are available from aroyl chlorides with Me_3SiN_3/ZnI_2.[25] Mixed anhydrides have also been used to advantage (see section VI.A.4).

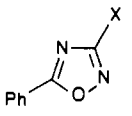
Similarly, (azidomethyl)bis(fluorodinitroethyl)amine (1, X = N_3) was prepared from its bromo congener (1,



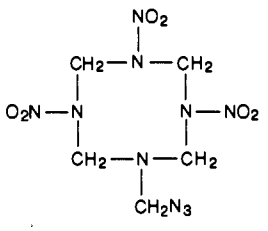
X = Br) by treatment with sodium azide at 0 °C under

an inert atmosphere,[26] the azidoadamantane analogue (**2**, X = N_3) was obtained from **2** (X = Cl or OH) with NaN_3/57% sulfuric acid[27] (the chlorine in the equatorial position, as shown, was more reactive than that in the axial), azidothiabrendane (**3**) was isolated in quantitative yield from treatment of the bromo precursor with NaN_3/EtOH at 90 °C,[28] and the tertiary azides (**4**, X = N_3; R = Me, *t*-Bu) resulted from azide ion displacement of the corresponding bromo compounds (**4**, X = Br; R = Me, *t*-Bu).[29] In the latter, other dienones either did not react or gave only tar under the same conditions. Additionally, the reaction gave an 85% yield of the azido product in DMF at room temperature for 24 h but did not proceed in tetrahydrofuran or diethyl ether. Tertiary alkyl azides (as well as allyl or benzyl azides) have also been prepared by the action of $NaN_3/ZnCl_2$ on the appropriate halide.[30]

With alkali metal azides (mainly sodium azide) it is usually helpful to use a polar solvent (typically DMF or DMSO, although acetone or even alcohols have found some use) to provide some homogeneity. In this regard, the increased solubility of lithium azide in such solvents can enhance the reaction rate or, in some cases, allow reaction where none occurred with sodium azide. Thus, the rate of reaction of azide ion with poly(vinyl chloride) was increased by the use of lithium azide in DMF or acetone.[31] Additionally, the azidooxadiazole **6** could be prepared from the bromide **5** only by treatment with lithium azide in DMF or potassium azide and 18-crown-6.[32] Attempted displacement with sodium azide/DMF, lithium azide/methanol, or tetrabutylammonium azide/acetonitrile led to a quantitative recovery of **5**.



5. X = Br
6. X = N_3



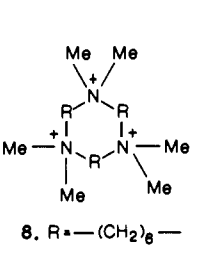
7

While good results can generally be obtained when DMF or DMSO is used, the difficulties associated with azide isolation from such solvents as well as the desire for homogeneity have stimulated considerable interest in alternatives.

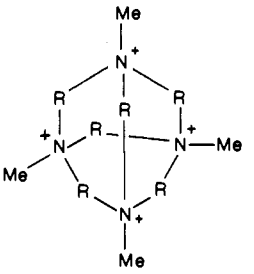
One such is the utilization of organic azides, e.g., $MeCON_3$ and Me_3SiN_3, as the azide source. Both are soluble in organic solvents and permit azide synthesis under nonbasic conditions. The former has been used in a novel synthesis of the trinitro azide **7** from its bromo congener in 79% yield.[33] The acetyl azide is generated in situ and used at 10–15 °C to avoid decomposition into methyl isocyanate. A previous attempt to prepare **7** by treatment of the corresponding acetate with NaN_3 was unsuccessful.[34] The generality of this process has not been assessed but it would appear that activated halides are necessary. Trimethylsilyl azide also reacts with activated halides (benzyl chloride and benzyl bromides, allyl bromides, chloroacetonitrile, and ethyl chloroacetate) in hexamethylphosphoramide at 60 °C to give the azido compounds in good to excellent yield under homogeneous, neutral, nonaqueous conditions.[35] Olah and co-workers[36] have shown that both secondary and tertiary cyclic azides can be prepared in 48–92% yield from the chlorides or bromides by using trimethylsilyl azide in the presence of stannic chloride.

Another widely used approach is the addition of a phase-transfer catalyst, permitting use of solvents such as benzene. Thus, as previously mentioned, **6** could be prepared from **5** by using potassium azide and 18-crown-6,[32] and numerous alkyl azides were synthesized from the corresponding bromides by heating under reflux in benzene in the presence of 5–10 mol % of tetrabutylammonium bromide.[37] The crude azides were reduced in situ by the Staudinger process (see section III.A.4). It was claimed[37] that better yields of the azides were obtained with an anhydrous solid–liquid PTC system (i.e., with solid sodium azide suspended in benzene) than from the reported[38,39] liquid–liquid cases. The rates of nucleophilic substitution by N_3^- (as the hexadecyltributylphosphonium salt) in a series of *n*-octyl halides (and sulfonates) have been measured in different solvents (MeOH, DMSO, PhCl, cyclohexane). For the halo derivatives, the highest rates were in DMSO (cyclohexane for the mesylates), and in all solvents used the nucleofugacity scale was I > Br > Cl (their positions relative to mesylate and tosylate differed depending on the solvent).[40] While not a synthetic study, per se, the results obtained allow selection of an appropriate solvent and leaving group for a particular synthetic goal.

Along similar lines, the S_NAr reaction of azide ion with 1-halogeno-2,4-dinitrobenzenes is subject to significant catalysis by micelles of cetyltrimethylammonium bromide.[41,42] It is claimed that the rate of these reactions can be further enhanced by the use of macrocyclic quaternary ammonium salts (cf. **8** and **9**).[43,44] Apparently, the azide ion is incorporated into the cavity of the cationic host prior to the rate-limiting step.



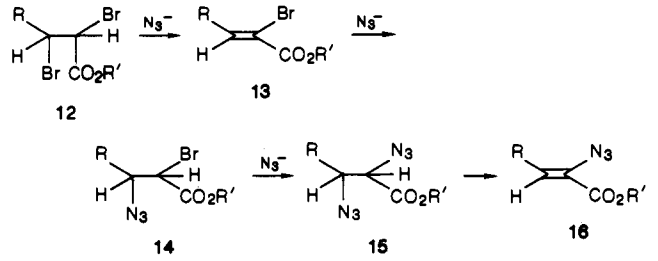
8. R = —$(CH_2)_8$—



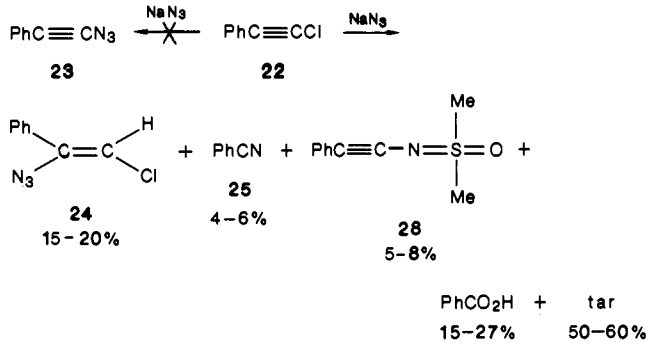
9. R = —$(CH_2)_8$—

An interesting modification of this process has been developed recently.[45] Thus, graft polymerization of acryloyl onium salts (A–C_n–$^+XR_3$, *n* = 2, 6, 10; X = N, P; R = Me, Bu) onto a large, porous ultrathin nylon-2,12 capsule membrane provides phase-transfer catalysts that accelerate reactions between benzyl bromide in the inner organic phase (chloroform) and water-soluble azide ion in the outer phase. It is claimed[45] that there is no observable induction period for the reaction, in contrast to many other insoluble polymer-supported PTC wherein swelling of the resin occurs.[46] The reaction rate is affected by azide ion concentration and the length and hydrophobicity of the onium salt side chain. Hassner has shown[47] that essentially quantitative azidation of activated and nonactivated alkyl halides can be achieved at room temperature with a polymeric

SCHEME 1



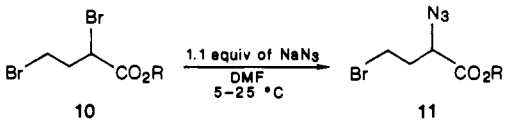
SCHEME 2



quaternary ammonium azide.

A useful addition for activated primary halides is ultrasound-promoted azidation in aqueous solution.[48] Reaction time is short (1–4 h), conditions are relatively mild (60 °C), isolation is straightforward, and yields are good to excellent. However, the reaction is apparently limited to propargyl-, allyl-, or cyanomethyl-activated species since 1-bromopropane under the same conditions gave only a 20% conversion to propyl azide.

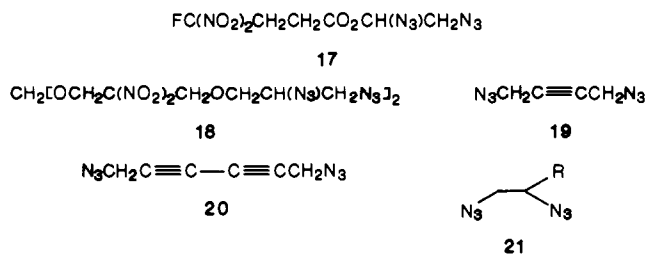
Treatment of dibromo ester **10** (R = Me) with a slight excess of sodium azide in DMF at 5 °C gives monoazide **11** (R = Me) in high yield and about 15% of the diazido



species.[49] The trimethylsilyl analogue **11** (R = $Me_3SiCH_2CH_2$) has been similarly prepared.[50] Presumably, steric factors favoring displacement at the primary site are countered by the electron-withdrawing effect of the ester function.

The related dibromo esters **12** (R = H, Me, Et, cyclohexyl; R′ = Me, Et) react with 3 equiv of sodium azide to yield (*Z*)-2-azido-2-alkenoates (**16**) in good yield. The mechanism outlined in Scheme 1 has been proposed on the basis of model studies.[51] Thus **12** (R = H, R′ = Et) gave diazido ester **15** (R = H, R′ = Et) in quantitative yield on treatment with 3 equiv of sodium azide at 20 °C in DMF, whereas **12** (R = Me, R′ = Et) gave only **13** (R = Me, R′ = Et). A similar product, **13** (R = H, R′ = Et), was obtained from the reaction of **12** (R = H, R′ = Et) with 1 equiv of sodium azide in DMF at 25 °C.[51] Eliminative azidation has also been observed[52] in the treatment of a 1,2-dibromobenzazepine derivative with sodium azide at room temperature.

1,2-Diazides containing other energetic groups (cf. **17** and **18**) can be prepared from the corresponding dibromo compounds by overnight treatment with sodium azide.[26] Propargylic diazides **19** and **20** are similarly obtained.[53] The latter are extremely explosive and

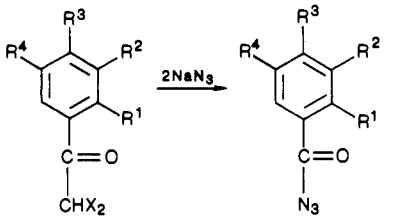


must be stored at low temperature; they survive several weeks at −25 °C. The results of a recent study concerning the stability of functionalized vicinal diazides (cf. **21**) in the presence of mild base suggest that unsaturated functional groups (−M type, e.g., R = COMe, CN, and COPh) destabilize the diazide.[54]

2. With Rearrangement

In an attempt to prepare the elusive azidophenylethyne (**23**), chlorophenylethyne (**22**) was allowed to react with sodium azide in DMSO for 3 days at 25 °C.[55] Not unexpectedly,[56] the desired compound was not obtained (see Scheme 2) but one of the products (viz., **26**) was rationalized as arising from decomposition of **23** to the nitrene and subsequent reaction with DMSO. The isolation of **24** suggests that attack at C-2 is a major competing process, as it is in other nucleophilic reactions with halogenoarylethynes.[57]

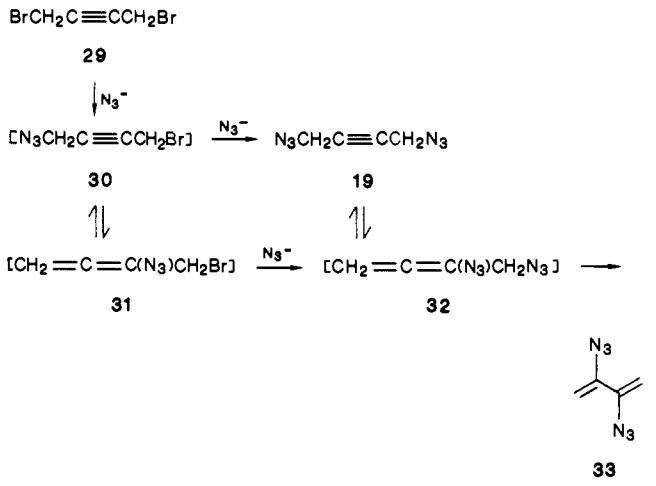
The ω,ω-dibromoacetophenone derivatives **27** (X = Br) react with 2 equiv of sodium azide to form the aroyl azides **28**.[58] The process is apparently not merely displacement of dibromomethane anion but is rationalized as involving rearrangement of the initially formed diazide **27** (X = N_3) and subsequent extrusion of HCN and N_2.



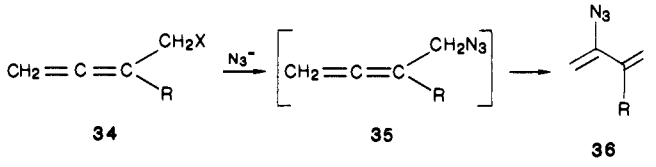
R^1 = H, NO_2, NHCOMe; R^2 = H, NO_2, Cl
R^3 = H, halogen, NO_2, OMe, Ph, SO_2Me, NHCOMe; R^4 = H, Br

As previously noted the propargylic diazide **19** can be isolated and stored at low temperature. However, warming solutions of **19** in benzene, chloroform, or aqueous acetone to 40–70 °C gives 2,3-diazido-1,3-butadiene (**33**).[59] This is the first example of direction of an azido group to a vinyl position by allyl rearrangement. Previously, only allyl rearrangements to allyl positions were known in propene and butene systems.[60] Diazide **33** could also be prepared directly from **29** (1 equiv) by heating (50 °C) with sodium azide (4 equiv) in ethanol/water. The series of reactions and equilibria shown in Scheme 3 has been postulated to explain these results. The rate of formation of **33** from **19** and thermodynamic data suggest a nonionic process involving sequential migration of the two azide groups in **19**. Although none of the postulated intermediates

SCHEME 3

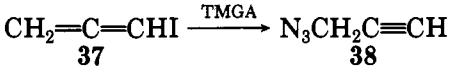


SCHEME 4

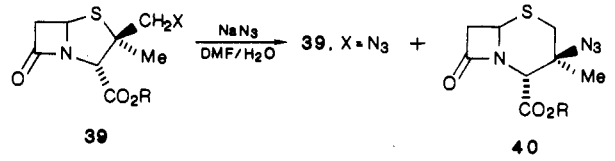


(30–32) to 33 could be isolated, the likelihood of their existence was strengthened by the isolation of 2-azido-1,3-butadiene (36, R = H) from the reaction of 4-bromo-1,2-butadiene (34, X = Br, R = H) with sodium azide in aqueous methanol for 5 days (Scheme 4). Compound 36 (R = H) could be more conveniently prepared from 34 (X = Br, R = H) and tetramethylguanidinium azide in sulfolane (1.5 h, 55–60 °C).[59] The postulated intermediate, viz., 35 (R = H), could not be isolated in the present study; however, in a closely related examination of the reaction of 34 (X = Cl, R = Me) and sodium azide, it was found that if the reaction was prematurely terminated, then 34 (X = Cl, R = Me), 36 (R = Me), and 35 (R = Me) were obtained.[61] Better yields of 35 (R = Me) resulted from treatment of 34 (X = Cl, R = Me) with hexadecylphosponium azide.

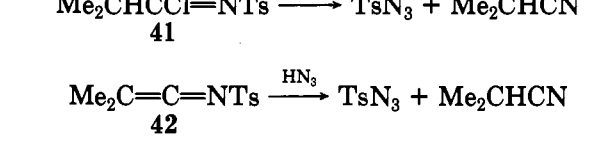
Tetramethylguanidinium azide (TMGA) in sulfolane also reacts with iodoallene (37) to give 3-azido-1-propyne (38).[53]



Treatment of the halopenams 39 (X = Br, Cl) with sodium azide in DMF/water at 25 °C gave both azidopenam (39, X = N_3) (60–65%) and azidocepham (40) (35–40%).[62]

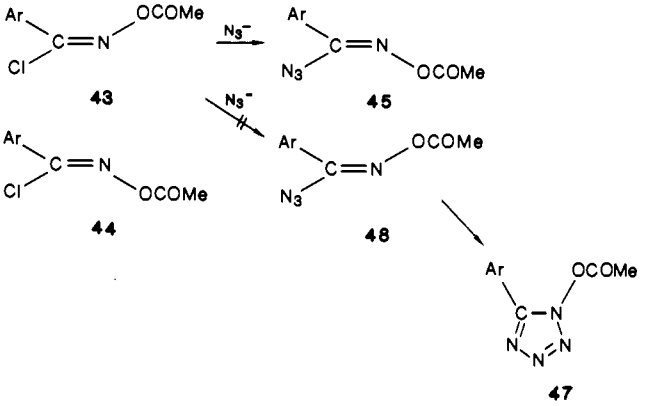


Eliminative azidation to form tosyl azide and isobutyronitrile occurs on treatment of the *N*-tosylimidoyl chloride 41 with lithium azide or the *N*-tosylketenimine 42 with hydrazoic acid.[63]

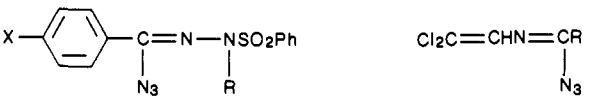


3. By Displacement at Unsaturated Sites

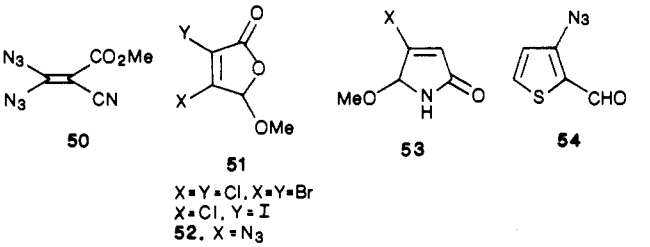
Both *E* and *Z* O-acyl imidoyl chlorides (43 and 44, respectively) react stereospecifically with sodium azide in acetone/water (1:1) at 25 °C to give quantitative formation of the *Z* azide (45).[64] No *E* azide (46) or tetrazole (47) (to which 46 should cyclize;[65] see section VI.B.4) was present in the reaction mixtures. The results have been rationalized mechanistically.



Hydrazonoyl azides (48)[66] and the unstable 1-azido-2-aza-1,3-butadiene derivatives (49)[67] have been prepared in standard fashion by the action of sodium azide on the corresponding chlorides.

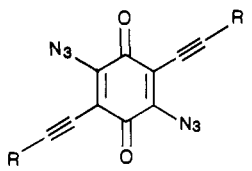


Methyl 3,3-dichloro-2-cyanoacrylate and sodium azide in acetone/water at −15 °C react in a few seconds to form diazide 50.[68] The 4-azido-2-furanones 52[69] are

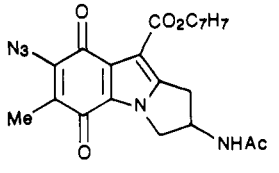


formed by Michael addition of sodium azide on the furanones 51 in methanol. The halide α to the carbonyl function remains intact. Bromopyrroline 53 (X = Br) reacts analogously to form 53 (X = N_3) in 85% yield.[70] No reaction occurred in THF. The yield (from the bromo species) of 3-azidothiophene-2-carbaldehyde (54) was increased from 45%[71] to 75%[72] by use of NaN_3 in HMPA rather than in DMSO.

Azidoquinones 55,[73] 56,[74] and 57[75] are similarly prepared from the corresponding halides. However, due to its instability, 57 was not isolated but used in situ for further transformations. The azidouracil derivatives 58 and 59 were likewise obtained.[76]



55, R = *n*-Bu



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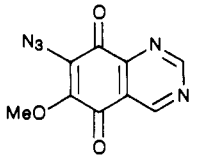

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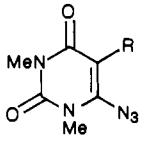
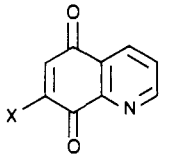


58, R = Ph
59, R = CH_2Ph

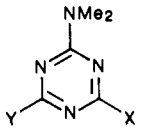
Recently, Boger and co-workers[77] studied azide attack on 7-bromoquinoline-5,8-quinone (**60**) as a model for the



60, X = Br
61, X = N_3

preparation of the AB ring system in lavendamycin. Thus, treatment of **60** with sodium azide gave 7-azidoquinoline-5,8-quinone (**61**) in 91% yield. Interestingly, with excess reagent (1.5 equiv) 7-amino-6-azidoquinoline-5,8-quinone was the major product. Similar results had been observed previously with 2-bromo-1,4-naphthoquinone.[78]

Displacement of activated heterocyclic halides is also possible (cf. **62** (X = Y = Cl) → **62** (X = Y = N_3) and **62** (X = NMe_2, Y = Cl) → **62** (X = NMe_2, Y = N_3),[79] although on occasion rearrangements occur. Thus, 4-carbethoxy-5-chloro-1,2,3-thiadiazole (**63**) gave diazo compound **64** in 77% yield on treatment with sodium azide in acetone/water at 0 °C. The corresponding azide was postulated as an intermediate.[80]



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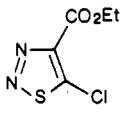

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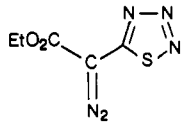

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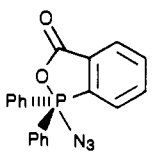
4. By Displacement at Atoms Other than Carbon

Various heteroazido species are commonly encountered: inter alia, halogen azides (see section II.G), tosyl azide (see section II.J)[81] and other sulfonyl azides,[82,83] diphenyl phosphorazidate,[84] and trimethylsilyl azide,[85] all of which can be made from the action of NaN_3 on the appropriate halide. The last two of these (viz., $(PhO)_2P(O)N_3$ and Me_3SiN_3) are now commercially available.[86]

The *gem*-diazido-[87] and triazidosilanes[88] $Me_2Si(N_3)_2$ and $PhSi(N_3)_3$ have been prepared for photolysis and thermolysis studies.[89,90]

Azidophosphoranes **65–67** were synthesized by the action of trimethylsilyl azide on the chlorophosphoranes.[91] Previous to these preparations only one azidophosphorane (viz., **68**) had been reported.[92] Bis(diisopropylamino)phosphinyl azide is derived from the chloride in the same manner.[93]



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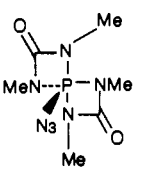

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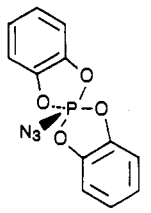

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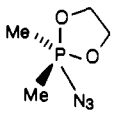
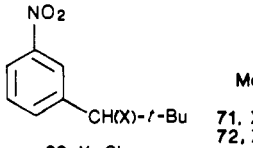


68

Similarly, aryl-,[94] alkyl-,[95] and heteroalkylazidoboranes[96] (R_2BN_3) and diazidoboranes[96] have been prepared. Dibutyltin and dibenzyltin chlorides react with sodium azide to give the dialkyltin azides.[97] For kinetic studies, solutions of benzenesulfinyl azide ($PhSON_3$) were prepared at −20 °C from benzenesulfinyl chloride and sodium azide in 1,2-dimethoxyethane or acetonitrile,[98] an improvement on the literature method.[99]

5. Via $S_{RN}1$ Reactions

Chloro compound **69** undergoes an $S_{RN}1$ reaction with sodium azide to provide the corresponding azide **70**.[100] Similarly, an $S_{RN}1$ mechanism has been implicated in the preparation of the α-nitro azide **72** from the corresponding bromo compound **71**.[101] Interestingly, with excess azide ion, **72** reacts further to give the diazido species **73**.



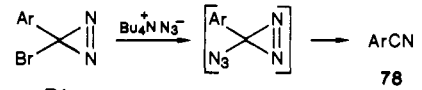
69, X = Cl
70, X = N_3

$Me_2C(X)Y$

71, X = Br; Y = NO_2
72, X = N_3; Y = NO_2
73, X = Y = N_3

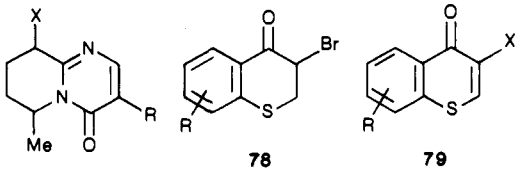
6. Thwarted Attempts

The reaction of arylbromodiazirines **74** with tetrabutylammonium azide gave the corresponding nitriles **76**, presumably via azide **75** intermediacy.[102,103]



74 75 78

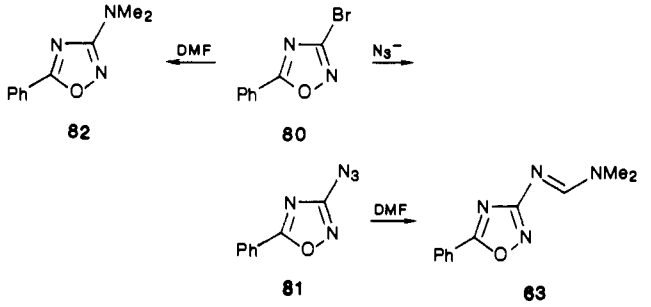
Attempted azidation of the bromo compounds **77** (X = Br; R = $CONH_2$, CN) with sodium azide in acetone at 25 °C gave moderate yields (42% and 55%, respectively) of the amino congeners **77** (X = NH_2; R as above).[104] Presumably the azide is initially formed and cleavage occurs via neighboring group participation by a pyrimidine ring nitrogen. The aminothiochromone **79** (X = NH_2) resulted from azide treatment of **78** in $MeOH/H_2O$.[105] Interestingly, in DMF/H_2O, elimination to form **79** (X = H) occurred.



77 78 79

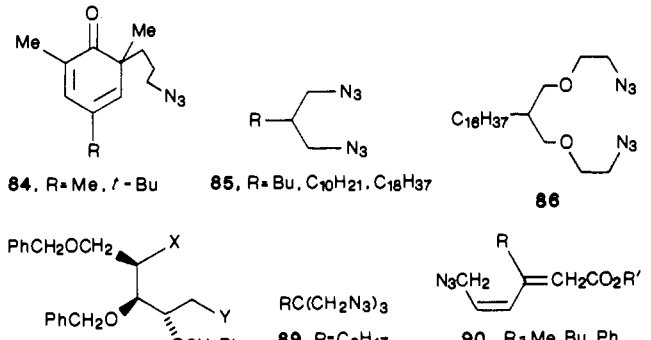
R = H, 6-Me or 8-Me

Treatment of 3-bromo-5-phenyl-1,2,4-oxadiazole (80) with sodium azide in DMF at 130 °C gave 3-(dimethylamino)-5-phenyl-1,2,4-oxadiazole (82) (39%) and 3-(((dimethylamino)methylene)amino)-5-phenyl-1,2,4-oxadiazole (83) (34%).[106] The azide 81 was formed at lower temperature and was shown to be a precursor of 83.



B. From Sulfonates and Acetates

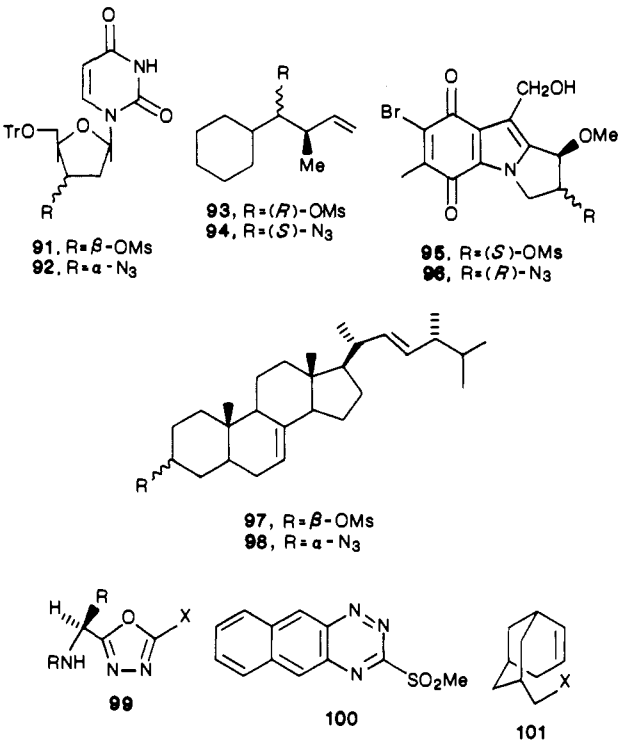
The displacement of sulfonates by azide ion, or congeneric species, is another important route to organic azides, especially alkyl examples. Overall, the process can be used as an indirect conversion of an alcohol to an azide (see section II.E for direct conversion). The most commonly employed sulfonate leaving group is the methanesulfonate (mesyl) moiety. Choice of conditions for displacement by azide ion is dictated by the same factors as described for halide leaving groups (see section II.A). Thus, in DMF, the azido compounds 84,[107] 85,[108] and 86[108] are prepared in good yield by the action



of NaN_3 on the mesylates (also $PhSO_2$ for 85). Selective displacement of a primary mesylate in the presence of a secondary mesylate can be effected in the same manner (cf. 87 → 88).[109] Similarly, triazide 89 is obtained by using NaN_3/Bu_4NCl in HMPA.[108] For the long-chain azides 85, 86, and 89, the nucleophilic substitutions leading to their formation required polar, aprotic solvents rather than ethylene glycol (as previously described for shorter chain analogues[110]). The 6-azidohexa-2,4-dienoates 90 were also prepared from the corresponding mesylates.[111]

The S_N2 nature of the substitution (i.e., inversion of configuration) is apparent from a number of examples: inter alia, 91 → 92,[112] 93 → 94,[113] 95 → 96,[74] and 97 → 98.[114]

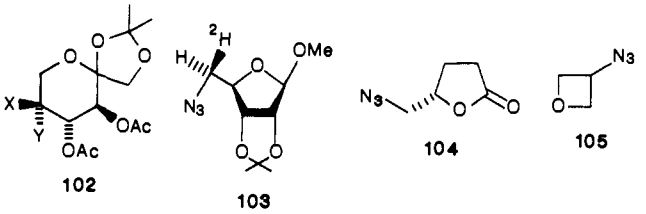
Displacement can be extended to activated aromatic systems; thus, oxadiazole 99 (X = N_3) results from treatment of 99 (X = SO_2Me) with NaN_3 in EtOH.[115]



A similar attempt with 100 gave a tetrazole derivative (see section VI.B.4) presumably derived from the initially formed azido compound.[116]

Tosyl groups can also be displaced, although not always efficiently, as evidenced by the attempts to prepare 101 (X = N_3) from the tosylate 101 (X = OTs).[117] Thus, with sodium azide in dipolar aprotic solvents a low yield of the azido species was obtained, presumably because of competing π-route cyclization to adamantan-2-ol. With a 9-fold excess of sodium azide in DMSO at 90 °C for 5 days, a mixture of the required azide (34%) and adamantan-2-ol (65%) resulted. A 15-fold excess of sodium azide in DMF in the presence of 15-crown-5 at room temperature for 4.5 days gave 101 (X = N_3) (21%) and adamantan-2-ol (12%). Various other reaction conditions were employed, with no improvement in results.

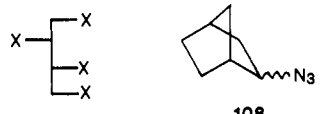
In contrast, tosylate 102 (X = OTs, Y = H) gave the azido compound 102 (X = H, Y = N_3) in 74% yield by treatment with lithium azide in DMF.[118] Similarly, high yields (95% and 87%, respectively) of the azido sugar 103 and lactone 104 were obtained with sodium azide in DMF at 100 °C[119] and reflux,[120] respectively.



Reaction of 3-(tosyloxy)oxetane with liquid ammonia gave only a low yield of the corresponding amino compound, and hence a two-step process via 105 was instead employed (see section III.A).[121] A 50% yield of 105 was obtained with KN_3 at 87 °C in HMPA and a 28% yield in refluxing acetonitrile in the presence of 18-crown-6. However, using NaN_3 and the tosylate in tetraethylene glycol (or higher homologues) at 120–130 °C and 7–10

mmHg gave an 86% yield of **105**. The explosive azide distilled from the reaction mixture but was handled safely by collection in dichloromethane and use in solution.

The benzenesulfonate leaving group has been little utilized. One interesting example, however, is the conversion of **106** to the tetraazide **107** en route to the corresponding tetraamine.[122] Likewise, there are very

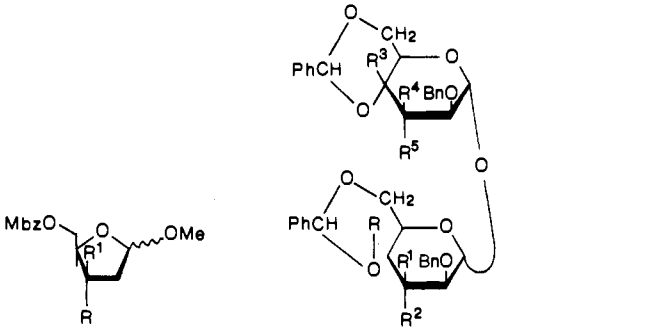


106, X = OSO_2Ph
107, X = N_3

108

109, R = H, Me

few reports concerning displacement of 4-bromobenzenesulfonate (brosyl) groups by azide ion. In part, this may be due to the known incidence of competitive S_NAr bromine substitution.[123,124] However, despite this difficulty, excellent yields of 2-norbornyl azides (**108**) were obtained by S_N2 displacement of the appropriate brosylates with tributylhexadecylphosphonium azide in toluene.[123] The same reagent also effects S_N2 displacement of cyclopropyl trifluoromethanesulfonates to give the cyclopropyl azides **109** and allylic azides as minor products.[125] The percentage of the product mixture comprising the cyclic azide decreased with growing steric hindrance. The use of the trifluoromethanesulfonyl (triflyl) group can sometimes be advantageous in that conversion occurs under very mild conditions; e.g., **110** (R = N_3, R^1 = H) was prepared



110

111, R = R^1 = R^3 = R^4 = H; R^2 = R^5 = OTf
112, R = R^2 = R^3 = R^5 = H; R^1 = R^4 = N_3
113, R, R^1, R^2 = R^3, R^4; R^5 = double bond
114, R, R^1, R^2 = double bond; R^3 = R^5 = H; R^4 = N_3

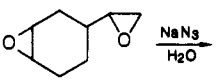
from the triflate **110** (R = H, R^1 = OTf) by treatment with LiN_3 in ethanol at room temperature for 40 min.[126] Competing elimination can be a problem, however; treatment of the ditriflate **111** with lithium azide under a variety of conditions gave a mixture of the required diazide **112** and the mono- and dialkenes **113** and **114**.[127]

The first report of palladium-catalyzed azidation of allylic acetates appeared recently.[128] The conversion was effected under mild conditions (room temperature) and in good yield (66–88%) with sodium azide and a catalytic amount of $Pd(Ph_3)_4$ in THF/water. The process can be used as a "one-pot" amine preparation by in situ azide reduction (triphenylphosphine/NaOH) (see section III.A).

C. From Epoxides

Azidation of epoxides often proves advantageous in that the azido alcohol normally formed is difunctional (see section III.C for further transformations). Several other examples of this process are reported in section V.

Reaction of the diepoxide **115** with sodium azide gave a mixture of azides (**116**, **117**) derived only from ring epoxide cleavage. Further treatment of the mixture (**116**, **117**) with NaN_3 gave the expected diazides (**118**, **119**).[129] Similar treatment of **120** gave a mixture of the azido alcohols (**121**, **122**) and the diol **123**.[129]



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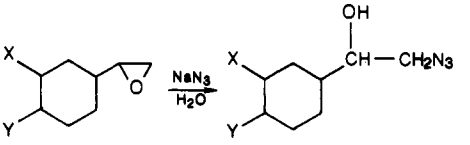
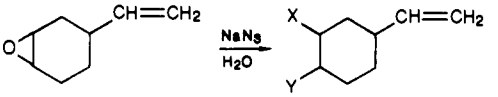


116, X = N_3; Y = OH
117, X = OH; Y = N_3

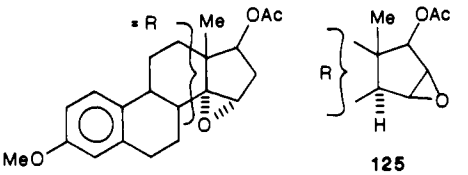
118, X = N_3; Y = OH
119, X = OH; Y = N_3



120

121, X = N_3; Y = OH
122, X = OH; Y = N_3
123, X = Y = OH

The reaction has been extended to the steroidal epoxides (**124**, **125**) to give the 15- and 16-azido steroidal alcohols, respectively.[130] Additionally, in an attempt to transform the epoxide to an aziridine using Blum's two-step procedure ((1) NaN_3, (2) Ph_3P)[131] (see section III.C), the epoxy ester **126** was transformed to azido alcohol **127** in >90% yield by treatment with sodium azide in $MeOH/NEt_3$ for 3 h at room temperature. The subsequent cyclization was unsuccessful.[132]



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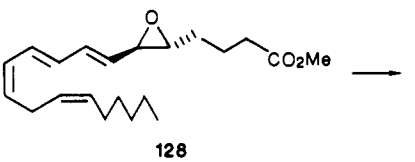

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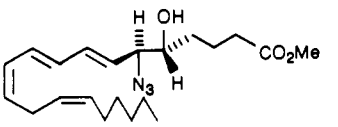
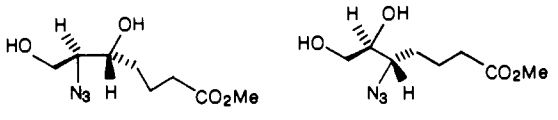


127

The mixture of azido alcohols (**128**, **129**) was similarly prepared.[132] Regioselective addition was also observed for the reaction of various polycyclic aromatic hydrocarbon epoxides (cf. **130** → **131**) with sodium azide in acetone. Depending on reaction conditions the other azido alcohol was formed in 0–20% yield.[133]

The deuteriated cyclohexadienyl epoxide **132** reacts with NaN_3 in water to give a mixture of three azido alcohols (**133**–**135**), postulated as arising from initial



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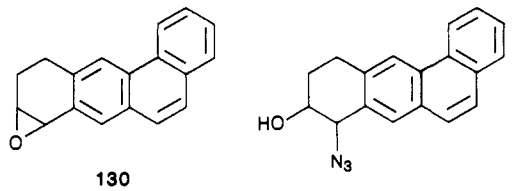
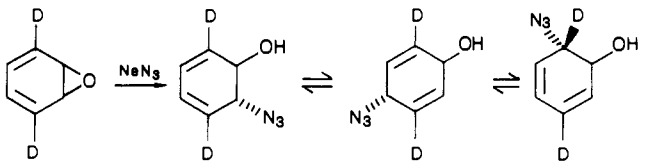
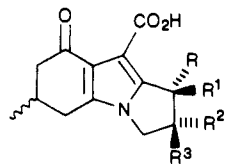


130 131



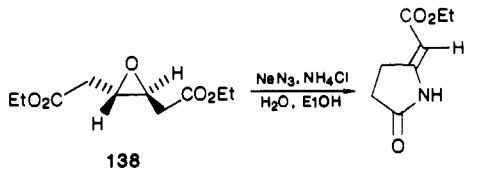
132 133 48% 134 11% 135 41%

1,2-addition followed by [3,3]-sigmatropic rearrangement.[134] An intermediate epoxide is probably involved in the regio- and stereospecific conversion of **136** to **137**.[74] Interestingly, the oxirane **138** gives a 67% yield



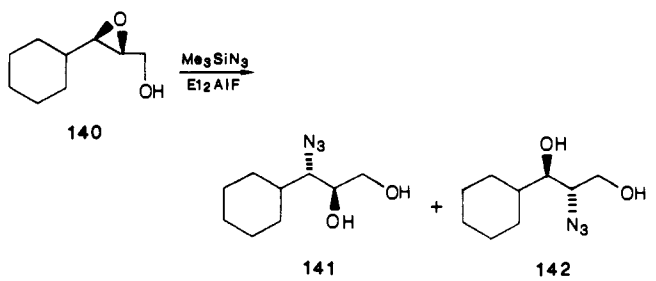
138, R = R^3 = H; R^1 = OH, R^2 = Br
137, R = N_3; R^1 = R^2 = H; R^3 = OH

of a mixture of *E* and *Z* isomers of **139** on refluxing with NaN_3 and NH_4Cl in 60% EtOH for 18 h[135] (for similar transformations, see section III.C).



138 139

Greater control of regio- and stereoselectivity is often possible with Me_3SiN_3 (TMSA) and a Lewis acid catalyst. Thus, cyclohexene oxide and propylene oxide react slowly at room temperature with trimethylsilyl azide in the presence of a variety of Ti or V catalysts to give the anti and primary azido alcohols, respectively.[136] Similarly, the 2,3-epoxy alcohol **140** gives the azido diols (**141**, **142**) (98:2) in 85% yield by treatment with TMSA and Et_2AlF in dichloromethane at room temperature. Other Lewis acids led to decomposition.[137] Similar regioselectivity was observed with other 2,3-epoxy alcohols using TMSA and a stoichiometric quantity of $Ti(O\text{-}i\text{-}Pr)_4$,[138,139] TMSA and a catalytic quantity of $Ti(O\text{-}i\text{-}Pr)_4$,[136] and TMSA and $ZnCl_2$.[140] These methods apparently circumvent the steric difficulties encountered in the conventional method with azide ion. Thus, conventional azidation of **140** reportedly provides a (1.7–2):1 ratio of **141**:**142**.[141] More recently, a 13-compound study of the regioselectivity of ring opening with ammonium azide in analogues of **140** has been reported.[142]

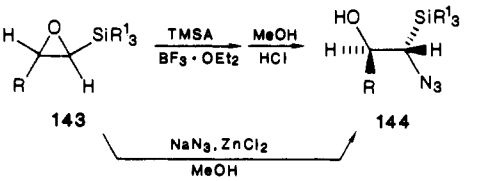


140 141 142

By comparison with sodium azide supported on alumina or silica, or the sodium azide/ammonium chloride system, sodium azide impregnated on a calcium cation exchanged Y-type zeolite (CaY) induced C-3 opening of **140** (and two analogues) with much greater selectivity to form predominantly **141** (or congeners).[143]

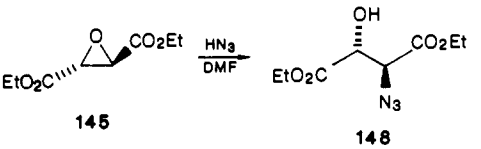
$Ti(O\text{-}i\text{-}Pr)_4$ also catalyzes the regioselective ring opening of monofunctional epoxides with trimethylsilyl azide.[144] The primary azido species is formed with remarkable regioselectivity (92:8 → 100:0).

The boron trifluoride diethyl etherate catalyzed reaction of 1,2-epoxysilanes **143** (R = H, 1-hydroxy-1-cyclohexyl; R^1 = Me, Et) with TMSA followed by brief treatment with a trace amount of HCl in methanol afforded (1-azido-2-hydroxyalkyl)silanes **144** in 74–86% yield.[145] Direct conversion of **143** (R = alkyl, R^1 = Me, Et) to **144** could be effected in lower yield by prolonged treatment with sodium azide/zinc chloride in methanol.



143 144

On occasion hydrazoic acid itself has been utilized for the oxirane ring opening. Thus, epoxysuccinate **145** was converted to azido alcohol **146** in 97% yield by treatment with HN_3 in DMF.[146] The hydrazoic acid was generated in situ from TMSA and methanol in DMF.[147] Other azide ion oxirane cleavage methods did not satisfactorily effect the transformation, and DMF appears to be essential. Regioselective ring opening by HN_3/Et_3Al has also been reported.[148]

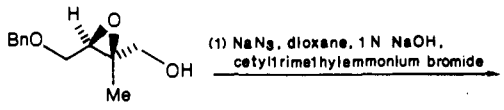


145 146

Under Payne rearrangement conditions epoxy alcohol **147** reacts with excess sodium azide to give azido diol **148** in 52% yield.[149] The use of a phase-transfer catalyst is essential and it appears that the PTC facilitates the Payne rearrangement. Support for this premise comes from the fact that two minor products (**149**, **150**) formed in the catalyzed reaction become major components in the noncatalyzed process.

D. From Ketals

Ketals (cf. **151**) can be converted to the corresponding α-alkoxy azides (**152**) or diazides (**153**) by treatment with trimethylsilyl azide (1 or 2 equiv, respectively) and



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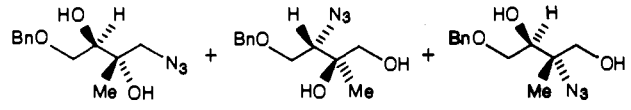
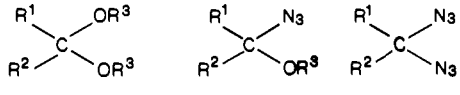


148 149 150

tin(IV) chloride.[150] With 2 equiv of trimethylsilyl azide,



151 152 153

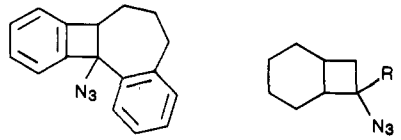
R^1, R^2 = alkyl, aryl
R^3 = alkyl

diphenyl ketal **151** ($R^1 = R^2 = Ph$) is converted to a tetrazole, presumably via diazide (**153**) intermediacy.[150] Similar results were obtained with the α-hydroxy analogues **151** ($R^1 = CH_2OH$; R^2 = 4-$MeOC_6H_4$, 4-MeC_6H_4; R^3 = Me). The necessity for activating substituents is manifest since **151** ($R^1 = CH_2OH$; R^2 = Ph, 4-ClC_6H_4; R^3 = Me) gave monoazido silyl ether **152** ($R^1 = CH_2OSiMe_3$).[151] For a similar transformation to a tetrazole, see section VI.B.4.

E. From Alcohols

Azides can be prepared from alcohols in a two-step process involving conversion to a sulfonate and subsequent azide ion displacement (see section II.B). Direct conversions will be enumerated here.

Tertiary alcohols can be converted directly to azides (cf. **154** and **155**) by using hydrazoic acid and boron trifluoride as catalyst.[152-154] Other Lewis acids can be

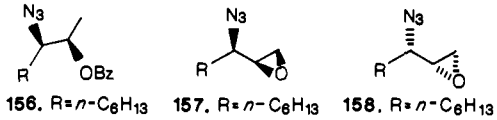


154 155

R = Me, Ph, Bn, allyl

utilized and recently it was shown that $HN_3/TiCl_4$ smoothly converts benzylic, allylic, or tertiary alcohols to the corresponding azides in good yield.[155] Primary alcohols are unaffected and stereochemistry is not maintained, indicative of a carbocation intermediate.

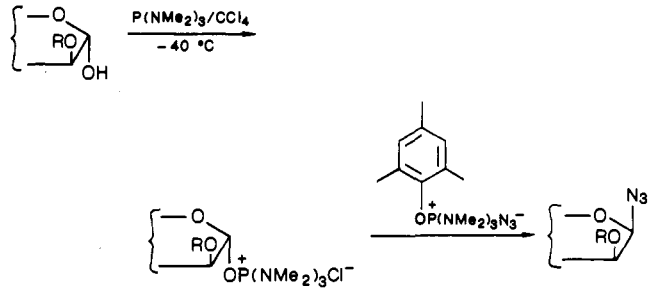
The modified Mitsunobu reaction[156] (Ph_3P, DEAD, HN_3, benzene, 2 h, 20 °C) converts alcohols to azides with inversion of configuration. Thus, azido benzoate **156** and epoxides **157** and **158** were prepared from the appropriate alcohols.[157]



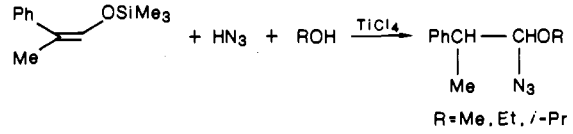
156. R = n-C_6H_{13} 157. R = n-C_6H_{13} 158. R = n-C_6H_{13}

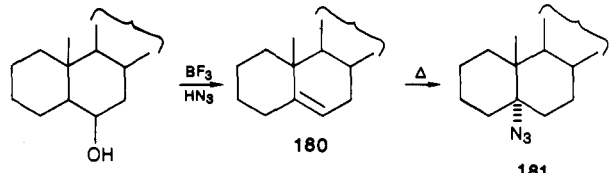
In some cases apparent rearrangement occurs; e.g., the secondary alcohol 6β-hydroxypregnane (**159**) reacts with BF_3/HN_3 to give the 5-azido analogue **161**, presumably via HN_3 addition to a Δ^5-pregnene (**160**) intermediate.[158]

SCHEME 5



SCHEME 6





159 160 161

Activation of the alcohol function by formation of a phosphonium salt has also been reported. Thus, protected sugars with a free anomeric OH can be directly converted to the glycosyl azides (with inversion of configuration) under extremely mild conditions as shown in Scheme 5.[159]

F. From Carboxylic Acids

The preparation of acyl azides from acyl halides has been previously described (see section II.A). Similar two-step procedures (from the carboxylic acid) have been developed by using the reaction of a mixed anhydride with sodium azide.[23,160]

One-pot reactions are potentially more useful, however, since one synthetic step is excised. A few such transformations have been reported. Thus, carboxylic acids react with *O,O*-diphenylphosphoryl azide to give the corresponding acyl azides.[161] More recently, *N,N*-dimethyl(chlorosulfonyl)methaniminium chloride ($Me_2{}^+N{=}CHOS(O)Cl\ Cl^-$; from thionyl chloride and DMF) was used as an activating reagent for the reaction of carboxylic acids with NaN_3.[162] For the four examples studied, yields were good to excellent (75–96%) and the conditions employed were mild (15–20 h, room temperature). Similar activation has been achieved with phenyl dichlorophosphate.[163] With the latter the conditions were also mild and outstanding yields were obtained (85–100%).

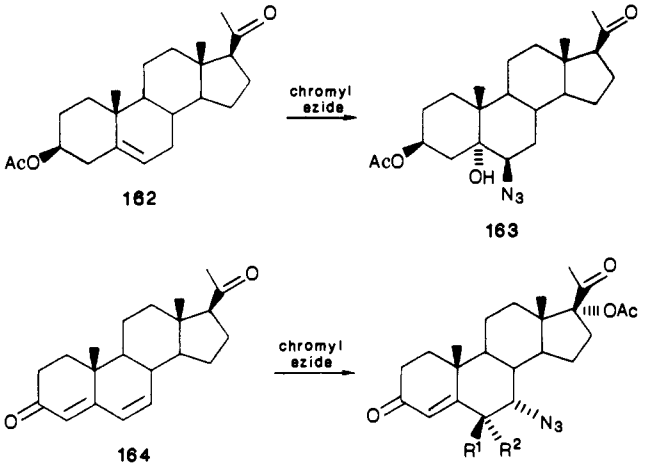
G. From Alkenes

In an extensive study of the reactions of hydrazoic acid with alkenes, Hassner[155] has shown that enol ethers and silyl enol ethers react to give azido ethers in good yield. A similar process occurs with trifluoroacetic acid catalysis.[164] Interestingly, $TiCl_4$-catalyzed hydrazoic acid addition to silyl enol ethers in the presence of

primary and secondary alcohols gave products derived from ether exchange (Scheme 6).

Olefins bearing a phenyl or two geminal alkyl substituents require the presence of a Lewis acid (best with $TiCl_4$); mono- or 1,2-dialkyl olefins do not react. These data, in conjunction with the regiospecificity of the addition, are suggestive of a carbocation intermediate. This premise is further supported by the isolation of a mixture of 5α- and 5β-azidocholestanes from 5-cholestene. Previously, hydrazoic acid had been shown to add readily only in the case of cyclopropene[165] or in Michael additions to unsaturated carbonyl compounds.[166] A recent example of the latter has been reported.[167] Attempts to add HN_3 to diarylethylene in the presence of sulfuric acid led to considerable decomposition due to Schmidt rearrangement[166c] (see section III.E).

Pregnenolone acetate (**162**) reacts with chromyl azide (formed in situ from chromium trioxide and sodium azide[168]) to provide the azidohydrin **163**. However, the situation with **164** was more complex. Three products (**165–167**) were formed, the major of which was the unexpected azidohydrin **165**.[169] Similar results were



162 **163** **164**

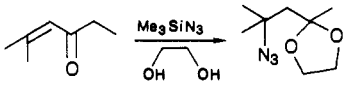
165. R^1=OH; R^2=H
166. R^1=N_3; R^2=H
167. R^1R^2=O

obtained with some other steroidal dienones.

Diazido species (cf. **166**) were the major products when steroidal 4,6-diene-3-ones were reacted with lead tetraacetate and trimethylsilyl azide.[170] The mechanism was presumed to involve an initial conjugate nucleophilic attack by azide ion and subsequent electrophilic azide addition. Vicinal diazides have also been prepared from alkenes by using Fe(III)[171] and Pb(IV)[172,173] reagents. The latter converted 1,3-dienes to 1,4-diazides.[174] Recently, modifications of this approach have been reported.[175,176] Thus, 1,2-diazides were the major products from treatment of alkenes with NaN_3/$Mn^{III}(OAc)_3$; $Mn^{III}N_3$ species are presumably formed in situ.[175] The mechanism apparently involves ligand transfer to generate a β-azidoalkyl radical which subsequently reacts with a second $Mn^{III}N_3$ species. Similarly, vicinal diazides were formed in 34–85% yield under mild conditions by reaction of the corresponding alkene with PhIO and sodium azide.[176]

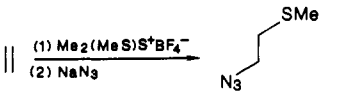
The lead tetraacetate/trimethylsilyl azide system has been previously utilized for the introduction of "positive" azide to a large variety of olefins and acetylenes;[177] with isolated trisubstituted steroidal olefins, allylic azides[178] or seco keto nitriles[179] are formed, depending upon temperature. In contrast, isolated disubstituted olefins provide α-azido ketones.[180] Trialkylboranes (prepared from alkenes) react with lead(IV) acetate azide (formed in situ from LTA and TMSA at −25 °C) in a "one-pot" process to form the corresponding alkyl azides.[181]

Interestingly, reaction of mesityl oxide **168** with trimethylsilyl azide and ethylene glycol in the presence of $SiCl_4$ (1%) leads to the azido ketal **169**.[182]



168 **169**

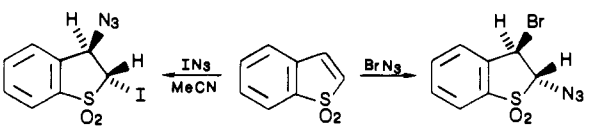
Nucleophilic attack by azide ion or congeneric species on nonconjugated alkenes can be facilitated by dimethyl(methylthio)sulfonium tetrafluoroborate.[183] The products (cf. **170**) result from trans addition, and, in general, the greater the nucleophilicity of the azido species, the greater the amount of anti-Markovnikov product and vice versa. Olefin substitution also greatly affects orientation; monosubstitution favors anti-Markovnikov addition, and trisubstitution, Markovnikov addition. Control either way is possible with 1,1-disubstituted olefins, the nucleophilicity of the azido species being the deciding factor.



170
trans addition

Halogen azides react with alkenes to form the corresponding halo azides, and the utility of this process has been reviewed.[184] It has been stated that iodine azide usually adds to olefins via a three-membered iodonium ion intermediate[185] whereas bromine azide can add either in an ionic or a free radical fashion, the latter being favored by nonpolar solvents.[186]

Tamura and co-workers have examined the reactions of iodine azide with indoles[187–189] and benzo[*b*]furan.[187] Extension to benzo[*b*]thiophene 1,1-dioxide (**171**) gave intriguing results. Treatment of **171** with IN_3 provided the 3-azido species **172** whereas with BrN_3 the 2-azido product **173** was obtained.[190] The formation of **172** presumably involves azide attack on an iodonium intermediate; a similar mechanism has been proposed for open-chain vinyl sulfones.[191]

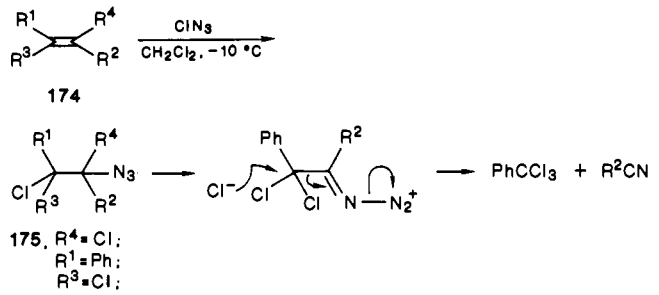


172 **171** **173**

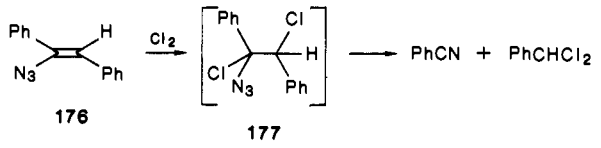
In contrast, it was suggested[190] that the reaction with bromine azide involves attack of $N_3^{\bullet}$ radical on the double bond and subsequent Br• attack at the benzylic position. A mixture of azide-containing products was obtained from benzo[*b*]thiophene and iodine azide but their unstable nature precluded their characterization.[190]

The α,α-dichloro azide **175** (R^1 = R^2 = Ph, R^3 = Cl, R^4 = H) had been prepared by addition of chlorine

SCHEME 7



SCHEME 8

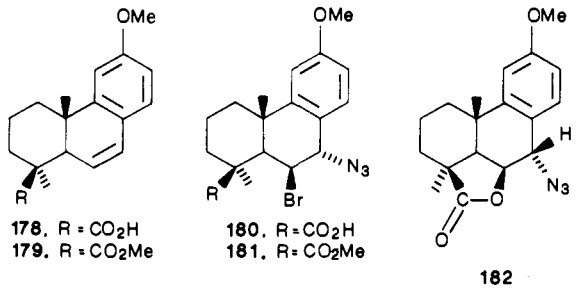


azide to the vinyl chloride 174 ($R^1 = R^2 = Ph$, $R^3 = Cl$, $R^4 = H$).[192] However, an attempt to synthesize the analogous trichloro azides 175 ($R^1 = Ph$, $R^2 = H$ or Ph, $R^3 = R^4 = Cl$) from the dichloroalkenes 174 ($R^1 = Ph$, $R^2 = H$ or Ph, $R^3 = R^4 = Cl$) led to the formation of α,α,α-trichlorotoluene and the appropriate nitrile.[193] A plausible mechanism is shown in Scheme 7.

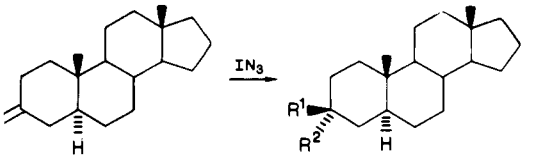
Support for the instability of α-chloro azides was provided by the observation that azidostilbene (176) reacted with chlorine to give PhCN and $PhCHCl_2$; the expected addition product (177) could not be isolated[193] (Scheme 8).

A recent reinvestigation of the regiochemistry of addition of iodine azide to 1-arylcyclohexenes has shown that the products obtained in 77–89% yield are 2-azido-1-iodo-1-arylcyclohexanes[194] and not 1-azido-2-iodo-1-arylcyclohexanes as previously reported.[195]

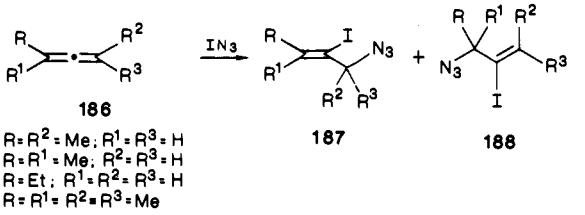
A considerable body of data has been amassed regarding the addition of halogen azides to unsaturated steroids and related species. Thus, addition of bromine azide to the unsaturated acid 178 or its methyl ester 179 gave unexpected 6β-bromo-7α-azido species 180 and 181, respectively. Treatment of 180 with methanol/pyridine under reflux gave 182 in 77% yield, presumably via neighboring group participation by the azido group.[196]



The addition of iodine azide to 3-methylene-5α-androstane (183) in the presence of oxygen is regioselective but not stereoselective; iodomethyl-containing products 184 and 185 are formed.[197] The overall yield (up to 98%) and the relative amounts of 184 and 185 depend on the choice of solvent and mode of generation of iodine azide. The β-azido compound 184 is always the major component and is the sole product from treatment of 183 with *N*-iodosuccinimide/HN_3. Under a nitrogen atmosphere, products containing an azidomethyl group are obtained, suggestive of a radical mechanism.

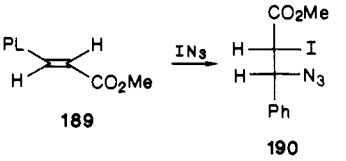


Alkyl-substituted allenes (186) react with iodine azide regioselectively to give allyl rather than vinyl azides.[198] It appears that the primary product is the allyl azide derived from azide attack at the most substituted site (i.e., 187). However, depending on the allene structure and the reaction temperature, substantial amounts of the [3,3]-rearrangement product (188) can also be formed.[198]



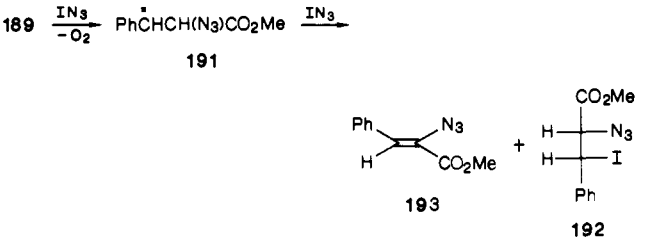
Similarly, norborn-2-ene reacts with IN_3 in the presence of oxygen to give products derived from an ionic process and in the absence of oxygen to give products derived from a radical addition.[199]

The reaction of α,β-unsaturated esters and ketones with iodine azide was examined by Hassner and coworkers.[200] Due to the regio- and stereoselectivity thus encountered, they proposed a mechanism comparable to that for the addition to alkenes. Thus, methyl *trans*-cinnamate (189) gave a 43% yield of the erythro adduct (190). The same reaction was later shown[201] to provide a crude yield of 79%. With thallium(I) azide–iodine a mixture of products (not including 190) was obtained.

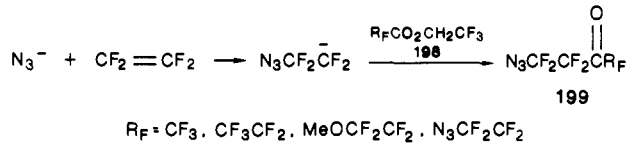


As before, under nitrogen, a regioisomer of 190 (viz., 192) was obtained in 21% yield. Additionally, methyl (*Z*)-2-azido-3-phenylpropenoate (193) (16%) was isolated. Presumably, under nitrogen, azido radical attack occurs to form the more stable radical 191, which on reaction with more IN_3 would afford 192 (Scheme 9). Vinyl azide 193 was shown not to arise from 192, but it is possible that it was formed from 190 via a diazide

SCHEME 9

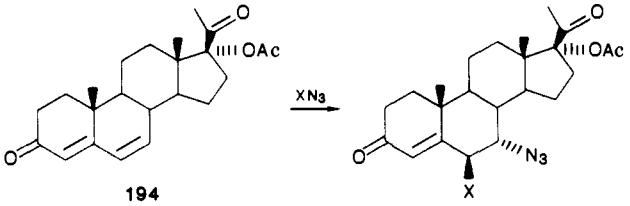


SCHEME 10



intermediate or by loss of a hydrogen atom from **191**.

Another mechanism is indicated for the reaction of conjugated steroidal enone **194** with halogen azides.[202] Thus, **194** combines with bromine azide or iodine azide to give the corresponding 7α-azido-6β-halogeno 4-en-3-ones **195** or **196**, respectively. The latter could be



194

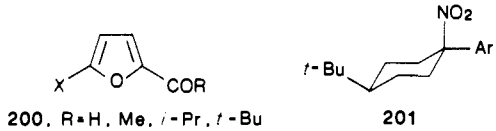
195, X = Br
198, X = I
197, X = OH

isolated but was unstable and easily hydrolyzed to **197**. The regio- and stereochemistry can be explained in terms of initial conjugate addition of azide ion from the less hindered α-face followed by attack of the intermediate azido dienol on positive halogen. Similar results were obtained with other conjugated steroidal enones.

Nucleophilic addition of azide ion to tetrafluoroethylene followed by fluoro ester (cf. **198**) trapping of the generated fluoro carbanions has been utilized as a versatile, one-step synthesis of functionalized fluoro ketones (cf. **199**) (Scheme 10).[203] The latter are formed in 39–88% yield.

H. From Nitro Compounds or Nitrates

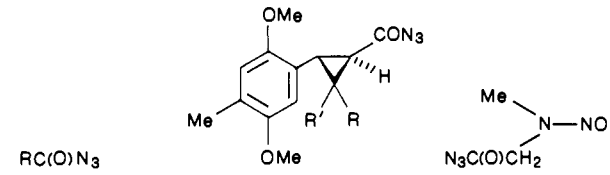
Activated nitro groups can be displaced by azide ion. Thus, the 2-acyl-5-nitrofurans (**200**, X = NO_2) react with NaN_3 in DMSO to give the corresponding unstable azido compounds (**200**, X = N_3).[204] Displacement of the nitro group in the cyclohexane derivative **201** gives a mixture of C-1 azido epimers via an $S_{RN}1$ mechanism.[205] The preparation of azide polymers by reaction of poly(vinyl nitrate) with sodium or lithium azide has been examined.[31]



200, R = H, Me, *i*-Pr, *t*-Bu **201**

I. From Amines or Hydrazines

Nitrosation of hydrazines is a standard route to azides[206] and in this regard, nitrous acid,[207,208] nitrosyl chloride,[209] and organic nitrites[210] have been previously employed. Recently, aryl, carbonyl, and sulfonyl hydrazines were reacted with N_2O_4 at low temperature to give the corresponding azides in excellent yield (84–95%).[211] Nitrous acid is by far the most common reagent and has been recently utilized for the preparation of phosphinoacyl azides (cf. **202** and **203**),[212] cyclopropylacyl azides (**204**),[213] long-chain alkoxyacyl azides,[18] and the *N*-nitrosoacyl azide **205**.[214] A new approach is the use of clay-supported ferric nitrate (clayfen);[215] conditions are mild and yields are good to excellent.

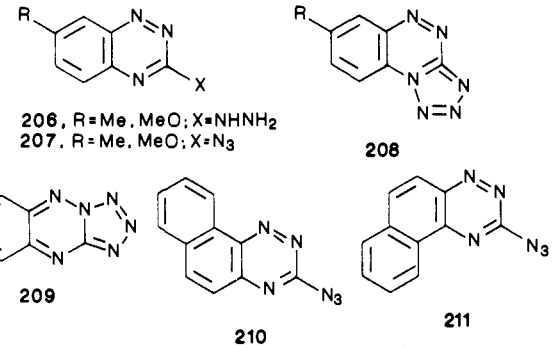


202, R = $Ph_2P(O)C_6H_4$
203, R = $Ph_2P(O)CH_2$

204, R = Me; R' = H
R = H; R' = Me

205

In line with previous studies it was shown that azides (cf. **207**) were not the principal products from treatment of 3-hydrazinobenzo-*as*-triazines containing electron donors at the 7-position (e.g., Me, MeO) (cf. **206**) with nitrous acid; instead cyclization to an angular tetrazole (**208**) (with 7-Me) or linear tetrazole (**209**) (with 7-MeO) occurred.[216] In contrast, the unstable azidonaphtho-*as*-triazines **210** and **211** could be isolated in crude form; both cyclized on standing or attempted recrystallization, respectively[116] (see section VI.B.4).



206, R = Me, MeO; X = $NHNH_2$
207, R = Me, MeO; X = N_3

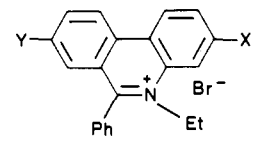
208

209

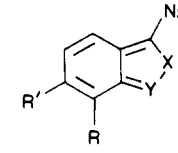
210

211

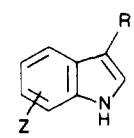
Diazotization of amines (aromatic and heteroaromatic) and subsequent treatment with sodium azide have been routinely employed for azide synthesis.[206] Recently, this approach has been used for the preparation of photoaffinity-labeling analogues of both substance P, and undecapeptide neurotransmitter,[217] and the β-adrenergic antagonist carazolol.[218] A variety of heteroaromatic azides has been thus prepared, including ethidium bromide (**212**) analogues **213**–**218**,[219] unstable azidoindazole **219**, azido-2,1-benzisothiazoles **220** and **221**,[220] and azidoindoles **222** and **223**.[221,222] The azidoanthraquinone analogues **224**[223] are similarly obtained.



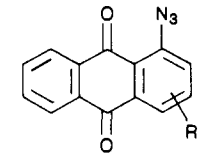
212, X = Y = NH_2
213, X = N_3; Y = NHCOMe
214, X = N_3; Y = NH_2
215, X = NH_2; Y = N_3
216, X = N_3; Y = H
217, X = H; Y = N_3
218, X = Y = N_3



219, X = NPh; Y = N; R = R^1 = H
220, X = S; Y = N; R = CF_3; R^1 = H
221, X = S; Y = N; R = H; R^1 = Br



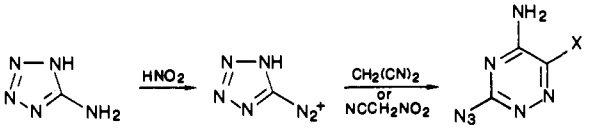
222, R = CH_2CO_2H; Z = 4-N_3
223, R = H; Z = 4-, 5-, 6-N_3
R = $CH_2CH(NH_2)CO_2H$; Z = 6-N_3



224, R = various groups

The yields of the azidoindoles **223** (from their amino congeners) were drastically improved by the simple expedient of substituting aqueous 80% acetic acid for the dilute HCl or H_2SO_4 commonly employed in such diazotizations.

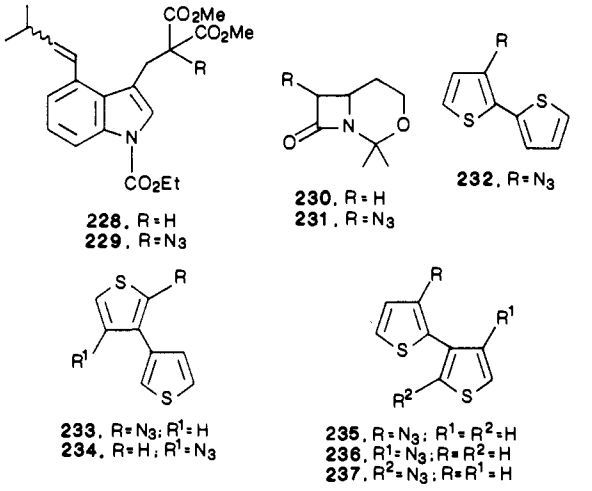
Interestingly, diazotization of aminotetrazole (**225**) and subsequent treatment with malononitrile or nitroacetonitrile gave the azidotriazines **226** and **227**, respectively.[224]



225 **226**, X = CN; **227**, X = NO_2

J. By Azide Transfer

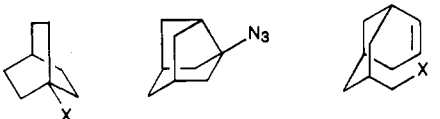
The 3,4-disubstituted azido indole **229** was prepared in 62% yield by deprotonation of the malonate derivative **228** with sodium hydride and subsequent reaction with tosyl azide.[225,226] A similar process was used to



228, R = H; **229**, R = N_3; **230**, R = H; **231**, R = N_3; **232**, R = N_3; **233**, R = N_3; R^1 = H; **234**, R = H; R^1 = N_3; **235**, R = N_3; R^1 = R^2 = H; **236**, R^1 = N_3; R = R^2 = H; **237**, R^2 = N_3; R = R^1 = H

yield the azido β-lactam **231** (69% from **230**, LDA as base).[227] Metal–halogen exchange followed by treatment with tosyl azide and subsequent low-temperature fragmentation of the resultant triazenyllithium salts with sodium pyrophosphate gave the bithienyl azides **232–237** from the corresponding bromo compounds.[228] The 3-azido derivatives **232** and **234–236** were obtained in good yield and were quite stable, but the 2-azido species **233** and **237**, obtained in 30–40% yield, were somewhat unstable at room temperature. Accordingly, the sodium pyrophosphate induced fragmentation of the triazene salts of the latter to the azides **233** and **237** was conducted at considerably lower temperature (−70 °C) than that employed for the preparation of the 3-azido analogues (5 °C).[228]

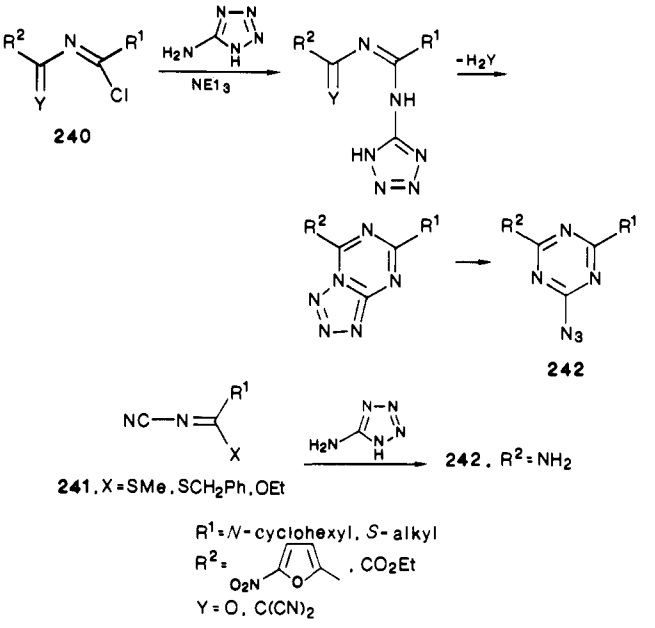
1-Azidobicyclo[2.2.2]octane (**238**, X = N_3) was prepared in 83% yield from the corresponding amine (**238**, X = NH_2) by reaction with sodium hydride and then tosyl azide[229] using Quast and Eckert's procedure.[230]



238 **239** **101**

3-Azidonoradamantane (**239**) was similarly prepared in

SCHEME 11



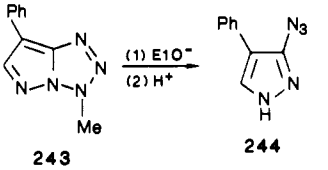
240 **241**, X = SMe, SCH_2Ph, OEt **242**, R^2 = NH_2 **242**

92% yield.[229] With a 1.6-fold excess of *n*-butyllithium and a 1.3-fold excess of tosyl azide, amine **101** (X = NH_2) was converted to the corresponding azide in only 28% yield.[117] Using a large excess of sodium hydride (Quast and Eckert's procedure[230]) increased the yield to 87%. 9-Triptycyl azides have been prepared similarly.[231] Since this review was prepared, Evans[738] has developed an efficient, stereoselective electrophilic azidation of basic enolates.

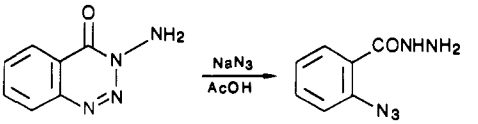
K. By Fragmentation of Heterocycles

As described previously (see section II.I) tetrazoles can result from diazotization of heterocyclic hydrazines, presumably via azide intermediacy. The reverse process (viz., tetrazole → azide) can sometimes be realized (cf. Scheme 11).[232]

The demethylated azidopyrazole **244** was prepared in 77% yield by treatment of the pyrazolotetrazole **243** with 3 equiv of sodium ethoxide in ethanol under reflux for 60 h.[233] Treatment of 3-amino-1,2,3-benzotriazin-4(3*H*)-one (**245**) with sodium azide in acetic acid gave an excellent yield of the hitherto unknown *o*-azidobenzohydrazide (**246**).[234]



243 **244**



245 **246**

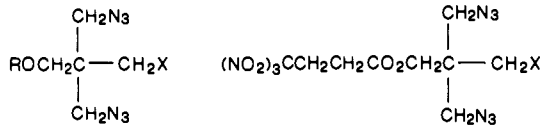
L. From Preformed Azides

One of the most exciting aspects of recent azide chemistry has been the extent to which it is possible to modify other functional groups without affecting the azide moiety. Much of the work in this area has been

developed by carbohydrate chemists (see section V). The reader is cautioned that owing to the explosive nature of some azides such transformations should be attempted on a small scale with appropriate safety precautions, especially where the generality of the process has not been assessed.

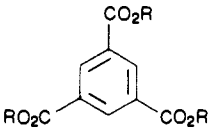
1. Alcohols and Derivatives

Various alcohol modifications have been performed in the presence of the azido group. Thus, the di- and triazides **247** and **248**, respectively, react with nitric acid



247, X = ONO_2; R = H
248, X = N_3; R = H
249, X = R = ONO_2
250, X = N_3; R = ONO_2

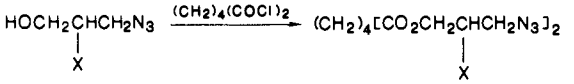
251, X = ONO_2
252, X = N_3



253, R = $CH_2C(CH_2N_3)_3$

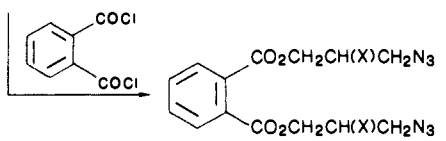
to give the corresponding di- and mononitrates **249** and **250**, respectively.[235] The utility of **247** and **248** for the preparation of energetic esters has also been explored. Thus, both reacted with 4,4,4-trinitrobutyryl chloride to form the corresponding esters **251** and **252**, respectively. Additionally, triester **253** was obtained from **248** and 1,3,5-benzenetricarboxylic acid chloride.[235]

Similar results were obtained by reaction of diazido alcohols **254** and **255** with adipoyl chloride or phthaloyl chloride; the resultant tetraazides **256–259**, respectively, were thermally stable and relatively insensitive to impact.[236]



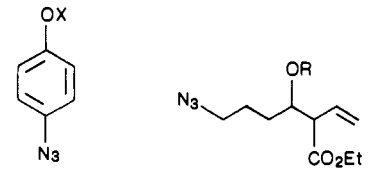
254, X = N_3
255, X = CH_2N_3

258, X = N_3
257, X = CH_2N_3



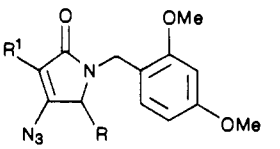
258, X = N_3
259, X = CH_2N_3

4-Azidophenyl methacrylate (**261**) was prepared in an analogous fashion by treatment of 4-azidophenol (**260**) with methacrylic acid chloride.[219] Copolymerization of **261** with styrene and ((*tert*-butoxycarbonyl)-amino)ethyl methacrylate was examined. Acetylation can also be performed in the presence of the azido group; acetates **264**[237] and **265**[238] were prepared in high yield from the corresponding alcohols **262** and **263**. The ester **266** was similarly synthesized from **263** (prepared from the lactone and 2,4-dimethoxybenzylamine) and 4-nitrobenzoyl chloride in 94% yield.[238] Acid-catalyzed reaction of **263** with ethanethiol gave the dithioether **267** in 50% yield.[238] Displacement from alkyl halides can also occur. Thus, azido alcohol **254** reacts with $[FC(NO_2)_2CH_2]_2NCH_2Br$ to give the corresponding



260, X = H
261, X = COC(Me)=CH_2

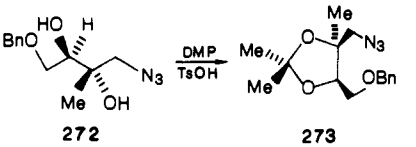
262, R = H
264, R = Ac



263, R = OH; R^1 = Cl
265, R = OAc; R^1 = Cl
266, R = 4-$NO_2C_6H_4CO_2$; R^1 = Cl
267, R = R^1 = EtS

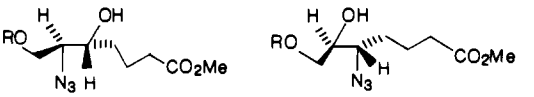
ether,[19] and a carbamate results from treatment of $HOCH(CH_2N_3)_2$ with $(NO_2)_3CCH_2CH_2NCO$.[19]

Silylation of a primary alcohol in the presence of a secondary alcohol (and the azide moiety) was effected by allowing the inseparable, isomeric mixture (**268**, **269**) to react with *tert*-butyldiphenylsilyl chloride in DMAP/Et_3N; a separable 7:1 mixture of **270** and **271**, respectively, resulted.[131]



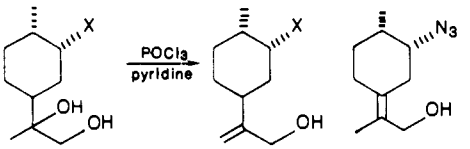
272

273



268, **269**, R = H
270, **271**, R = *t*-BDPSi

An acetonide (**273**) was obtained by protection of diol **272** with DMP and a catalytic amount of *p*-toluenesulfonic acid.[239] Dehydration of the diol **274** with $POCl_3$/pyridine occurred to form the less substituted double bond (as in **275**); none of **276** was observed.[240] Only resinous material resulted when the same transformation was attempted with the amino diol **277**;[240] the utility of the azido group as a masked amine (see section III.A) is thus manifest.

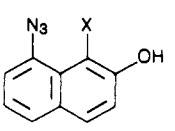


274, X = N_3
277, X = NH_2

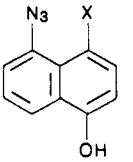
275, X = N_3

276

In a reaction not directly involving the OH group, azidonaphthols (cf. **278** and **279**) couple with aryldiazonium chlorides to provide the corresponding azo products **280** and **281**, respectively.[241]

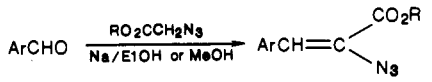


278, X = H
280, X = ArN=N



279, X = H
281, X = N=NC_6H_4Me-4

SCHEME 12

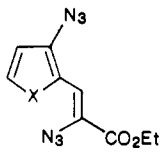


2. Carbonyl Compounds

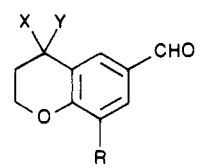
(a) Carboxylic Acids and Derivatives. One of the most widely employed transformations with azido carboxylates is the preparation of vinyl azides by base-induced condensation with aryl or heteroaryl aldehydes (Scheme 12).[71,72,242-246]

The method has been recently utilized for the preparation of azido acrylate precursors to indoles,[242a,243,244a,b] isoquinolines,[242] thienopyrroles,[245] azaannulenes,[246] and related heterocycles[242a,243] (see section VI). The interesting diazido furan **282** and thiophene **283** derivatives (precursors to furo- and thienopyridazines and (from **283** only) an isothiazole) have been prepared similarly.[71,72]

In general, product stereochemistry about the double bond is not known but is assumed to be *Z*.[242a] Various other bases (inter alia, Na_2CO_3, KOH, or NaOH under phase-transfer conditions) gave unsatisfactory results, as did an attempt at acid-catalyzed condensation using $TiCl_4$. Extension to azidoacetonitrile and azidonitromethane was also unsuccessful. Condensation of ethyl azidoacetate with formylchromanones (cf. **284**) did not occur; the hemiacetals **285** were instead obtained.[244a] Protection of the keto group as the dioxolane (**286**) permitted efficient condensation.[244a]



282, X = O
283, X = S



284, X, Y = O
285, X = OH; Y = OMe
286, X,Y = —OCH_2CH_2O—

However, yields for the condensation are generally good[242-246] and it has been reported[242a] that the best results accrue from reaction temperatures between −10 and −15 °C using 4 equiv of ethyl azidoacetate.

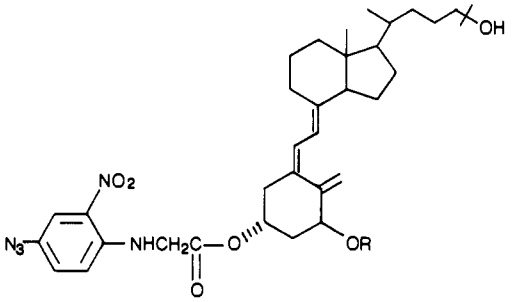
The acidity of hydrogens α to the ester function has also been utilized in the preparation of cyclopropyl azido carboxylates. Thus, treatment of the bromo azido ester **287** with potassium carbonate/NMP at 20 °C for

287, R = Me
288, R = $(TMS)CH_2CH_2$

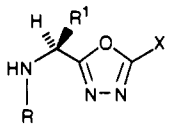
289, R = Me
290, R = $(TMS)CH_2CH_2$
291, R = H

64 h gave a modest yield of the azidocyclopropane **289**.[49] A modification of the procedure using the (trimethylsilyl)ethyl ester **288** and DBU/DMF provided **290**.[50] The latter could be converted to the parent carboxylic acid **291** by deprotection with tetrabutylammonium fluoride.[50] Base-catalyzed hydrolysis of analogues of **289** to the corresponding carboxylic acids under mild conditions has also been reported.[246a] Deprotection of the *tert*-butyldimethylsilyl ether **292** to the corresponding alcohol **293** has been accomplished by using 5% HF.[247]

Removal of the Boc group in **294** with trifluoroacetic acid gave the crystalline amino acid derivatives **295**.[115] Attempted deprotection of **296** with HBr/acetic acid led to simultaneous azide reduction to give **297**[115] (see section III.A).

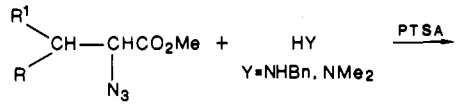


292, R = $SiMe_2$-*t*-Bu
293, R = H

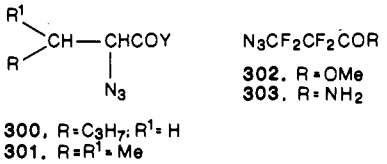


294, R = *t*-Boc; X = N_3
295, R = H; X = N_3
296, R = CBz; X = N_3
297, R = H, X = $NH_2 \cdot 2HBr$
R^1 = various groups

Nucleophilic attack at the ester function has been reported.[248] Thus, azido esters **298** and **299** react with benzylamine and dimethylamine in the presence of a catalytic amount of *p*-toluenesulfonic acid to give azido amides **300** and **301**, respectively,[248] and fluoro azide **302**



298, R = C_3H_7; R^1 = H
299, R = R^1 = Me

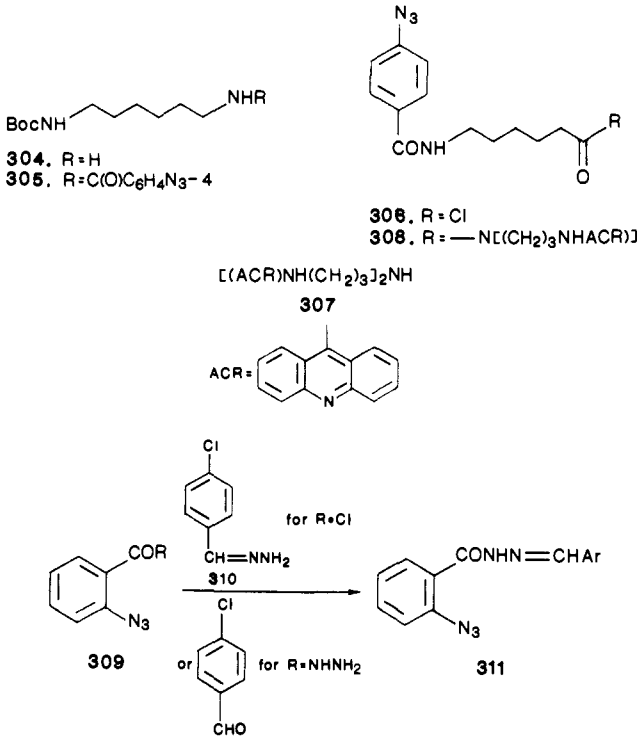


300, R = C_3H_7; R^1 = H
301, R = R^1 = Me

302, R = OMe
303, R = NH_2

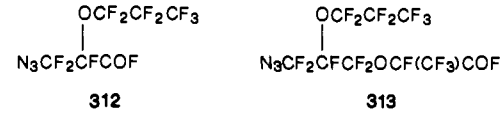
was converted to amide **303** in 84% yield by treatment with ammonia.[249] More commonly, the carboxylic acid has been activated toward nucleophilic attack by conversion to the acid chloride or by use of activating agents such as dicyclohexylcarbodiimide (DCC) or trifluoroacetic anhydride. Thus, 4-azidobenzoyl chloride reacts with primary amine **304** to form amido species **305**.[250] The Boc group in the latter could be removed subsequently with HCl.[250] Diamide **308** was similarly prepared from **306** and **307**.[250]

2-Azidobenzoyl chloride (**309**, R = Cl) combines with hydrazone **310** to provide benzylidene derivative **311**, which can also be prepared from 2-azidobenzohydrazide (**309**, R = $NHNH_2$).[234] Attempts to synthesize the latter by treatment of methyl *o*-azidobenzoate (**309**, R = OMe) with hydrazine hydrate[251] or hydrolysis of **311**[252] were unsuccessful.

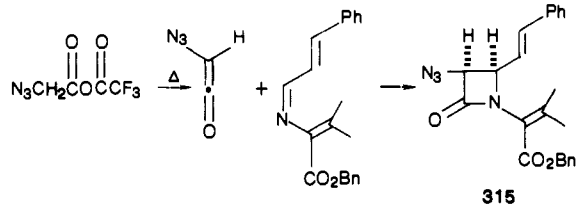


(Azidodinitrophenyl)glycine derivative **292** results from the reaction of the corresponding 3β-alcohol with *N*-(4-azido-2-nitrophenyl)glycine and DCC in the presence of DMAP.[247]

Recently, acid fluoride **312** was prepared from the carboxylic acid and sulfur tetrafluoride.[249] Reaction of the analogous acid fluoride **313** with methanol gave the corresponding ester.[249]



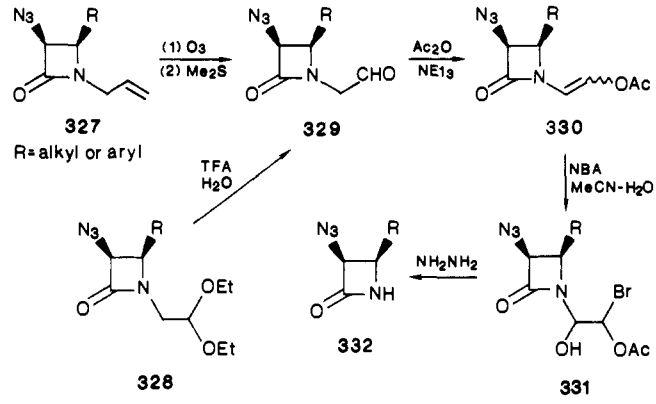
Similar approaches have been utilized for the preparation of β-lactams from azido carboxylic acid derivatives and imines. Thus, the mixed anhydride formed from azidoacetic acid and trifluoroacetic anhydride added to the imine **314** in the presence of triethylamine



316. R = 4-MeOC6H4; R1 = Ph
317. R = H; R1 = Ph
318. R = 2,4-(MeO)2C6H3CH2; R1 = Ph
319. R = 4-MeOCH2OC6H4; R1 = CH2CH(OEt)2
320. R = 4-HOC6H4; R1 = CH2CH(OEt)2
321. R = 4-MeOCH2OC6H4; R1 = Ph
322. R = CH3CH(OH)CHCO2R2; R1 = Ph; R2 = PNB
323. R = CH3CH(OH)CHCO2R2; R1 = Ph; R2 = Me
324. R = CH3CH(OH)CHCO2R2; R1 = Ph; R2 = Bn
325. R = HOCH2CHCO2Me; R1 = Ph
326. R = CH3C(OH)=CCO2R2; R1 = Ph; R2 = as above

to provide the azetidin-2-one **315**.[253] An analogous

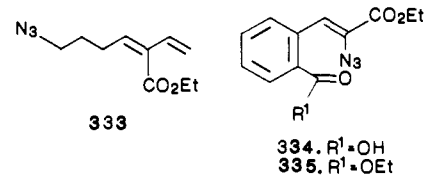
SCHEME 13



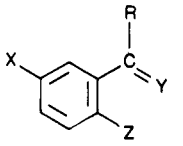
transformation occurs with the imine derived from *p*-anisidine and cinnamaldehyde; **316** is formed in 60% yield.[254] There have been several reports of imines from *p*-anisidine reacting with acid chlorides or anhydrides of azidoacetic acid to give azetidinones, usually with a high degree of cis stereoselectivity.[255,256] Dearylation of **316** to **317** with ceric ammonium nitrate (CAN) occurred in 68% yield under mild conditions.[254] The yield of **317** was substantially better than that from potassium persulfate mediated debenzylation of **318** (<-25%).[254] The dearylation of azidoazetidinones (cf. **319**) with CAN (after treatment of **319** with HCl, MeOH, and $CH(OMe)_3$) had been previously reported[257] and the intermediacy of a phenol (cf. **320**) has been suggested.[254] However, it is apparently not necessary to cleave the methoxymethyl ether prior to oxidation since **317** results in 69% yield from treatment of **321** with CAN.[258] Deprotection of other side chains has also provided **317**. Thus, oxidation of the *cis*-β-lactams **322–325** (prepared from azidoacetyl chloride and the appropriate imines) with Jones reagent gave the β-keto esters **326** and/or **317** depending on how much oxidant was utilized.[259] Similar N-substituted β-lactams (cf. **332**) have been prepared by deprotection of *N*-allyl (cf. **327**) or diethyl acetal (cf. **328**) species[260] in excellent overall yields (Scheme 13).

The azidoacetyl chloride/imine cyclization process has also been applied recently to the preparation of azidoazetidinones bearing a ((methoxycarbonyl)diethylphosphono)methyl group[261] and for proof of imine structure by the preparation of identifiable bicyclic β-lactams.[262]

Other manipulations with azido carboxylic acid derivatives have included conversion of **262** to diene **333** (96% yield, 5 min, 0 °C) by the action of DBU in DME[237] and esterification of **334** with ethanol/HCl to give **335**.[242b]



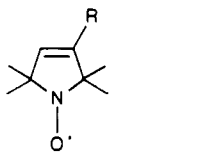
(b) Ketones and Aldehydes. 2-Azidoacetophenone oxime (**337**) was prepared in 45% yield by treatment of 2-azidoacetophenone (**336**) with hydroxylamine.[263] This oxime (**337**) had been previously reported[264] as arising from the reaction of *o*-chloroacetophenone oxime (**338**) with sodium azide. However, the reported melting



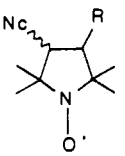
338, X = H; Y = O; Z = N_3; R = Me
337, X = H; Y = NOH; Z = N_3; R = Me
338, X = H; Y = NOH; Z = Cl; R = Me
339, X = Cl; Y = O; Z = N_3; R = Ph
340, X = Cl; Y = NOH; Z = N_3; R = Ph

point was different from that obtained by Boulton,[263] and repetition of the procedure apparently did not provide any azide-containing material.[263] It is thus reasonable to conclude that the current synthesis has afforded authentic material. 2-Azido-5-chlorobenzophenone (**339**) can also be converted to the oxime (**340**) by reaction with hydroxylamine.[263,265]

In a reaction analogous to that performed with azido esters (see section II.L.2a), nitroxide spin labels **341–343** condense (base catalyzed) with *p*-azidobenzaldehyde or *p*-azidoacetophenone to give difunctional spin labels **344–346** in moderate to good yield.[266]

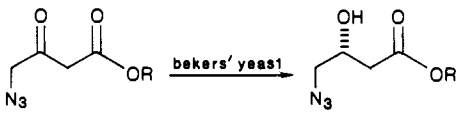


341; R = COMe
343; R = CHO
344; R = COCH=CHC$_6$H$_4$N$_3$-4
346; R = CH=CHCOC$_6$H$_4$N$_3$-4



342, R = COMe
345, R = COCH=CHC$_6$H$_4$N$_3$-4

Bakers' yeast mediated reduction of alkyl 4-azido-3-oxobutyrates (**347**) (prepared by azide displacement from the 4-bromo compounds) gave the corresponding alcohols (**348**) in 70–80% isolated yield. The ee values for **348** were determined by ^{1}H NMR on the *O*-acetyl derivatives in the presence of a chiral europium shift reagent and ranged from 0.8 to approximately 1.0.[267]



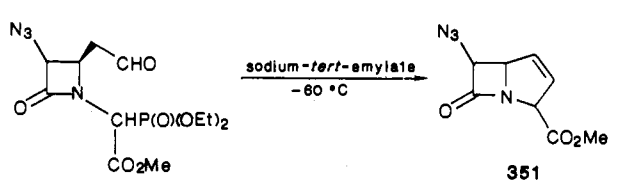
347
R = alkyl

348

Azido alcohol **262** can be prepared from aldehyde **349** by the vinylogous Reformatsky reaction[268] (Scheme 14).[237]

The same alcohol has also been prepared in 91% yield from **349** by the action of $CH_3CH{=}CHCOOEt$/LDA.[269] Subsequent dehydration was effected in high yield.

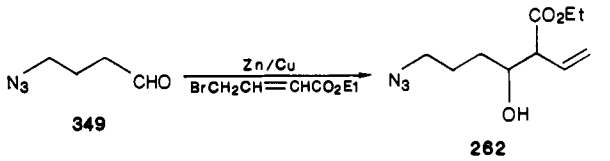
Azidocarbapenem **351** was obtained in low yield (ca. 1%) from **350** via intramolecular Wittig–Horner reaction.[261] The low yield was ascribed to the instability of the 6-azido-1-carbapen-2-em nucleus.[261]



350

351

SCHEME 14

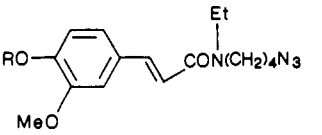


349

262

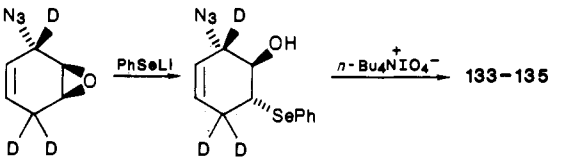
3. Ethers, Epoxides, and Related Species

Debenzylation of **352** with trifluoroacetic acid afforded the corresponding phenol (**353**).[270]



352, R = CH_2Ph
353, R = H

Reaction of epoxide **354** with PhSeLi in THF at room temperature gave a 53% yield of **355**. Subsequent

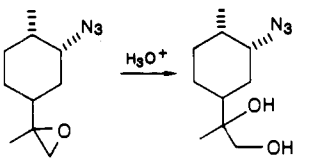


354

355

oxidation of the latter with tetrabutylammonium periodate and selenoxide elimination (6 h at room temperature) gave the same mixture of dienols, in essentially the same product ratios, as from addition of N_3^- to the parent epoxide (cf. **132** → **133–135**, section II.C).[134]

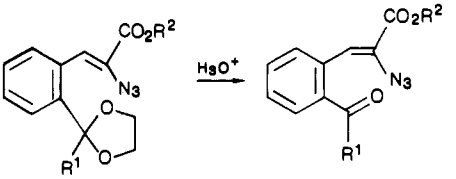
Acid hydrolysis of epoxide **356** gave diol **274** in reasonable yield.[240]



356

274

Hydrolysis of the dioxolane ring in **357** to yield **358** also occurred under acidic conditions.[242b]



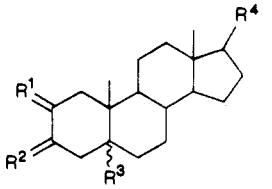
357, $R^1 = R^2 = Me$
$R^1 = H$; $R^2 = Me$

358

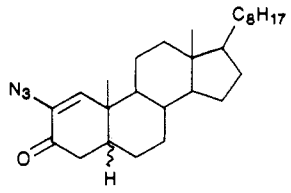
4. Oximes

Steroidal azido oxime **359** can be converted to α,β-unsaturated ketone **360** in modest yield by the action of PPA at 120 °C or P_2O_5 in refluxing benzene.[271] In the latter case the ring-cleaved dicyano compound **361** is the major product.[271] In contrast, the side-chain α-azido oximes **362** and **363** reacted with $POCl_3$ at 70 °C to give the nitriles **364** and **365** (20% and 32%,

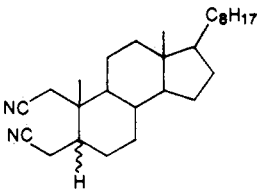
respectively) and the Beckmann fragmentation products **366** and **367** (45% and 47%, respectively).[271]



359, R^1 = α-N_3; R^2 = (*E*)-NOH; R^3 = H; R^4 = C_8H_{17}
362, R^1 = H_2; R^2 = β-OAc; R^3 = α-H; R^4 = C(=NOH)CH_2N_3
363, R^1 = H_2; R^2 = β-OAc; R^3 = Δ⁵; R^4 = C(=NOH)CH_2N_3
364, R^1 = H_2; R^2 = β-OAc; R^3 = α-H; R^4 = CN
365, R^1 = H_2; R^2 = β-OAc; R^3 = Δ⁵; R^4 = CN
366, R^1 = H_2; R^2 = β-OAc; R^3 = α-H; R^4 = $NHCOCH_2N_3$
367, R^1 = H_2; R^2 = β-OAc; R^3 = Δ⁵; R^4 = $NHCOCH_2N_3$



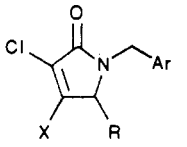
360



361

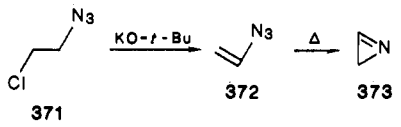
5. Halides

The 4-nitrobenzoate **266** was converted to the dichloro species **368** by treatment with dry HCl. The latter was not isolated but was reacted directly with benzenethiol to give **369** in 84% yield. The azido compound **369** could also be prepared from **370** by halide displacement with azide ion.[238]



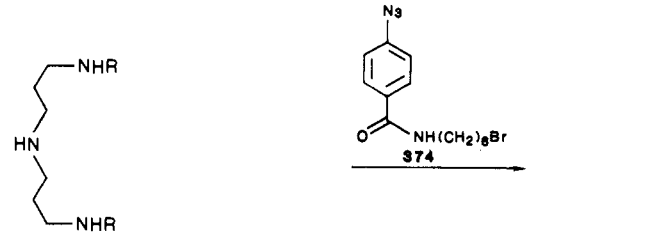
266, R = OPNB; X = N_3
368, R = Cl; X = N_3
369, R = SPh; X = N_3
370, R = SPh; X = Cl

Halide elimination (to form an alkene) in the presence of the azido functionality has been reported for **371**. Thus, treatment of **371** with potassium *tert*-butoxide at 80 °C and 0.1 Torr gave vinyl azide **372**, which was transformed to Δ^1-azirine (**373**) at 400 °C and 0.1 Torr. The whole process, including preparation of the chloro azide **371**, could be performed as a gas–solid phase multistep sequence by means of flash vacuum pyrolysis.[272]

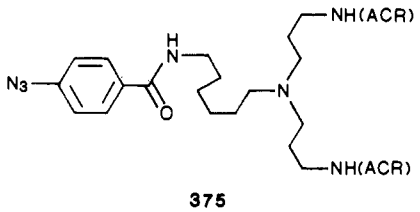


371 **372** **373**

The secondary amine **307** displaces the bromine from **374** to yield **375**. The latter, one of a series of potential photoaffinity-labeling reagents, could also be prepared by reaction of **376** with **374** followed by HCl deprotection and subsequent reaction with 9-phenoxyacridine.[250]

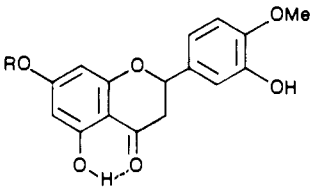


307, R = ACR(9-phenoxyacridinyl)
376, R = *t*-Boc



375

Alkylation of hesperetin (**377**) with bromo compound **11** occurred under basic conditions (potassium carbonate) only at the 7-hydroxy group. The yield of the alkylation product (**378**) was unusually dependent on the time and temperature of the reaction, apparently due to its reversion to **377** after extended periods. A careful study of the effects of base, solvent, temperature, and time upon the reaction led to optimization of the process (85% yield) using potassium carbonate in *N*-methylpyrrolidone (solvent) and $ICH_2CH_2CH(N_3)$-COOMe at 35 °C. A similar reaction occurred with 4-hydroxyacetophenone.[49]



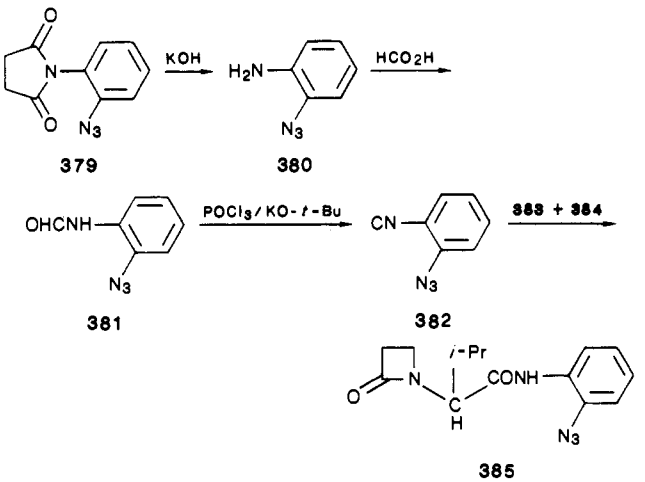
377, R = H
378, R = $CH_2CH_2CH(N_3)CO_2Me$

6. Amines and Derivatives

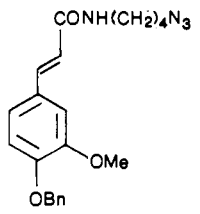
2-Azidoaniline (**380**) (prepared by KOH desuccinylation of **379**) can be converted to the β-lactam-containing azido species **385** via N-formylation (to **381**), dehydration of the latter with $POCl_3$/potassium *tert*-butoxide (to **382**), and subsequent condensation of **382** with β-alanine (**383**) and isobutyraldehyde (**384**) in methanol (Scheme 15).[273]

Alkylation of amines (in the presence of the azido group) has been reported. Thus, N-alkylation of **386** with EtBr/NaOH occurs under phase-transfer conditions to yield **352**.[270] Many similar processes have been described.

SCHEME 15



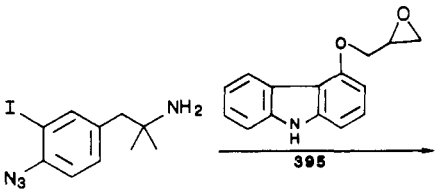
379 **380** **381** **382** **385**



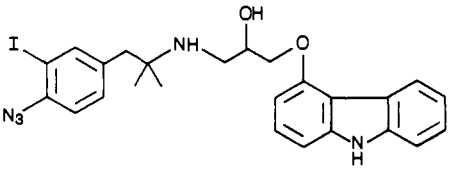
386

The synthesis of the potential bisintercalating photoaffinity-labeling reagent **393** was achieved in three steps from the thiourea **387** (Scheme 16).[250] Attempted preparation of the key intermediate **392** by reaction of the carbodiimide **389** with **390** did not succeed. It was surmised that the addition of amines to carbodiimides to give guanidines was limited to carbodiimides containing at least one phenyl group.[250]

The β-adrenergic photoaffinity ligand **396** was prepared in low yield from amino azide **394** and epoxide **395** (7 days at 65 °C).[218]

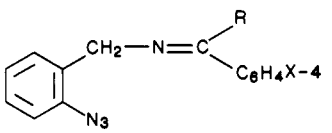


394 395



396

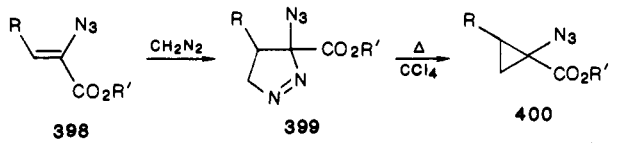
Condensation of *o*-azidobenzylamine with benzaldehyde or substituted acetophenones in refluxing benzene or toluene gives the imines **397** in moderate to good yield.[274]



397, R=X=H; R=Me; X=MeO, Me, Cl, NO_2

7. Alkenes and Alkynes

Vinyl azido esters **398a–d** react with excess diazomethane in ether at room temperature to give the corresponding pyrazoline derivatives **399a–d** in >90% yield (except for **398d** → **399d**; 48%). Thermolysis of

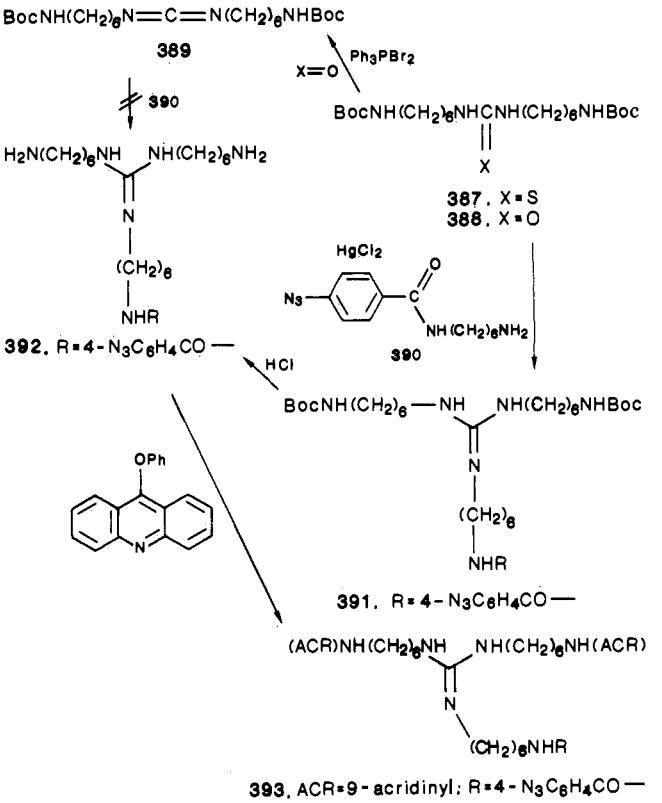


398 **399** **400**

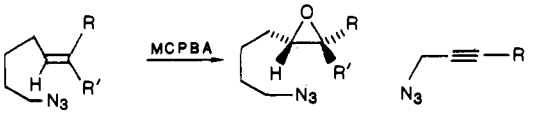
(a) R=H, R'=Et; (b) R=Me, R'=Et; (c) R=Et, R'=Me; (d) R=Ph, R'=Et

399a–d in carbon tetrachloride at 80 °C gave moderate to good yields of 1-azidocyclopropanecarboxylate derivatives **400a–d**.[246a] The latter (**400**) could be hydrolyzed to carboxylic acids (see section II.L.2a) and subsequently hydrogenated to biologically important 1-aminocyclopropanecarboxylic acids (see section III.A).

SCHEME 16



Epoxidation of **401** to give **402** occurs in high yield (>80%) under mild conditions (MCPBA, CH_2Cl_2, 0 °C).[275]



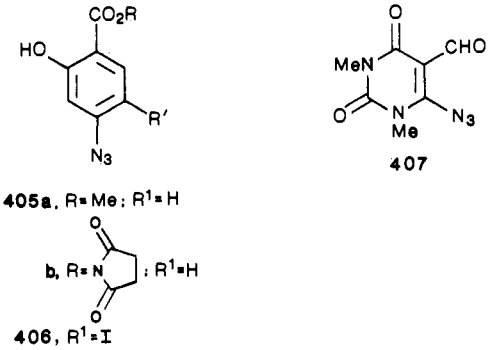
401, R=H; R'=Et
R=Et; R'=H

402 **403**, R=H
404, R=D

Deuteriated alkyne **404** was prepared from its hydrogen analogue (**403**) by treatment with potassium deuterioxide in D_2O at 0–10 °C under ultrasonic irradiation. After 1 h, 77% deuteriation had occurred. After three repetitions, the degree of deuteriation increased to over 99%.[53]

8. Aryl and Heteroaryl Derivatives

Iodination of the azidophenols **405a,b** with Chloramine T/sodium iodide in DMF or acetonitrile gave iodo compounds **406a,b** in 88% and 42% yield, respectively, under mild conditions (1 h at 25 °C). The



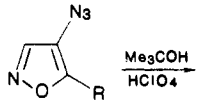
405a, R=Me; R^1=H

406, R^1=I

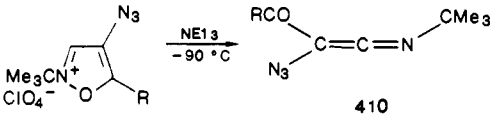
407

latter were of interest as radioiodinated, cleavable, bi-

functional cross-linking reagents.[276] Formylation of 6-azido-1,3-dimethyluracil provided 5-formyl derivative **407**, a useful precursor to fused pyrimidines.[76] Quaternization of **408a,b** with *tert*-butyl alcohol and perchloric acid at 0 °C gave isoxazolium perchlorates **409a,b** in 17% and 50% yield, respectively. The low



408



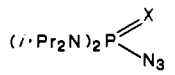
409a, R = Me
b, R = CMe_3

410

yields were reportedly due to extensive azide decomposition during this procedure.[277] Interestingly, treatment of the perchlorates **409a,b** with triethylamine at −90 °C in an IR cell provided evidence for their conversion to azidoketenimines **410a,b**. Decomposition of the latter occurred at −60 °C; the ketenimine group apparently disappeared faster than the azide moiety.[277]

9. Phosphorus Compounds

Bis(diisopropylamino)phosphine azide (**411**) is converted to the oxide (**412**) with ozone (DMSO or H_2O_2 had no effect), to the sulfide (**413**) with sulfur, and to the iminophosphine (**415**) (via the spectroscopically



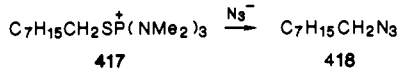
411–416, respectively, X = lone pair, O, S, NN=NPh, NPh, $NSiMe_3$

characterized adduct **414**) with phenyl azide.[93] The silylated iminophosphine **416**, formed from a photochemically induced reaction of **411** and trimethylsilyl azide, was postulated as arising from a [2 + 3] cycloaddition followed by ring opening of the resulting phosphatetrazole.[93]

M. Other Preparations

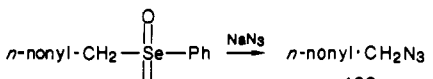
A number of methods for azide synthesis have been developed that do not fall into the sections thus far described.

Thus, the thiaphosphonium salt **417** could be converted to the corresponding azide **418** in 79% yield.[278]



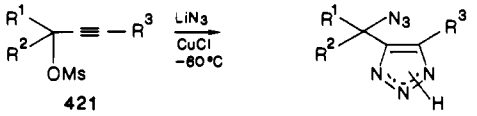
417 **418**

Decyl phenyl selenone (**419**) reacted with sodium azide in DME/water at 20 °C to form decyl azide (**420**) in 93% yield.[279] Facile displacement with other nucleophiles was also observed.



419 **420**

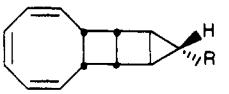
Attempted azide substitution of the propargyl sulfonates **421** gave azido triazoles **422** in low yield (4–24%) rather than the anticipated allenyl azides.[280]



421

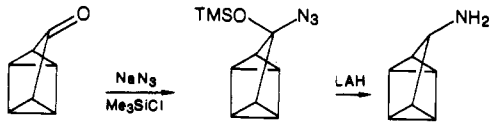
422. R^1 = *t*-Bu, Ph; *m*-$NO_2C_6H_4$
R^2 = H, Ph; R^3 = *t*-Bu, Ph

The unusual tetracyclic azide **424** was prepared in low yield (14%) from the *N*-nitrosourea **423** and lithium azide in methanol.[281] The same reaction was used for other tetracyclic azides.[282]



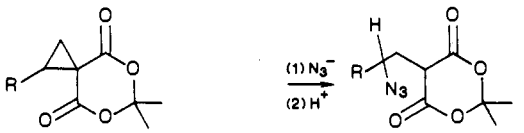
423. R = $N(NO)CONH_2$
424. R = N_3

The quadricyclanone **425** was converted to the azido silyl ether **426** by treatment with sodium azide and trimethylsilyl chloride.[283] Subsequent reduction with lithium aluminum hydride (LAH) gave **427**.



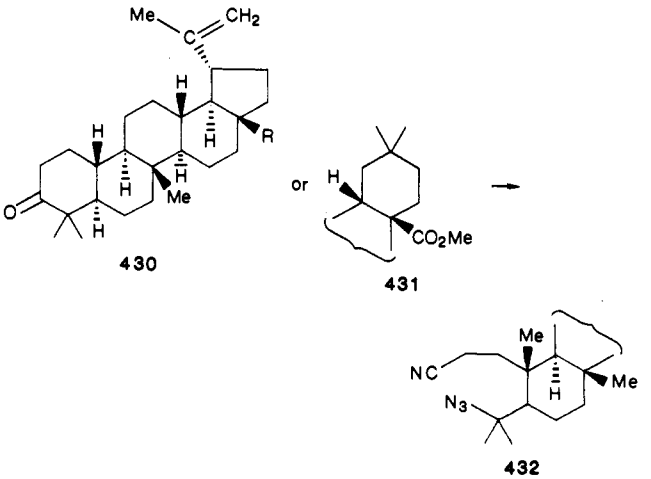
425 **426** **427**

Ring opening of the spirocyclopropane derivatives **428** with azide ion occurs at the soft cyclopropane C-1 position to give azidoalkyl derivatives **429**.[284] With harder nucleophiles (e.g., ^-OR) attack instead occurs at a carbonyl carbon.



428. R = Ph, 4-$MeOC_6H_4$, 4-$NO_2C_6H_4$ **429**

Ring opening was also observed in the reactions of 3-oxopentacyclic triterpenes **430** (R = Me, COOMe) and **431** with excess $HN_3 \cdot BF_3$ etherate to give the cyano azido secopentacyclic triterpenes **432**.[285]



430 **431** **432**

Thermolysis of some arylalkylsulfonyl azides gave the corresponding arylalkyl azides, generally in low yield (Scheme 17).[83]

SCHEME 17

$$ArCH_2CH_2SO_2N_3 \xrightarrow{\Delta} ArCH_2CH_2N_3 + SO_2$$

In a series of papers, Desbene and co-workers have studied the reactions of azide ion with pyrylium and thiopyrylium species.[286,287] Azidopyrans (and congeners) resulted only when the pyrylium ring was hindered; otherwise charge-transfer complexes were obtained. Extension to oxazinium[288] and chromylium[289] species and their subsequent conversions to β-tetrazolo-*trans*-benzal acetophenones and benz[*f*]oxazepins, respectively, has been reported (see section VI.C.1).

III. Reactions

A. Reduction to Amines

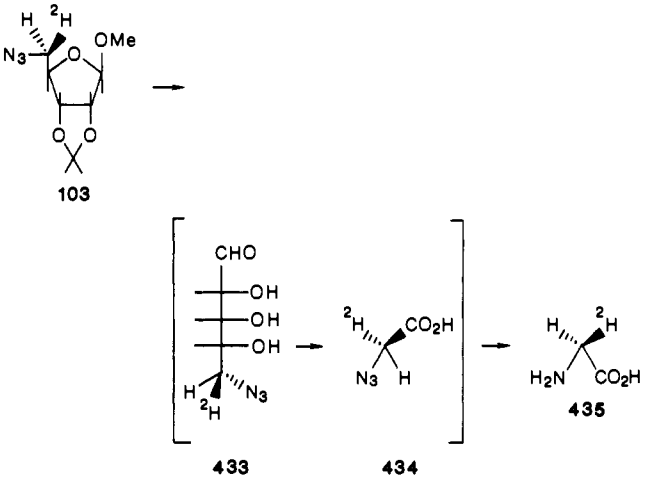
Reduction of the azide moiety to an amine constitutes a synthetically important process, and, since many azides can be prepared with regio- and stereocontrol (see section II), subsequent reduction permits a controlled introduction of the amine function. The reaction is of wide applicability and has been effected with a variety of reagents, including $LiAlH_4$,[290] $NaBH_4$,[291] catalytic hydrogenation,[292] Ph_3P,[292d,293] H_2S,[294] dithiol/NEt_3,[295] Na_2S/NEt_3,[296] diborane,[297] Cr(II),[298] V(II),[299] Ti(III),[300] Mo(III),[301] Bu_3SnH,[302] Zn/HCl,[298a] and HBr/AcOH.[291b] Applications of some of these and others have been described.[303] More recent examples of these and other reagents are included in Table 2.

1. By Hydrogenation

Hydrogenation methods have been very commonly applied to the reduction of azides (entries 1–13). The yields are generally excellent provided that no other reducible groups are present. In this regard some selectivity is possible; e.g., the azido function can be reduced without affecting the O-benzyl group (entries 6, 12, and 13) (the latter is removable under more forcing hydrogenation conditions). Additionally, as shown in Table 2, azide reduction without concomitant reduction of alcohol, ester, carboxylic acid, amine, amide, ketal, sugar, β-lactam, heterocyclic, or some ketone functionalities is possible.

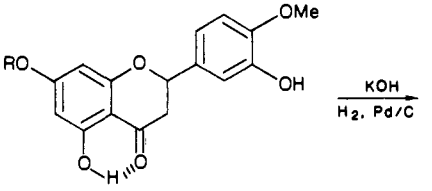
Interestingly, Lindlar's catalyst proved to be the most effective method for reduction of 1,2-diazidodecane (entry 5). Although a 44% yield of the corresponding 1,2-diacetamide was obtained by hydrogenation with Pd/C in acetic acid/acetic anhydride, a variety of other approaches, including the use of sodium borohydride, Pd/C/H_2, propanedithiol, diborane, $LiAlH_4$, and Na/NH_3/MeOH,[305] failed to completely reduce the diazide without polymer formation. Successful reduction of 1,2-diazides to the diamines using Adam's catalyst had been previously reported.[306]

Conversion of the azidoribofuranoside **103** to (*S*)-[2-$^2H_1$]glycine (**435**) (in overall 60% yield) was effected by initial treatment with 5 N H_2SO_4/AcOH to give **433** followed by room-temperature permanganate oxidation (to give **434**) and catalytic reduction (10% Pd/C/AcOH) of the latter (entry 9).[119] In order to minimize epimerization and loss of deuterium, compounds **433** and **434** were not isolated. Overall, this preparation provided an unequivocal confirmation of the absolute configuration of chiral glycine.

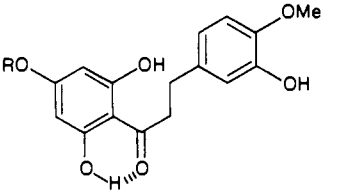


103 → **433** → **434** → **435**

Dissolution of **378** in 10% KOH at room temperature or above followed by low-pressure hydrogenation gave the ring-opened amino acid **436** as major product, contaminated with other products, including **437**. However, at ice bath temperature, nearly quantitative conversion to **436** occurred[49] (entry 11).



378. R = $(CH_2)_2CH(N_3)CO_2Me$



436. R = $(CH_2)_2CH(\overset{+}{N}H_3)CO_2^-$
437. R = H

Catalytic transfer hydrogenation, largely introduced by Braude,[309] involves the use of a hydrogen donor, usually cyclohexene,[310] in place of hydrogen gas. However, when this process has been used, reduction of alkyl azides has given variable results. In contrast, the recent use of ammonium formate as the hydrogen donor has permitted clean reduction of azides to amines (entry 13).[308] The yields were excellent though generally slightly poorer than for the corresponding reductions with hydrogen gas (entry 12).[308] However, the greater safety of the procedure is manifest.

Reduction of some 15-azido steroids (prepared in situ) with hydrazine/Raney nickel gave the corresponding amines, which were isolated as the acetamido derivatives by treatment with pyridine/Ac_2O (entry 14).[130] Overall, the process was used to convert steroidal 14,15-epoxides to 14-hydroxy-15-acetamido species in reasonable yields without isolation of the intermediates.

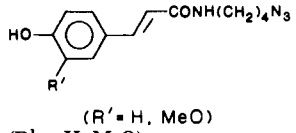
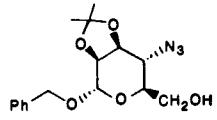
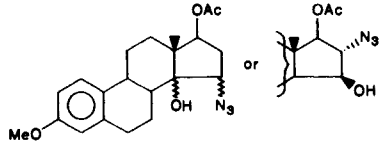
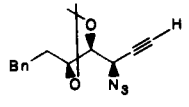
2. By Lithium Aluminum Hydride

Lithium aluminum hydride (LAH) effectively reduces azido species to the corresponding amines (entries 15–22). The reagent has been widely employed for examples where its lack of selectivity is unimportant.

Concomitant azide and epoxide reduction with LAH converted the epoxy azides **157** and **158** to the amino

TABLE 2. Reduction of Azides to Amines

$RN_3 \rightarrow RNH_2$

entry	RN_3	reductant	conditions[a]	% yield	ref
1	**348**, R = H	H_2/PtO_2	AcOH		267
2	**108**	H_2/PtO_2	toluene	97.8 exo (from presumed exo azide) 97.4 endo (from presumed endo azide)	123
3	$NaO_2CCH(N_3)CH_2CH_2N(Me)Ad$ (Ad = adamantyl)	H_2/PtO_2	EtOH/MeOH, rt, 690 kPa, 3 days	83	304
4	 (R′ = H, MeO) (R^1 = H, MeO)	H_2/Lindlar	EtOH, rt, 2 h	95–97	270
5	$C_8H_{17}CH(N_3)CH_2N_3$	H_2/Lindlar		73 (other methods, including $Pd/C/H_2$, unsuccessful)	175
6		H_2/Pd black	MeOH, 4 h	quantitative	307
7	*threo*- or *erythro*-**107**	$H_2/Pd/C$	EtOH	>80	122
8	3′-azido-2′,3′-dideoxycytidine or 3′-azido-2′,3′-dideoxyuridine	$H_2/Pd/C$	EtOH, 1.5 h, rt	46–65	112
9	**103**	$H_2/Pd/C$	AcOH	>60 (2 steps)	119
10	**385**	$H_2/Pd/C$	MeOH, 1 h, 20 °C	90	273
11	**378**	$H_2/Pd/C$	10% KOH, 0 °C	nearly quantitative (product **436**)	49
12	alkyl azide (alkyl = hexyl, $HOCH_2C(Me)(Pr)CH_2CH_2$, 2-octyl, $H(C_2H_4O)_n$, $PhCH_2(C_2H_4O)_n$ [n = 3–6]	$H_2/Pd/C$	MeOH, rt, 10–15 h	88–94	308
13	same as above	$HCO_2NH_4/Pd/C$	MeOH	74–93 (lower yields than entry 12, but avoids use of H_2 gas)	308
14		hydrazine hydrate/ Raney Ni	EtOH, 5 min, reflux	32–68 (as acetamido derivative)	130
15	**157**, **158**, R = n-C_6H_{13}	LAH			157
16	**98**	LAH	THF, reflux, 6 h	quantitative	114
17	**121** + **122**	LAH			129
18		LAH	ether, 0 °C	76 (after *N*-Boc protection)	311
19	**94**, R = (*R*)- or (*S*)-N_3	LAH			113

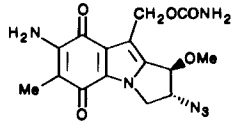
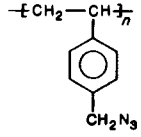
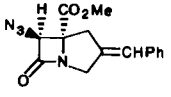
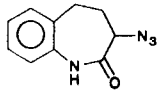
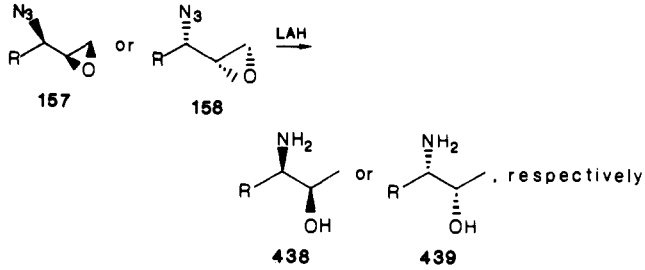
20	**3**, exo or endo	LAH	ether, 30–55 °C, 4.5 h (endo → endo amine only; exo → 4:1 exo:endo amine)	32	28
21	**274**, **275**	LAH	ether, 30 °C, 3 h	70–80	240
22	**85**, **89**	LAH	THF, 60 °C, overnight	67–77	108
23	alkyl, aryl, arylsulfonyl	$NaBH_4$	H_2O, toluene, PTC 1–6 h, rt, Ar or $ArSO_2$ 16 h, 80 °C, alkyl (can be used as a one-pot halide to amine conversion)	79–92	38
24		1. Ph_3P 2. pyridine, aq NH_3	rt, 36 h	~30 (as *N*-acetyl)	74
25	**105**	1. Ph_3P 2. NH_3	1. CH_2Cl_2, 0 °C to rt, 4 h 2. MeOH, 40 h, 0–5 °C	96 (more consistent yields than with H_2/Pd/C)	121
26		1. Ph_3P 2. NaOH	60 °C, MeOH	50	Cohen, H. L. *J. Polym. Sci., Polym. Chem. Ed.* **1985**, *23*, 1671
27	**440** + **441**, X = N_3	1. Ph_3P 2. H_2O/HCl	1. pentane, 20 h, rt 2. 1 h, rt		125
28	**442**, **443**	Ph_3P	H_2O, THF, rt, 18 h	80–85	275
29	alkyl, cycloalkyl, 4-nitrophenyl	Ph_3P/H_2O	rt, 6 h (longer for hindered)	62–95 (thioether, alkene, ester, nitro, epoxide, ketal, alkyne all unaffected)	293c, 315
30	2,4,6-$(NO_2)_3$-3,5-Cl_2phenyl	1. Ph_3P 2. CF_3CO_2H, MeOH			316
31	alkyl, aralkyl, alkenyl	1. $(EtO)_3P$ 2. HCl	rt	0–80 (low yields with steric hindrance) [alkyne, alkene, ester unaffected]	37
32	**322**	H_2S/NEt_3	CH_2Cl_2, 0 °C, 1.5 h	68.5 (isolated as the phenoxyacetamido derivative)	259
33		H_2S/NEt_3	CH_2Cl_2, 0 °C	75 (isolated as the phenoxyacetamido derivative)	262
34	**56**	$Na_2S_2O_4$	90–100 °C, 7 h	33	74
35	**448**	$Na_2S_2O_4$			318
36	**273**	Na/NH_3		60 (as Boc derivative **451**) [benzyl ether also cleaved]	239
37	**452–454**	Me_2NH, Et_3N, or $MeNH_2$	25% aqueous solution, 40–50 °C, 3–5 h	82 (ester in **454** converted to amide)	320
38	2-nitro-3-azidopyridine	NaOH, RONa, KCN, or $NaSC_6H_4Me$-4	proton donor solvents, rt	~25	322

TABLE 2 (Continued)

entry	RN_3	reductant	conditions[a]	% yield	ref
39	aryl, *n*-hexyl or benzoyl	$KHFe(CO)_4$	CO, EtOH, rt, 12 h (benzoyl azide → ethyl phenyl carbamate at rt and benzamide at −40 °C)	70–100 (aryl halide, methoxy unaffected)	323
40		$NaH_2PO_2/Pd/C$	rt → 50–65 °C (ketone, alkene, *N*-oxide, *O*-benzyl, aryl chloride, benzyl chloride, epoxide all potentially reducible)	73 (ester, cyclic ketone, amide, alkyl chloride, nitrile unaffected)	324
41	aryl, benzylic, *n*-butyl, cyclohexyl, Ph_3C, ArCO, $ArSO_2$	NaTeH	$EtOH/Et_2O$, rt, 15 min	55–100 (alkene, alkyne, carbonyl, carboxyl, amide, ester, nitrile, haloaryl, haloalkyl, sulfone unaffected)	325
42	aryl	$HSCH_2CO_2H/NEt_3$	EtOH, 50–60 °C	89–100 (nitro, methoxy, chloro unaffected)	326
43	MeN_3, $HOCH_2CH_2N_3$	$(n\text{-}Bu_4)_3[Mo_2Fe_6S_8(SPh)_9]$	MeOH, THF or H_2O, resp		327
44	$PhCH{=}C(N_3)CO_2Me$	Hg/Pt or graphite cathodes + electrons		almost quantitative with careful addition of H^+ donors	328
45	α-azidostyrene	Hg electrode + electrons, Ac_2O		reasonable yields of a mixture of N-acylated enamines	329
46	PhN_3	$Fe_2(CO)_9$	CH_3CN/H_2O, 50 °C	mix of aniline (67) and diphenylurea (23)	331
47	ArN_3	$RhCl_3/CO$	150 °C, 20 kg cm^{-2}, 4 h	26–70 (chloro and nitro unaffected)	332
48	ArN_3	P_2I_4	C_6H_6, reflux, several hours	13–86 (nitro, methoxy unaffected)	333
49	aryl or alkyl N_3	$SnCl_2$	MeOH, rt, 0.25–1 h	85–98	334

[a] rt = room temperature.

alcohols 438 and 439, respectively[157] (entry 15). The



latter could also be prepared by catalytic hydrogenation (H_2/Pd/C) of the corresponding azido alcohols.[157] Long-chain alkyldiamines and -triamines were prepared by LAH reduction of the appropriate diazides (cf. 85 and 86) and triazides (cf. 89).[108]

3. By Sodium Borohydride

Sodium borohydride does not usually convert azides to amines in good yield in homogeneous systems,[291b] except in the case of arylsulfonyl azides.[312] However, it has been shown recently that under phase-transfer conditions efficient reduction of aryl, arylsulfonyl, and alkyl azides can be effected[38] (entry 23). The process could be extended to permit "one-pot" conversion of halides or methanesulfonates to pure primary amines in overall yields comparable to those for the conversion of azides to amines alone. The susceptibility of other functional groups to this approach has not been assessed and in this regard it is interesting that treatment of *tert*-butyl 2-azido-2-phenylacetate with $NaBH_4$ under phase-transfer conditions gave a 72% yield of phenylglycine.[38]

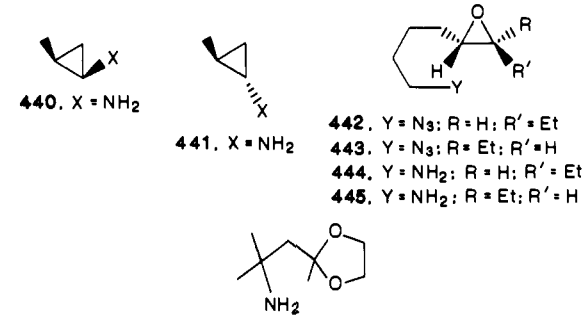
4. Via the Staudinger Reaction

One of the mildest and most selective routes to convert azides to amines involves reaction of the former with triphenylphosphine to form the corresponding iminophosphorane and subsequent hydrolysis (see Scheme 18). The first step has become known as the

SCHEME 18

$$RN_3 + Ph_3P \rightarrow RN{=}PPh_3 \rightarrow RNH_2$$

Staudinger reaction after its discoverer.[313] The same author reported that conversion of the iminophosphorane to the amine could be effected with ammonium hydroxide.[313] This method has been modified to a "one-pot" process by Letsinger and co-workers,[292d] and recent variants on the latter have allowed preparation of a mitosene[74] (entry 24) and 3-aminooxetane (**105**)[121] (entry 25). More commonly, conversion of the iminophosphorane to the amine has been effected by hydrolysis rather than ammonolysis. Thus, poly(vinylbenzylamine hydrochloride) was prepared from the azide via NaOH (MeOH, 60 °C) hydrolysis of the isolated phosphine imine (entry 26) and subsequent treatment with hydrochloric acid. Again this procedure can be performed without isolation of the intermediate iminophosphorane and, as such, has been used to prepare the mixture of cyclopropylamines **440** and **441**[125] (entry 27). Indeed, the triphenylphosphine and water can be present together, providing a convenient, mild, one-step azide to amine conversion. Thus, the epoxy azides **442** and **443** react with triphenylphosphine (1 equiv) in THF in the presence of water (1.2 equiv) at



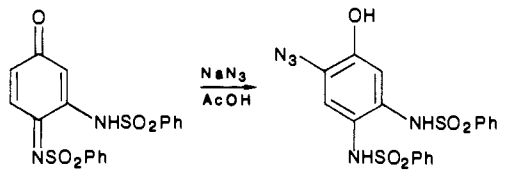
room temperature for 18 h to give the corresponding amines **444** and **445** in 80% and 85% yield, respectively[275] (entry 28). A seven-compound study of the generality of the process has been reported[293c] (entry 29). In general, clean conversion to the intermediate could be effected in 1 or 2 h at room temperature in dry THF. Addition of 1.2–1.5 equiv of water and further incubation at room temperature for 3–4 h gave good yields (80–91%) of the amines. Similar results were obtained when all reagents were premixed, except for in the case of the hindered amine **446**, where the two-step approach (72 h, toluene reflux; 24 h THF reflux) alone was successful. The reaction succeeds in the presence of a variety of functional groups (see entry 29) under very mild conditions and would hence appear to be the method of choice. Apparently, it is possible to selectively reduce an azide attached to a primary site in the presence of more hindered azides. A more comprehensive study has appeared recently.[315] In one reported case[316] the intermediate phosphazine was cleaved with trifluoroacetic acid/methanol (entry 30).

Phosphites have found limited use as phosphine congeners in the Staudinger type process. However, recently the reduction with trialkyl phosphites was declared the best available method for the azide to amine transformation.[37] This conclusion was based on the facility of the process (greater phosphine reactivity and easy deprotection) and the economic advantage accruing from use of the less expensive trialkyl phosphites. Thus, primary and secondary alkyl bromides can be converted to the primary amines in a one-pot procedure involving (a) azidation using solid–liquid PTC, (b) Staudinger reaction of the crude azide with triethyl phosphite, and (c) two-step deprotection using HCl gas in ether[37] (entry 31). The procedure reportedly offers a viable alternative to the Gabriel synthesis, especially in cases where nucleophilic displacement is accompanied by extensive elimination and/or when drastic deprotection conditions should be avoided.

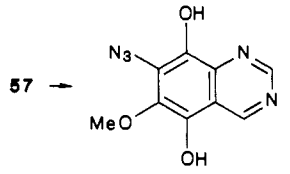
5. By Other Established Methods

(a) Hydrogen Sulfide/Triethylamine. Recent uses of H_2S/NEt_3 for azide to amine conversion have been limited and mainly in the β-lactam[259,262] (entries 32 and 33) and carbohydrate fields.[317] The mildness of the procedure is apparent but, in the light of the simplicity of the triphenylphosphine approach, will probably continue to receive scant attention.

(b) Sodium Dithionite. Reduction of azidoquinone **56** with sodium dithionite gave the corresponding amine in 33% yield[74] (entry 34). Azidophenol **448** (prepared from **447** by treatment with sodium azide/AcOH) reacted with sodium dithionite to give the amine, which



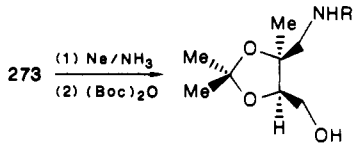
447 448



449

was further transformed in situ[318] (entry 35). Attempted reduction of the unstable azidoquinone **57** with excess sodium dithionite gave the unstable azidohydroquinol **449** and not the expected amino congener.[75] The aminoquinone (analogous to **57**) could be prepared from **449** using Watanabe's method.[319]

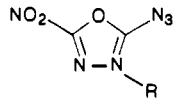
(c) Sodium/Ammonia. Acetonide **273** was reduced with Na/NH_3 to amino alcohol **450**, which was treated directly with $(Boc)_2O$ in aqueous NaOH to give the N-protected alcohol **451**[239] (entry 36).



450, R = H
451, R = Boc

6. By Nucleophiles

1-R-3-Nitro-5-azido-1,2,4-triazoles **452–454** were reduced to the corresponding amines in good yield by the action of methylamine, dimethylamine, or triethylamine (entry 37). The less basic ammonia and ethylenimine



452, R = Me
453, R = CH_2CO_2H
454, R = CH_2CO_2Me (CH_2CONHR' in product)

did not effect reduction. Unlike the 3,5-dinitro congeners no nitro (or azido) displacement occurred and 1-R-3-azido-5-R-1,2,4-triazoles did not react.[320] This unusual transformation had been previously observed in the pyridine series.[321] More recently, 2-nitro-3-azidopyridine was reportedly reduced to the amine in 25% yield by NaOH, RONa, KCN, or $NaSC_6H_4$-4-Me in proton-donor solvents[322] (entry 38). Additionally, with the first two reagents, concomitant reduction and 6-substitution occurred. In contrast, with the stronger nucleophile, $NaSC_6H_4$-4-Me, azide substitution took place and the reaction with KCN also provided a product derived from cyanide addition to the azido group.[322]

As previously described (section II.A), on occasion reduction to the amine occurs on attempted azidation of the halide precursor (cf. from **77** and **78**).[104,105]

7. By New Methods

Various new reagents for the azide to amine conversion have been developed recently (entries 39–49). Thus, tetracarbonylhydridoferrate ($HFe(CO)_4^-$) reacts with aryl and hexyl azides in ethanol at room temperature under an atmosphere of carbon monoxide to give good yields (70–100%) of the primary amines. Interestingly, under the same conditions benzoyl azide gave ethylphenyl carbamate; the amide was formed quantitatively at −40 °C[323] (entry 39). Sodium hypophosphite has been employed recently for the transfer hydrogenation of a number of functionalities, including an alkyl azide. The process may be of limited utility because of the range of other groups reduced[324] (entry 40). A reagent of more general applicability is sodium hydrogen telluride (prepared from tellurium and sodium borohydride), which reduces aryl, benzyl, alkyl, acyl, and sulfonyl azides in good to excellent yield under mild conditions[325] (entry 41). For aryl azides, mercaptoacetic acid appears to be a very efficient reductant[326] (entry 42).

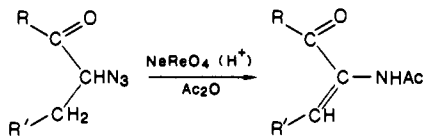
Multielectron reduction of methyl azide and 2-hydroxyethyl azide using a $(n\text{-}Bu_4N)_3[Mo_2Fe_6S_8(SPh)_9]$-modified glassy carbon electrode provided the appropriate amine plus hydrazine and ammonia (depending on concentration)[327] (entry 43). The method probably offers little synthetic scope at present. In the same vein, cathodic reduction of α-azidocinnamic ester[328] and nonterminal vinyl azides[329] has been examined. In the former, an excellent yield of α-aminocinnamic ester can be realized by careful addition of proton donors. N-Acylated species result from reduction in the presence of electrophiles (entries 44 and 45). Further work in this area has been reported recently.[330]

Azidobenzene was converted to a mixture of aniline (67%) and *N,N'*-diphenylurea (23%) by treatment with $Fe_2(CO)_9$ in acetonitrile/water at 50 °C[331] (entry 46). Azidoarenes were also converted to the aminoarenes in 26–70% yield by carbon monoxide and water in the presence of a $RhCl_3$ catalyst[332] (entry 47) and in 13–86% yield by P_2I_4[333] (entry 48). With the latter, aroyl and sulfonyl azides reacted sluggishly.

Both aryl and alkyl azides are reduced to the corresponding amines in excellent yield (85–98%) using stannous chloride in methanol[334] (entry 49).

B. Other Reductions

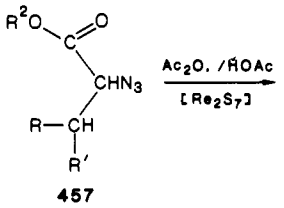
Cyclic and acyclic 2-azido ketones **455** eliminate nitrogen in the presence of catalytic amounts of perrhenate. When the reaction is conducted in acetic



455 **458**

R, R' = carbocyclic
R = Ph, Me; R' = H

anhydride, containing small quantities of a mineral acid, if required, 2-(acetylamino)-2-alken-1-ones (**456**) are formed in good yield.[335] Similarly, α-azido esters **457** react with acetic anhydride in the presence of catalytic amounts of rhenium heptasulfide (and hydrochloric acid if necessary) to give good yields of the mono- and diacetylated esters **458** and **459**. If water is added before workup or a smaller $Ac_2O/AcOH$ ratio is employed, monoacetylated ester **458** is the sole product.[336]



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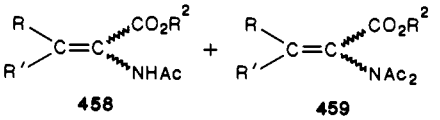
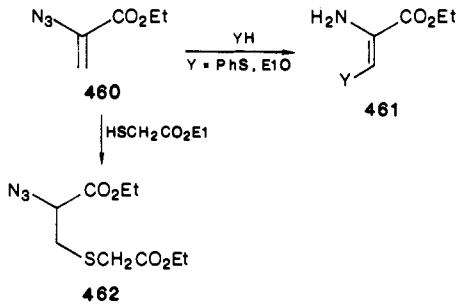


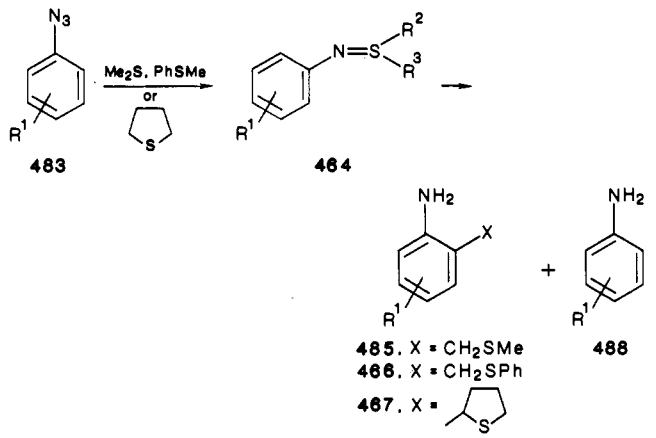
458 459

Treatment of ethyl 2-azidopropenoate (460) with thiophenol or with lithium ethoxide or sodium ethoxide gave (Z)-2-amino-3-(phenylthio)propenoate (461, Y = PhS) or (Z)-2-amino-3-ethoxypropenoate (461, Y = EtO), respectively, in reasonable yield.[337] In contrast, ethyl mercaptoacetate reacted with 460 to give the expected Michael adduct (462) without concomitant azide reduction.



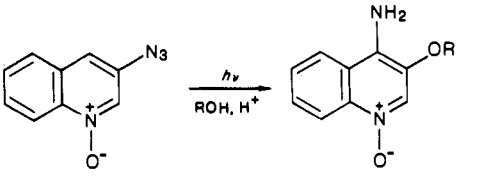
460 461 462

Aryl azides react with carbon monoxide at atmospheric pressure in the presence of a rhodium catalyst to give aryl isocyanates, which form urethanes with alcohols.[338] Substituted aryl azides (cf. 463) generally

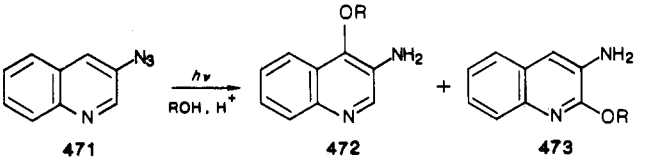


463 464 485. X = CH_2SMe 466. X = CH_2SPh 467. X = 468

decompose in the presence of dimethyl sulfide, thioanisole, or tetrahydrothiophene to give 2-substituted anilines 465–467, respectively, in modest yields.[339] Unsubstituted anilines 468 were also formed in variable yield. The mechanism apparently involves Sommelet–Hauser type rearrangement of intermediate N-aryl sulfimides 464, with Sommelet–Hauser products 465 and 466 being favored by electron-withdrawing groups. 2-Substituted arylamino compounds (and/or ring-expansion products) can also be prepared by photolysis of aryl azides in the presence of nucleophiles.[340] More recently, Tsuchiya and co-workers have extensively examined similar reactions of pyridyl, quinolyl, and isoquinolyl azides under acidic conditions;[341] in some cases reactions involving a nitrenium ion intermediate also occur. Thus, 3-azidoquinoline N-oxide (469), upon irradiation in alcohols containing sulfuric acid, gave 470, whereas under the same conditions 3-quinolyl azide (471) afforded 4-alkoxy- (472) and 2-alkoxy-3-aminoquinoline (473) via the nitrenium ion.[342]



469 470



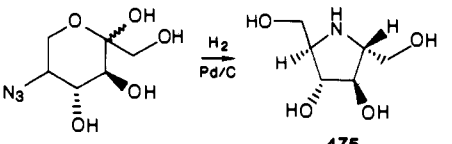
471 472 473

The same workers have examined the effects of reaction conditions upon the course of such reactions.[343] With hydrohalogenoic acids, α-halogeno amino compounds are formed (also via the nitrenium ion); lower yields result from thermolysis. Both photolysis and thermolysis of these azide types in alkanethiols afforded α-alkylthio amines, apparently via radical intermediates. More recently, this latter study has been extended to 3-, 4-, and 8-quinolyl azides and 4-isoquinolyl azide.[344]

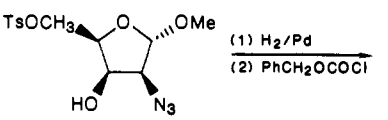
C. Reductive Cyclizations

On occasion, reduction of the azide function in the presence of displaceable functionalities (commonly hydroxyl groups) in the same molecule gives nitrogen heterocycles.

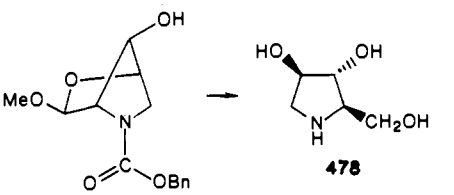
Thus, catalytic hydrogenation of 5-azido-5-deoxy-D-fructose (474) over 10% Pd/C gave pyrrolidine 475 in quantitative yield.[118] Similarly, reduction of 476 with H_2/Pd black in ethanol containing sodium acetate at 50 °C, followed by treatment with $PhCH_2OCOCl$/$NaHCO_3$, provided the bicyclic amine 477 in 36% yield. The latter could be further transformed to 478.[109] Aziridine rings can be prepared in an analogous fashion.



474 475

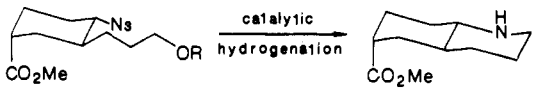


476



477 478

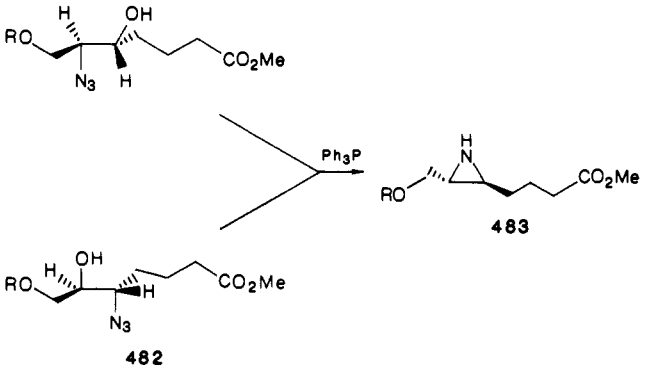
Azido alcohol 479 could not be cyclized to 481 using a variety of one-step procedures. However, conversion to tosylate 480 and catalytic hydrogenation did afford 481.[345]



479, R = H
480, R = Ts

481

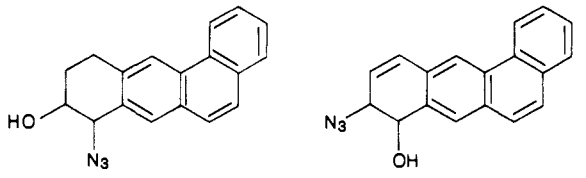
Cyclization of azido alcohols **482** to aziridine **483** (>80%) took place when either was heated in THF at 60–65 °C with triphenylphosphine.[132] Under the previously reported conditions (viz., triphenylphosphine in ether at reflux[131]) no cyclization occurred (see section II.A). The process was extended to the preparation of the aza analogue of LTA_4.[132] Aziridines also result[133] from treatment of **484** and **485** with tri-*n*-butylphosphine[346] or trimethyl phosphite.[347] Similar results were obtained with a chrysene analogue.[133]



483

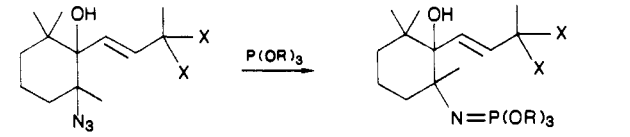
482

R = *t*-BDPSi



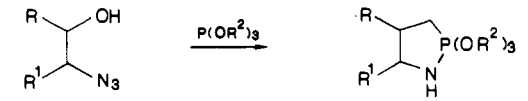
484 485

Azido alcohols **486** and **487** react with trialkyl phosphites to give the expected iminophosphoranes **488–490** (see section III.F) but, interestingly, azido alcohol **491** provided oxazaphospholidine **492** under the same conditions.[348] For further examples see section VI.A.7.



486, X,X = O
487, X,X = OCH_2CH_2O

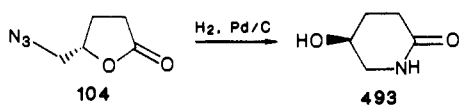
488, X,X = O; R = Me
489, X,X = O; R = Et
490, X,X = OCH_2CH_2O; R = Me



491, R = R^1 = *cis*-Ph

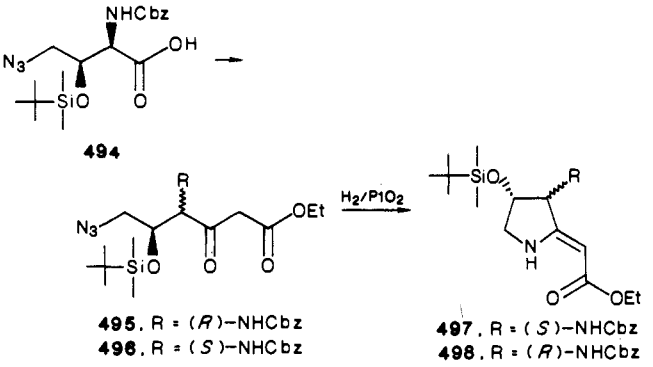
492, R = R^1 = *cis*-Ph, R^2 = Me

Reductive cyclization can also occur with azido carbonyl species. Thus, hydrogenation (H_2/Pd/C) of azido lactone **104** provides (*S*)-5-hydroxy-2-piperidinone (**493**) in 67% yield.[120]



104 493

Homologation of **494** with the magnesium salt of ethyl hydrogen malonate gave the β-keto ester **495** (and its anti diastereomer (**496**)) in an 88% crude yield. Using H_2/PtO_2, the mixture was reduced and cyclized to **497** and **498** in 57% overall yield from **494**.[349]

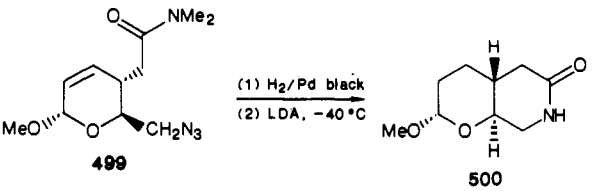


494

495, R = (*R*)-NHCbz
496, R = (*S*)-NHCbz

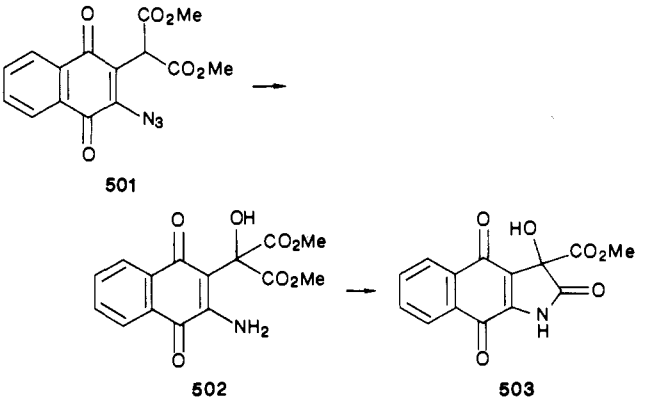
497, R = (*S*)-NHCbz
498, R = (*R*)-NHCbz

Hydrogenation of azido amide **499** in the presence of palladium black in ethanol reduced both the double bond and the azide to an amine, which was cyclized (68%) to lactam **500** with LDA.[350]



499 500

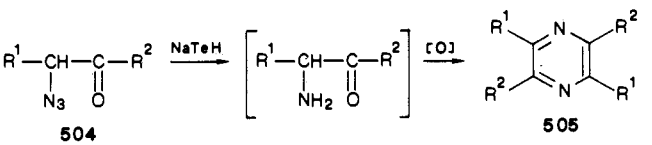
Refluxing an aqueous THF solution of azidoquinone **501** for 1.5 h results in the formation of aminoquinone **502** in 79% yield. However, extension of the reflux time to 5 h gives ring-closed indoloquinone **503** in 74% yield.[351]



501

502 503

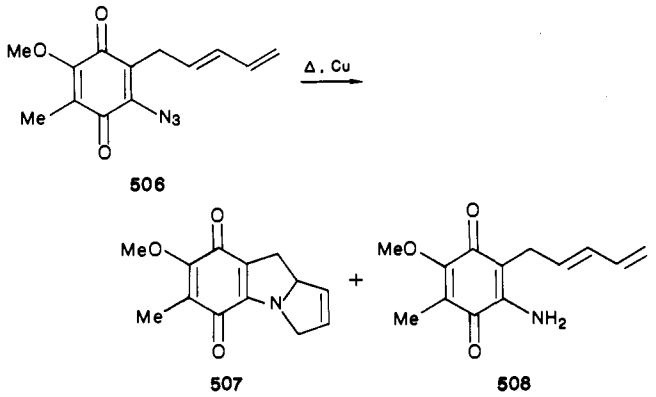
Treatment of α-azido ketones **504** with sodium hydrogen telluride at room temperature gives pyrazines **505** in 40–98% yield.[352] The process is not of general



504 505

applicability, however, since some primary azido ketones give complicated reaction mixtures. Pyrazines have been prepared previously from α-azido ketones by reduction with hydrogen over catalyst[353] or triphenylphosphine[354] and from ketones and iodine azide.[355]

Pyrolytic decomposition of azidoquinone **506** under reflux in benzene for 4 h in the presence of copper powder gave the reductive cyclization product **507** in 53% yield and the aminoquinone **508** in 35% yield.[356] Two other azidoquinones reacted similarly.



506 **507** **508**

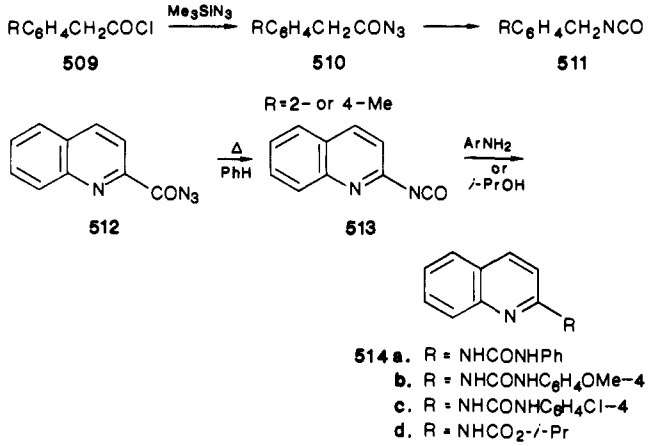
D. Curtius Reaction

The Curtius reaction is a general process involving the conversion of acyl azides (see section II.A) to isocyanates.[3,10] The yields of the latter are generally good since the process can be conducted readily in the absence of water. If desired, the reaction can be performed in the presence of water or alcohol, whereupon amines, carbamates, or ureas result. For Curtius reactions involving heterocyclic species, see section VI.A.4.

1. Thermal

Typically, the Curtius process can be carried out by thermolysis in an inert solvent and subsequent isolation of the isocyanate or trapping of the latter by reaction with a nucleophilic species.

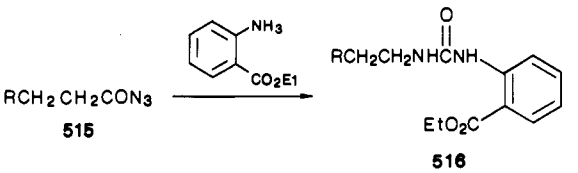
Recently, isocyanates **511** were prepared from the corresponding acyl chlorides **509** by treatment with trimethylsilyl azide and rearrangement of the intermediate acyl azides **510**.[357] Thermolysis of quinoline



514a. R = NHCONHPh
b. R = NHCONHC6H4OMe-4
c. R = NHCONHC6H4Cl-4
d. R = NHCO2-i-Pr

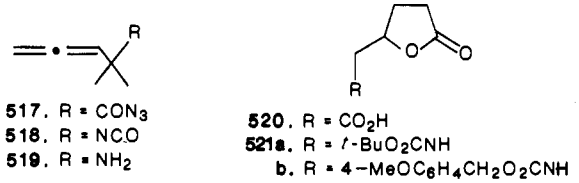
acyl azide **512** in benzene gave isocyanate **513**, which could be converted to urea derivatives **514a–c** with arylamines or to carbamate **514d** with isopropyl alcohol.[358] Similarly, urea derivatives **516a–c** were prepared by thermolysis of acyl azides **515a–c** (obtained from the carboxylic acids with ethyl chloroformate followed by NaN_3) in the presence of ethyl anthranilate.[359]

Most current utilizations of the Curtius rearrangement have involved isocyanates only as intermediates. Thus, allenic isocyanate **518**, formed from thermolysis



515 **516**

a. R = 3,4-(MeO)2C6H3–; **b.** 2-thienyl; **c.** 3-thienyl

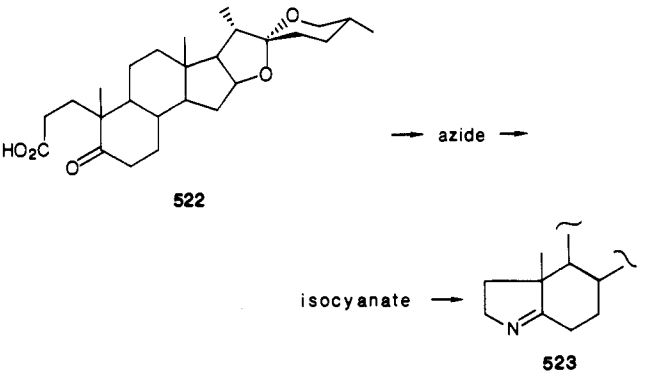


517. R = CON_3
518. R = NCO
519. R = NH_2

520. R = CO_2H
521a. R = t-BuO2CNH
b. R = 4-MeOC6H4CH2O2CNH

in benzene (18 h) of **517** (in turn prepared from the carboxylic acid), could be hydrolyzed to amine **519** in 39% overall yield.[20] Similarly, some tetrazolylmethyl isocyanates resulted from thermolysis of the acyl azides in toluene. Subsequent transformations to carbamates, amines, and ureas were reported.[360] As part of a synthetic pathway leading to a GABA analogue, carboxy lactone **520** was converted to the carbamates **521** by Curtius rearrangement and trapping of the isocyanate with *tert*-butyl alcohol or 4-methoxybenzyl alcohol.[361]

Without purification of the intermediates, keto acid **522** was converted to the acyl azide and thence to the corresponding isocyanate. The presence of these

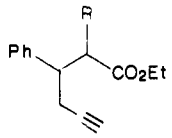


522 **523**

species was monitored by their characteristic infrared absorptions and, in the latter case, by reaction with methanol to form the urethane. Hydrolysis of the isocyanate under acidic or basic conditions gave the ring-closed steroid **523**.[362] A better route for the conversion of carboxylic acids to amines, via the Curtius rearrangement, has been reported recently. Therein, carboxylic acids were converted to isocyanates either by the usual acid → acid chloride → acyl azide → isocyanate sequence or by the more convenient one-pot procedure (using diphenylphosphoryl azide) developed by Shioiri, Ninomiya, and Yamada.[363] Subsequent addition of (trimethylsilyl)ethanol gave carbamates, which then could be cleaved with tetrabutylammonium fluoride to provide amines in 68–85% yield (from the carboxylic acids).[364] Previously, difficulties have often been encountered in the cleavage of other carbamates, especially where the R group contains sensitive functionalities. The present method appears to circumvent such problems.

As mentioned above, direct transformation of carboxylic acids to isocyanates has been effected by using diphenylphosphoryl azide. The scope of this process has been explored by Shioiri and co-workers.[365] Recent uses of this method include the preparation of benzyl

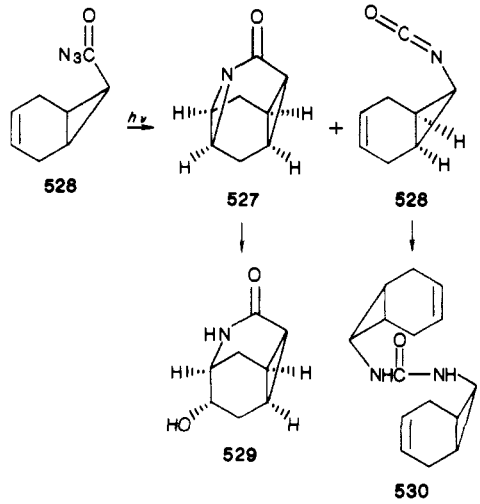
carbamate **525** from **524** (triethylamine/benzene, reflux 1.5 h followed by treatment with benzyl alcohol) in good yield (67%)[366] and similar transformations (see section VI.A.4).



524. R = CO_2H
525. R = $NHCO_2Bn$

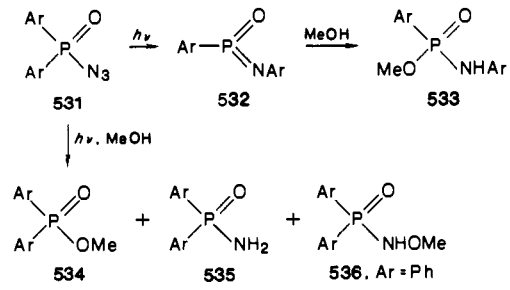
2. Photochemical

Photochemical Curtius rearrangements are often accompanied by products resulting from trapping of an intermediate nitrene. Thus, photolysis of **526** in pentane for 1 h at 0 °C gave **529** and **530**, presumably arising from **527** and **528**, respectively.[367]

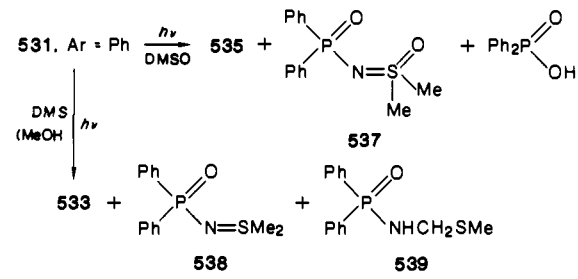


An excellent review of the photochemical (and thermal) rearrangements of heavier main group element (mainly B, Si, Ge, and P) azides has appeared recently.[368] Accordingly, no attempt has been made to cover this topic comprehensively herein, and the reader is directed to the review for full details.

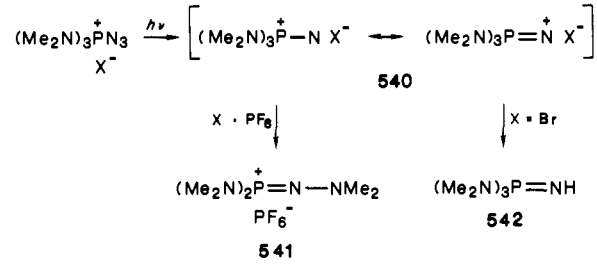
Diarylphosphinic azides (**531**)[369] rearrange on photolysis in methanol to form metaphosphonimidates (**532**), which are trapped by the solvent[370] to give methyl *N,P*-diarylphosphonamidates (**533**) in reasonable yield.[371] Methyl phosphinates (**534**), products of solvolytic azide displacement, and diarylphosphinic amides (**535**) are also formed.[371]



A careful study of the photolysis of diphenylphosphinic azide (**531** Ar = Ph) in methanol revealed that *N*-methoxy amide **536** was a minor product (ca. 2.5%). In an attempt to assess whether the Curtius rearrangement products **532** are formed via phosphinyl nitrenes (rather than directly from the azides), **531** (Ar = Ph) was photolyzed in DMSO (a known nitrene trap[372]). The products presumed to arise from singlet and triplet nitrenes, viz., **535** and **537**, were obtained in low yield (4.7 and 2.8%, respectively) and the major product was diphenylphosphinic acid ($Ph_2P(O)OH$). The latter was apparently not derived from direct hydrolysis of the azide. The same product was formed in 98% yield from thermolysis of diphenylphosphinic azide in DMSO.[373] Similar experiments conducted in the presence of dimethyl sulfide (DMS) (and methanol) provided sulfilimine **538** in addition to **533**.[374,375] The role played by nitrenes in these transformations is still unclear.



Recently, the first example of a Curtius type rearrangement involving a charged atom was reported.[376] Thus, irradiation of the azidophosphonium salt **540** (X = PF_6) at 254 nm for 15 h at room temperature gave the iminophosphonium salt **541**.[377] In contrast, similar



irradiation of the bromide salt **540** (X = Br) afforded iminophosphorane **542** in 80% yield. These results were rationalized in terms of an intermediate phosphonium nitrene, with subsequent migration of a phosphorus substituent to nitrogen (when the anion is a poor nucleophile, e.g., PF_6^-) or, with the good nucleophile Br^-, direct attack at nitrogen followed by photolytic scission of the halogen–nitrogen bond.

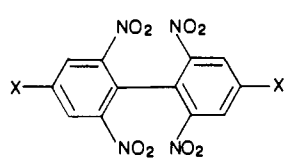
Recently, West and co-workers published their findings regarding the photolytic conversion of trimesitylazidosilane (Mes_3SiN_3) to the silanimine ($Mes_2Si{=}NMes$).[378]

E. Schmidt Reaction

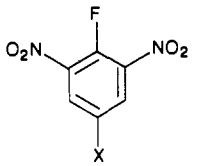
The Schmidt reaction (viz., conversion of a carboxylic acid to an amine or a ketone to an amide by the action of hydrazoic acid or congeners) has been known for many years.[10] Good results are generally obtained for aliphatic cases, but for aromatic examples the yields are variable. The main disadvantage of the procedure results from the use of more drastic conditions than for the closely related Hofmann or Curtius rearrangements. Consequently, the reaction is employed relatively infrequently for the acid to amine conversion, the Curtius (see section III.D) and Hofmann procedures being generally more facile. The Schmidt process is discussed only briefly in this section and the reader is directed

to the alicyclic (section IV.D) and heterocyclic (section VI.C.1) portions for further details.

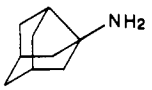
Recently, it was reported that diamino compound **544** could be obtained in excellent yield (93–100%) via a Schmidt reaction on the dicarboxylic acid **543**.[379] Ap-



543, X = CO_2H
544, X = NH_2



545, X = CO_2H
548, X = NH_2

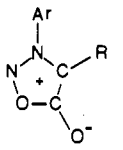


547

parently, in this case, the process is superior to those previously employed, viz., a four-step Curtius rearrangement (<70% yield overall) and a three-step Hofmann reaction (<8–30% yield overall),[380] and the hazard associated with hydrazoic acid (here generated from NaN_3 in fuming sulfuric acid at 80 °C) can be tempered somewhat by the addition of 1,2-dichloroethane. Similarly, **545** could be converted to **546** in 77% yield by using sodium azide in 20% oleum at 25 °C,[381] and 3-noradamantamine (**547**) is formed in 63% yield from the corresponding carboxylic acid.[382] The process has been extended to the formation of an acrylic acid–vinylamine copolymer by treatment of poly(acrylic acid) with sodium azide in sulfuric acid/chloroform.[383] The conversion of carboxylic acid to amino groups was limited to about 50%.

The reaction between a ketone and hydrazoic acid is a method for insertion of NH between the carbonyl group and one substituent to yield an amide. Generally, dialkyl and cyclic ketones react faster than alkyl aryl ketones, which in turn transform more rapidly than diaryl ketones. There is usually a preference for aryl migration (when in competition with an alkyl group) except when the alkyl is bulky, although even on this latter point exceptions do exist.

Recently, selectivity has been observed in some cases. Thus, MeCOCHRCO-Gly-OEt (R = H, Bn, Me, Et, Pr, Bu) gave MeCONHCHRCO-Gly-OEt and $MeCOCH_2CO$-X-OH (X = Phe, Leu) afforded $MeCONHCH_2CO$-X-OH on treatment with HN_3/H_2SO_4.[384] 3-Aryl-4-acetylsydnones (**548**, Ar = Ph, 4-Me-, 4-Br-, 4-MeO-, 4-EtO-C_6H_4) reacted to give only



548, R = COMe
549, R = CONHMe
550, R = CHO
551, R = CN
552, R = $CONH_2$

Ar = Ph, 2- and 4-Me-, 4-EtO-, 4-MeO-, 4-BrC_6H_4

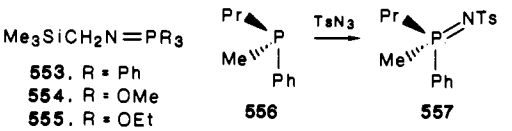
the corresponding *N*-methylcarboxamides **549** in reasonable yield (50–77%).[385] The expected 4-acetamido congeners (derived from heteroaryl rather than methyl migration) were apparently not products of the reactions, in line with previous unsuccessful attempts to place electron-donating groups at the 4-position of the sydnone ring.

The Schmidt reaction has been applied infrequently to aldehydes; nitrile products usually result. Recently, nitrile **551** was shown to arise from **550** in 67–77% yield on treatment with sodium azide in dilute sulfuric acid. However, in concentrated sulfuric acid, carboxamides **552** were obtained in 47–74% yield.[386] Aromatic aldehydes react with trimethylsilyl azide in the presence of zinc chloride to give the corresponding nitriles in 62–97% yield.[387]

F. Staudinger Reaction

As previously mentioned (see section III.A.4), the Staudinger reaction has been employed as a means to convert azides to amines. Numerous analogous transformations have been reported and recent examples of these are described herein. Iminophosphoranes are valuable species since they undergo Wittig type reactions with, inter alia, aldehydes,[388] ketones,[389] ketenes,[390] and other compounds containing polarizable oxygen or sulfur.[391] In addition, the reaction of iminophosphoranes with phthalic anhydride to form phthalimides in good yield has been reported.[392] For more details on "aza-Wittig" cyclizations, see section VI.A.7.

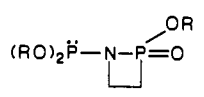
Reaction of azides (prepared by the action of "clayfen" on the hydrazines) with triphenylphosphine, triphenyl phosphite, or triethyl phosphite gives the corresponding iminophosphoranes, apparently via an intermediate phosphine–azide complex.[393] In some cases the latter could be isolated. Recently, the Staudinger process has been extended to the preparation of the [(trimethylsilyl)methyl]iminophosphoranes (**553–555**)[394] and reactions of azides with arsenic heterocycles,[395] an anionic phosphorus(III) complex,[396] and di- and triesters of phosphorous acid.[397] Chiral phosphine **556** reacts with tosyl azide with retention of stereochemistry to form iminophosphorane **557**.[398] Tosyl azide has also been used to convert the N-phosphorylated 1,2-azophosphetidine **558** to the corresponding iminophosphorane.[399]



$Me_3SiCH_2N{=}PR_3$
553, R = Ph
554, R = OMe
555, R = OEt

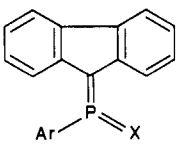
556

557



558

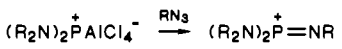
Interestingly, phosphaalkene **559** reacted with phenyl azide to give iminomethylenephosphorane **560**.[400]



559, X = lone pair
560, X = NPh
Ar = 2,6-$Me_2C_6H_3$

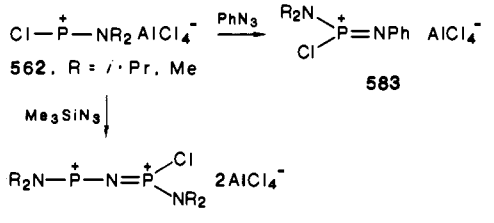
Even phosphorus cations can undergo the Staudinger reaction. Thus, azides were shown to react with bis(dialkylamino)phosphenium species to give the corre-

sponding bis(dialkylamino)iminophosphonium compounds (561).[377,401] More recently, the process has been



561

extended to the chlorophosphenium salts (562).[402] Reaction of 562 with phenyl azide gave the appropriate chloroiminophosphonium salts (563). Different results were obtained with trimethylsilyl azide, presumably since elimination of trimethylsilyl chloride is in competition with the Staudinger process. Thus, treatment of 562 with trimethylsilyl azide gave 564, the first examples of bisphosphocations. The latter are presumed to arise via intermediate phosphenium azides (R_2N–P^+–N_3 $AlCl_4^-$).

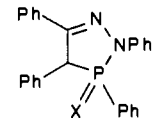


562, R = i-Pr, Me

563

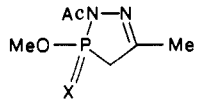
564

Heterocycles containing tricoordinated phosphorus usually form the pentacoordinated phosphorus imines on treatment with azides. Thus, the *cis*- or *trans*-2*H*-1,2,3-diazaphospholenes (565) gave the corresponding iminophosphoranes (566), with varying stereochemical results, on treatment with aryl azides.[403]

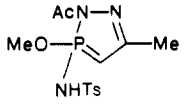


565, X = lone pair

566, X = NR (R = 4-ClC_6H_4, 4-$NO_2C_6H_4$, Ph, Ts)



567, X = lone pair
588, X = NTs



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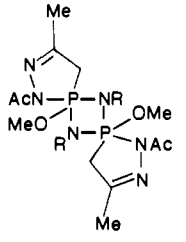
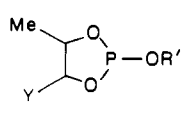
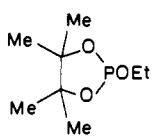


570

Similarly, reaction of 2-acetyl-3-methoxy-5-methyldiazaphospholene (567) with tosyl azide gave imino product 568 in 81.5% yield.[404] The latter is stable in the solid state but in dichloromethane forms the tautomer 569 and in ether affords the dimer 570. Similar dimers are also derived in 58–92% yield from the reaction of phenyl azide with the dioxaphospholanes 571.[405] In contrast, with *p*-nitrophenyl or tosyl azide the expected iminodioxaphospholanes resulted in 62–87% yield. Normal Staudinger products were also formed from tetramethyldioxaphospholane 572 and phenyl, *p*-methoxyphenyl, or *p*-nitrophenyl azides.



571, R = H, Me; R' = Me, Et



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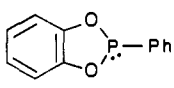
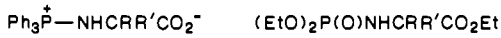
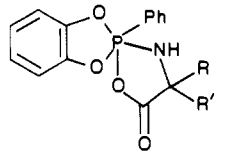


573

Azido carboxylic acids and related species also have been subjected to the Staudinger process.[406] In the latter, a systematic investigation of the imination of trivalent phosphorus compounds with aliphatic azides containing H atoms of different mobility (e.g., in carboxylic acids, amides, or amines) gave interesting results.[406] Thus, treatment of azidoacetic acid derivatives with triphenylphosphine, triethyl phosphite, or 573 gave the betaines (574), amido phosphates (575), or cyclic phosphoranes (576), respectively. The latter two presumably arise from further transformations of betaines similar to 574 (see section VI.A.7).

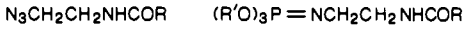


574 575

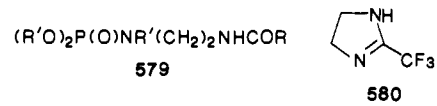


576

The key step of these transformations is certainly the transfer of the proton from the carboxylic acid to the imine nitrogen. In contrast, proton transfer does not occur from the amido group and an iminophosphorane results from treatment of 577 with $(Me_2N)_3P$. Trialkyl



577 578

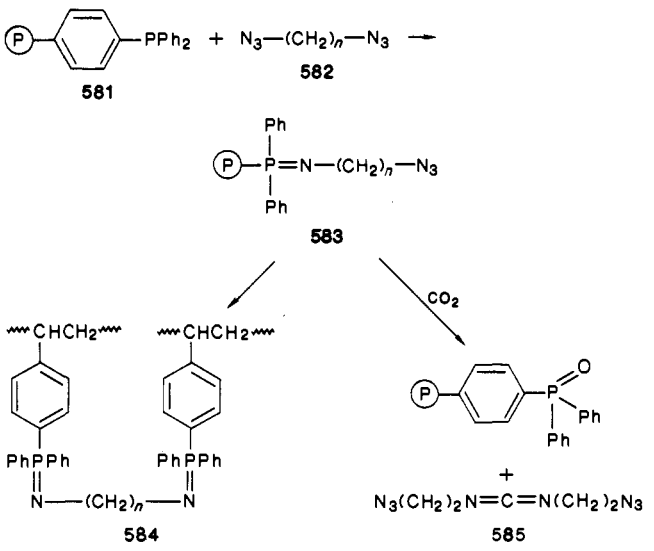


579 580

phosphites react with 577 to give the corresponding iminophosphoranes (578), which are converted to amido phosphates (579) on vacuum distillation. Interestingly, the trifluoromethyl analogues 578 (R = CF_3) decompose to form both 579 (R = CF_3) and 2-(trifluoromethyl)-imidazoline (580). The triphenylphosphine analogues of 578 could also be converted to imidazolines by thermolysis.

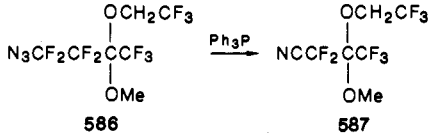
Polymeric phosphines can also be utilized in the Staudinger reaction. Thus, 581 combined with 1,2-diazidoethane (582, *n* = 2) to form the azidoiminophosphorane (583). With longer chain diazides the azide IR stretch in the products ranged from very weak (*n* = 4) to nonexistent (*n* = 6 and 10), apparently due to the formation of 584.[407] When 583 was allowed to react with carbon dioxide the unusual diazido carbodiimide (585) was obtained.

Some useful one-pot azide conversions (via the Staudinger process) have been developed. Thus, heating a mixture of a carboxylic acid, aryl or alkyl azide, and triphenylphosphine in benzene, hexane, or toluene for 12–120 h gave the corresponding amide in good yield. ω-Azido acids gave insoluble zwitterionic products (Ph_3P^+–$NH(CH_2)_nCO_2^-$) and under these conditions cyclization was not observed. However, in refluxing pyridine Ph_3P^+–$NH(CH_2)_3CO_2^-$ did provide 2-pyrrolidone in 95% yield.[406] More recently, a similar, but milder process was used for the preparation of small peptides. Therein, ethyl diphenylphosphinite (Ph_2POEt) proved to be the reagent of choice since on HCl workup its oxide is hydrolyzed to diphenylphosphinic acid, which can be extracted from the



mixture (in contrast to Ph_3PO, which has to be separated by column chromatography[408]), and the iminophosphorane so derived reacts cleanly at room temperature with carboxylic acids.[409]

An iminophosphorane is presumably involved in the high-yield conversion of azide **586** to nitrile **587**.[249]



Corey and co-workers[410] have utilized iminophosphorane intermediacy in a recent conversion of alkyl azides to nitro compounds in moderate to good yield (Scheme 19).

SCHEME 19

$$RN_3 + R'_3P \rightarrow RN{=}PR'_3 \xrightarrow[-78\ ^\circ C]{O_3} RNO_2 + R'_3PO$$

A reaction analogous to the aza-Wittig process has been developed using dialkyl tellurides.[411] Therein, heating tosyl azide and, e.g., diisobutyl telluride with an aldehyde in benzene for 15–20 h gives the corresponding *N*-tosyl imines in 28–82% yield (Scheme 20). The reaction is facilitated by the presence of copper powder and by the attachment of electron-donating groups to the aldehyde. The less basic aryl tellurides inhibit the process and ketones do not react under these conditions. The mechanism may involve a Staudinger-like reaction of the telluride with tosyl azide to form an intermediate tellurilimine.

SCHEME 20

$$TsN_3 + R_2Te \xrightarrow[PhH]{\Delta} R_2Te{=}NTs \xrightarrow{R'CHO} R'CH{=}NTs$$

R = alkyl; R′ = alkyl, aryl

G. Amination

As described in this review, azides can react with carbon nucleophiles to provide azido (see section II.J) or diazo compounds (see section III.I). Another pathway possible in certain cases is amination. While there is an overlap in concept with the following section (viz., section III.H), the importance of the amination process merits its inclusion as a separate section even when very different mechanistic principles are involved.

1. By Reaction with Alkyl- or Aryllithium or Grignard Reagents

It has been well established that organic azides react with Grignard or organolithium reagents to give 1,3-disubstituted triazenes[412a] which can be converted to amines by reductive workup.[412b]

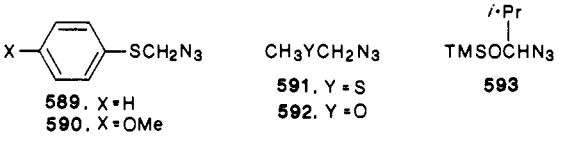
Trost and Pearson[413] have shown that azidomethyl phenyl sulfide (**588**) reacts with Grignard reagents to give triazene intermediates which can be hydrolyzed to the corresponding amines with KOH (Scheme 21). Recently, they further exemplified the utility of sulfur-activated azides for this process.[414]

SCHEME 21

$$\underset{\mathbf{588}}{PhSCH_2N_3} + RMgBr \rightarrow PhSCH_2N{=}NNHR \xrightarrow{KOH} RNH_2$$

R = aryl, alkyl

Therein, the efficacy of a series of heteroatom-substituted azides (**589–593**) for amine transfer was compared and it was clearly established that the order of reactivity was **589** ≅ **590** > **591** > **592** ≫ **593**. The activating effect of sulfur compared to oxygen and of arylthio compared to alkylthio is thus manifest.

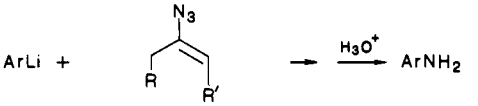


Low-temperature quenching of the intermediate triazene anion (from alkyl Grignards and **588** with acetic anhydride or aroyl chlorides followed by hydrolytic workup (tetrabutylammonium formate in DMF or KOH in DMSO) provides N-acylated or N-aroylated compounds in 64–98% yield.[414]

Complementary to this work is that of Hassner.[415] Whereas azidomethyl phenyl sulfide reacts more effectively with Grignard reagents than with organolithium species, the opposite is true with Hassner's vinyl azides (**594**). Thus, reaction of **594** with aromatic lithium reagents followed by dilute acid workup of the intermediate triazenes provides aromatic primary amines in fair to good yields (45–70%) (Scheme 22). Unlike with **588**, the vinyl azides can be used to prepare heterocyclic amines. They are limited in scope, however, in that simple alkyllithium species (e.g., MeLi, BuLi, and *t*-BuLi) react to give alkylated ketones rather than aminated products.[416]

More recently, the readily available reagent tosyl azide has been shown to react with aromatic lithio compounds.[417] The initially formed triazenes can be reduced in situ with Ni–Al/KOH in an aqueous environment to yield aromatic amines in modest to good

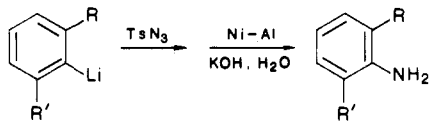
SCHEME 22



594, R = Ph, R′ = H
R = H, R′ = *t*-Bu

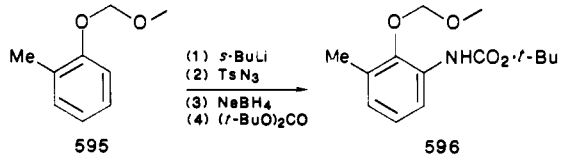
Ar = aryl, heteroaryl, benzyl, dithianyl

SCHEME 23



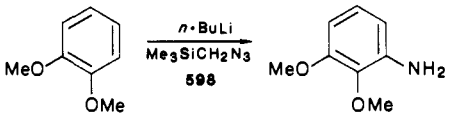
yield (34–85%) (Scheme 23).

Snieckus has reported a modification of this process utilizing tosyl azide and sodium borohydride,[418] and recently this approach was employed in the regiospecific transformation of *o*-methyl(methoxymethoxy)benzene (**595**) to carbamate **596** in 72% yield.[419]



595 596

A similar transformation, viz., **597** → **599**, has been effected in 78% yield using (trimethylsilyl)methyl azide (**598**) as the aminating agent.[420]



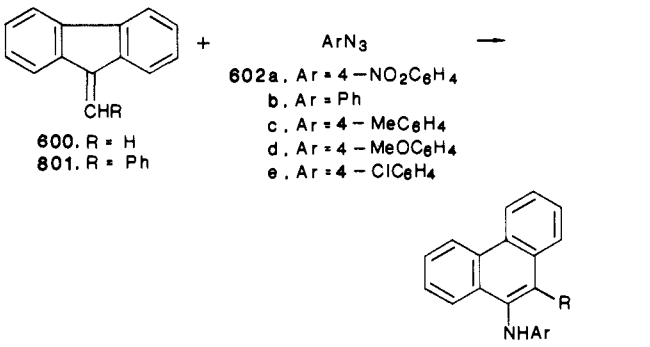
597 599

It should be noted that Guntrum[421] has reported that tosyl azide exhibits shock sensitivity similar to that of nitroglycerin. Accordingly, Kelly[420] has suggested that great caution is also advisable in the handling of the analogous reagent **598**.

The versatile reagent diphenyl phosphoroazidate [$(PhO)_2P(O)N_3$] (see section VII) also combines with aryl Grignard or aryllithium reagents to give labile triazenes which can be reduced to the primary amines with sodium bis(2-methoxyethoxy)aluminum hydride or lithium aluminum hydride.[422]

2. By Reaction with Alkenes and Related Species

The methylenefluorene derivatives **600** and **601** react with the aryl azides **602a** and **602a–e**, respectively, to give the ring-expanded arylamines **603** (37%) and **604** (36–66%).[423] Products **603** and **604** presumably arise by thermal breakdown of initially formed triazolines (isolable from **600** and **602b–e**). A similar ring expansion has been employed for the formation of heterocyclic (Section VI.B.3) and alicyclic (Section IV.C) systems.

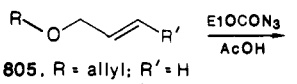


600. R = H
601. R = Ph

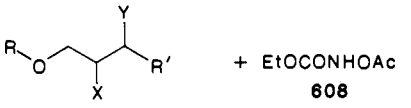
602a. Ar = 4-$NO_2C_6H_4$
b. Ar = Ph
c. Ar = 4-MeC_6H_4
d. Ar = 4-$MeOC_6H_4$
e. Ar = 4-ClC_6H_4

603. R = H; Ar = 4-$NO_2C_6H_4$
604a. R = Ph; Ar = 4-$NO_2C_6H_4$
b R = Ph; Ar = Ph
c. R = Ph; Ar = 4-MeC_6H_4
d. R = Ph; Ar = 4-$MeOC_6H_4$
e. R = Ph; Ar = 4-ClC_6H_4

Thermolysis of $EtOCON_3$ in the presence of **605** using acetic acid as solvent gave **606** (15%), **607** (38%), and **608** (47%).[424] The amount of the undesired byproduct **608** could be reduced substantially by employing considerably less acetic acid. With ether **609** a similar thermolysis reaction gave **610** (68%) and **611** (25%).

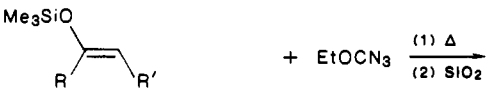


805. R = allyl; R' = H
609. R = Ph; R' = H

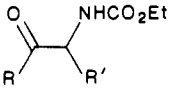


606. R = allyl; R' = H
X = $NHCO_2Et$; Y = OAc
607. R = allyl; R' = H
X = OAc; Y = $NHCO_2Et$
610. R = Ph; R' = H
X = $NHCO_2Et$; Y = OAc
611. R = Ph; R' = H
X = OAc; Y = $NHCO_2Et$

Ethyl azidoformate also combines with enol trimethylsilyl ethers (**612**). Thus, heating the reagents at 110 °C in a sealed tube, followed by silica gel chromatography, affords *N*-ethoxycarbonyl α-amino ketones (**613**) in 35–65% yield.[425]



812a. R = t-Bu; R' = H
b. R = Pr, R' = Et
c. R···R' = —$(CH_2)_4$—
d. R···R' = —(CH_2)CH-t-Bu—CH_2—
e. R = Ph; R' = H

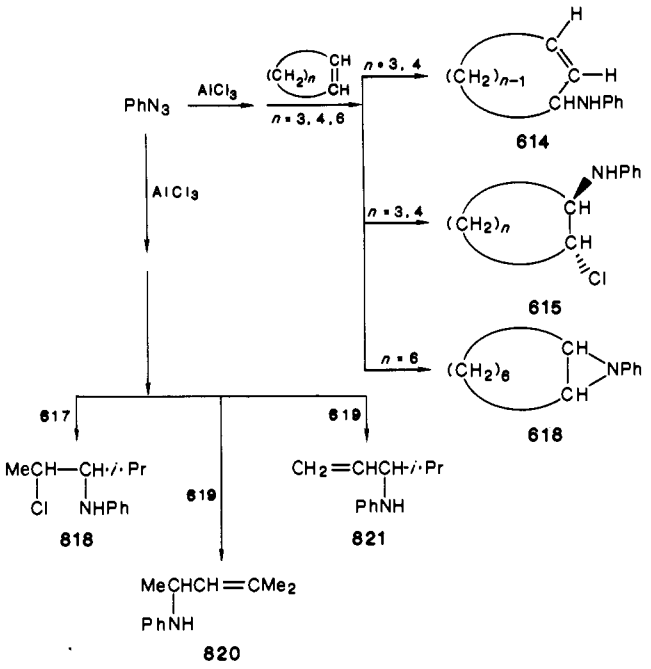


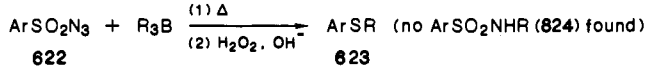
613

In the presence of $AlCl_3$, phenyl azide reacted with cyclohexene or cyclopentene to give *N*-allylanilines (**614**) and *N*-phenyl-β-chloroamines (**615**) (approximately 1:1) in 92% and 52% yield, respectively, after aqueous sodium carbonate workup.[426a] With *cis*-cyclooctene, aziridine **616** (47%) was instead isolated. Under the same conditions, *cis*-4-methylpent-2-ene (**617**) gave only the chloroamine **618** whereas *trans*-4-methylpent-2-ene (**619**) provided the allylamines **620** and **621**. Similar reactions occur in the presence of trifluoroacetic acid.[426b]

3. By Reaction with Boranes

For some time alkyl azides have been known to react with organoboranes to afford secondary amines.[427] A recent attempted extension of this process to arylsulfonyl azides (**622**) gave interesting results. Thus,



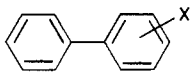


treatment of *p*-tolylsulfonyl or benzenesulfonyl azide with tricyclohexyl-, cyclopentyl-, hexyl-, or *exo*-norbornylborane gave the arylalkyl sulfides (**623**) in 45–70% yield instead of the expected sulfonamides (**624**).[428] The mechanism is unclear but the necessity for the azido function is manifest since tosyl chloride did not react under these conditions.

4. *Via Electrophilic Aromatic Substitution*

Examples involving cyclization are collected in section VI.A.3. Ethyl azidoformate reacts with benzene, toluene, or nitrobenzene in the presence of trifluoroacetic acid (TFA) to give ethyl *N*-arylcarbamates in 28–66% yield[429] (Scheme 24). With toluene, the product mixture consists of the ortho and para carbamates (42% and 24%, respectively), whereas ortho and meta carbamates (17% and 11%, respectively) are obtained from nitrobenzene. More recently, the study was extended to include naphthalene; (*N*-(1- and 2-naphthyl)carbamates were obtained in 42% and 12% yield, respectively) and the effects of other acids (viz., acetic, trichloroacetic, and trifluoromethanesulfonic).[430] The latter were less efficient in promoting the reaction than was TFA. The results of the study suggest that the mechanism involves electrophilic aromatic substitution by (ethoxycarbonyl)nitrenium ion.

Similar results were obtained for reactions of phenyl azide with benzene, toluene, or naphthalene in the presence of TFA; diarylamine products resulted.[431] In the reaction with benzene, C-substitution products, **625** and **626**, were also isolated in 11% and 12% yield, respectively.

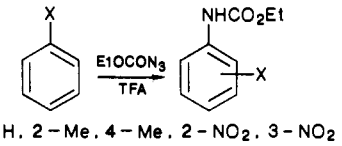


625. X = 2-NH_2
626. X = 4-NH_2

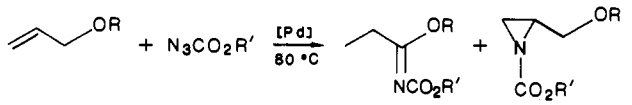
Aromatic N-substitution has also been reported for reactions of phenyl azide with benzene, toluene, cumene, chlorobenzene, bromobenzene, and biphenyl in the presence of a catalytic amount of trifluoromethanesulfonic acid.[432] Again, 2- and 4-substituted diarylamines were obtained in reasonable yield. Interestingly, with 1-azidonaphthalene, products of C-substitution resulted from the reactions with benzene and biphenyl.

Thermolysis of trifluoromethanesulfonyl azide in 1:1 mixtures of benzene and substituted benzenes gave trifluoromethanesulfonanilide and substituted analogues. The isomer ratios, the total rate ratios, and the partial rate factors for sulfonamidation were determined.[433]

SCHEME 24



SCHEME 25



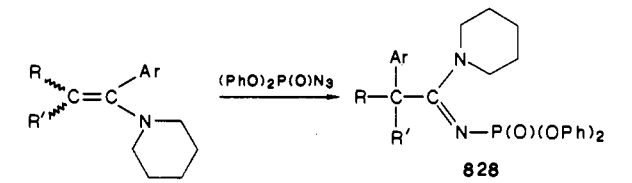
H. With Nucleophiles

Reactions of azides with nucleophiles leading to diazo compounds (Section III.I), amines (Section III.G), or iminophosphoranes (Section III.F) have been described previously.

Azidoformates exhibit reactivity toward a variety of nucleophiles at either the acyl group or the terminal nitrogen of the azide moiety.[13,434]

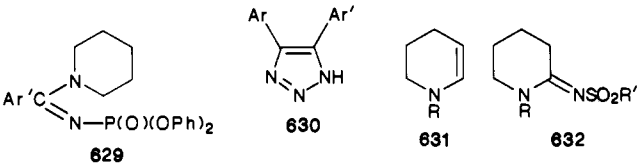
1. *Carbon or Silicon Nucleophiles*

A carbon–carbon double bond can play a nucleophilic role; often triazolines result (see section VI.B.2). On occasion, however, triazolines are intermediates and rearrangement products thereof are isolated (see section VI.B.3). α-Amino ketones have been obtained from azides and enamines[435] or enol acetates.[436] In contrast, the enamines **627** react with diphenyl phosphorazidate (DPPA) to give amidines **628**.[437] Interestingly, the



627 628

pyrrolidine enamines **627** (R = Ar′, R′ = H) reacted with DPPA to afford **628** as the major product (from **627** (R = Ar = Ph)), a mixture of **628** and **629** (from **627** (R = Ph; Ar = 2-pyridyl)), or the 1,2,3-triazole **630** as the main product (from **627** (R = 2-pyridyl; Ar = Ph)).[438] Presumably these products arise by different cleavage modes from the intermediate triazoline.



629 630 631 632

In light of these results it is perhaps surprising that N-substituted tetrahydropyridines (cf. **631**) form imines (cf. **632**) on treatment with aryl- or alkylsulfonyl azides.[439]

In contrast to the results of thermal and photoinitiated reactions, allylic ethers react with azidoformate in the presence of tetrakis(triphenylphosphine)palladium to give *N*-carboalkoxy imines as well as aziridines (Scheme 25).[440]

A more recent study of the generality of the reaction has shown that it is successful for acyclic unsaturated ethers in general and is catalyzed much more effectively by $PdCl_2(PhCN)_2$.[441] Under these conditions imines were formed in good yields (44–100%) and the corresponding aziridines were present in miniscule amounts.

Photolysis of ethyl azidoformate in the presence of some alkyl isonitriles gave carbodiimides and/or the corresponding ureas (Scheme 26).[442] A mixture of both products was obtained with R = cyclohexyl but with R = *tert*-butyl only the diimide was isolated (60%). Interestingly, 1-isocyano-2,3,4,6-tetraacetyl-β-D-glucopyranoside reacted to give only the corresponding urea in 75% yield.

SCHEME 26

$$R{-}N{=}C + N_3CO_2Et \xrightarrow[CH_2Cl_2,\ 24\text{-}36h]{h\nu} R{-}N{=}C{=}N{-}CO_2Et \xrightarrow{H_2O} RNHCONHCO_2Et$$

Silaketimine **635** is formed in quantitative yield from the reaction of azido-di-*tert*-butylchlorosilane (**633**) and (tri-*tert*-butylsilyl)sodium (**634**) at −78 °C in dibutyl ether.[433]

$$t\text{-}Bu_2SiClN_3 + t\text{-}Bu_3SiNa \rightarrow t\text{-}Bu_2Si{=}NSi\text{-}t\text{-}Bu_3$$
633 **634** **635**

2. Nitrogen Nucleophiles

Ethyl *N*-chlorocarbonate (**636**) reacts with ethyl azidoformate (to form diethyl iminodiformate (**637**)) or tosyl azide but not alkyl or aryl azides.[444] The reactions

$$EtOOC{-}\bar{N}ClNa^+ \xrightarrow{EtOCON_3} EtOCONHCO_2Et + NaCl + N_2$$
636 **637**

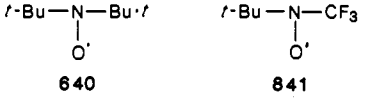
are enhanced by the use of Aliquat 336. Apparently, **637** is formed via attack of **636** at the carbonyl group of the azido species rather than at the terminal nitrogen, in agreement with hard and soft acid–base theory.

In a flowing afterglow device (trimethylsilyl)methyl azide (**638**) reacts rapidly with a variety of bases (F^-, NH_2^-, HO^-, MeO^-) to form an anion of m/z 28, to which

$$Me_3SiCH_2N_3 + B^- \rightarrow CH_2{=}N^- + CN^- + N_3^- + Me_3Si^-$$
638 **639**

was assigned the methanimine structure **639**.[445] Large amounts of cyanide ion and smaller quantities of azide and trimethylsilyl anions were also produced. Amide ion appears to generate the maximum amount of **639**.

Nitroxide radicals **640** and **641** were formed from the combination of trifluoromethanesulfonyl azide with 2-nitroso-2-methylpropane.[446] Similar results were obtained from the reactions of the latter with phenyl, tosyl, and benzoyl azides.



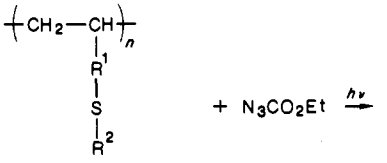
640 **641**

Displacement of the azido group, rather than attack at a nitrogen atom, occurred from treatment of benzenesulfinyl azide with nitrogen or sulfur nucleophiles.[447] Thus, with primary or secondary amines, sulfinamides were formed in 48–78% yield.

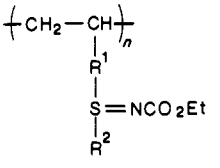
3. Sulfur or Selenium Nucleophiles

As alluded to in the previous section, benzenesulfinyl azide also reacted with thiols (at −20 °C) to give the corresponding thiosulfinates in 41–93% yield.[447]

In a process formally equivalent to the Staudinger reaction, sulfides react with azides to give iminosulfuranes.[448] Recently, this transformation was extended to sulfide-containing polymers.[449] Thus, **642** and **643** reacted with ethyl azidoformate under photolytic

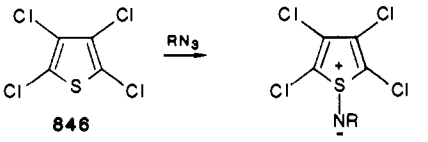


642. R^1 = *p*-C_6H_4, R^2 = Me
643. R^1 = nothing, R^2 = Et



644. R^1, R^2 as in **642**
645. R^1, R^2 as in **643**

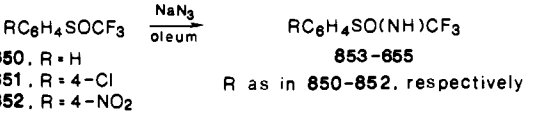
conditions to give the corresponding iminosulfuranes **644** and **645** in 17% and 30% yield, respectively. Similarly, iminosulfuranes **647–649**, the first examples of thienium-*S*-imides, were formed (44%, 23%, and 24%, respectively) by thermolysis of the appropriate azides in the presence of tetrachlorothiophene.[450] Similar intermediates from trithiapentalenes have been proposed (see section VI.C.2).



646

647. R = CO_2Et
648. R = CO_2Ph
649. R = $SO_2C_6H_4Me$-*p*

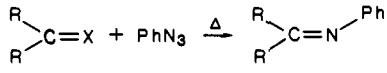
In contrast to aryl alkyl sulfoxides, aryl trifluoromethyl sulfoxides **650–652** do not iminate with sodium azide in sulfuric acid. However, if the latter is replaced by oleum, the *S*-(trifluoromethyl)-*S*-arylsulfoximides **653–655** are formed.[451]



650. R = H
651. R = 4-Cl
652. R = 4-NO_2

653–655
R as in **650–652**, respectively

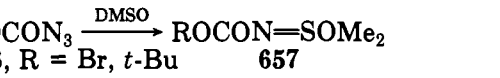
SCHEME 27



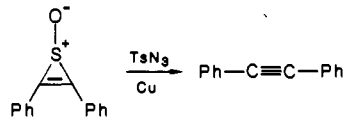
R = hindered alkyl; X = S, Se

SCHEME 28

Sulfoximides **657** are also formed in 50–60% yield by thermolysis of alkoxycarbonyl azides **656** in DMSO.[452]

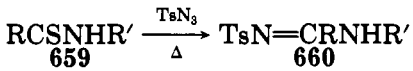


Diphenylthiirene 1-oxide (**658**) did not react with *p*-toluenesulfonyl azide to form the corresponding sulfoximide; instead diphenylacetylene resulted in 21.7% yield.[453]



858

Δ^2-Thiatriazolines are intermediates in the conversion of thioamides **659** to tosylamidines **660** (68–86%) with tosyl azide.[454]



R = Me, Ph; R′ = H, Ph, 4-tolyl, 4-anisyl, 4-$EtOC_6H_4$

Similarly, hindered thiones and selenones form *N*-phenylimines in 20–86% yield via thia- and selenatriazolines, respectively, on heating with phenyl azide (Scheme 27).[455]

I. Diazo Transfer

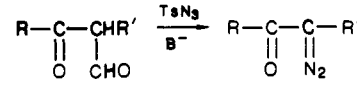
An excellent, comprehensive review of the diazo transfer process has appeared recently.[16] Accordingly, the present compilation is merely a synopsis of the general process with emphasis on recent uses.

The diazo transfer process generally involves attack of a carbon nucleophile upon an arylsulfonyl azide to form a diazo compound (Scheme 28). When the Z and Z′ groups are suitably electron withdrawing (e.g., COOR, CHO, COR, $CONR_2$, CO_2^-, CN, NO_2, SOR, SO_2R, SO_3R, SO_2NR_2, or one Ar), the carbon nucleophile can be generated by the action of a suitable base on the corresponding activated methylene species.[16,456] The efficacy of the process has been improved by the use of phase-transfer catalysis.[457] In the case of a ketone the nucleophilic species can be prepared by conversion to a (dialkylamino)methylene derivative.[458]

Introduction of the diazo group adjacent to a single carbonyl moiety can be achieved indirectly by converting the ketone to an α-formyl ketone and subsequent treatment with tosyl azide under basic conditions (vide infra) (Scheme 29).

Successful diazo transfer to simple aldehydes such as acetaldehyde has not been reported, presumably due

SCHEME 29

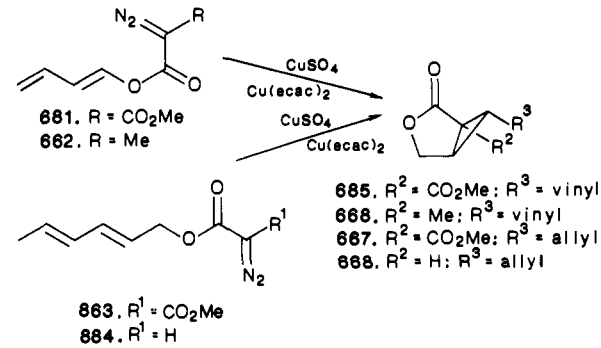


to competing reactions (viz., aldol condensation and polymerization) during the attempted preparation of the appropriate enolate ions. However, various workers[459] have demonstrated that the lithium enolate of acetaldehyde can be generated in the absence of such complications by the cycloreversion of THF in the presence of *n*-butyllithium, and recently this approach was extended to reaction of the incipient enolate with aryl and tosyl azides.[460] Except for azides having no electron-withdrawing groups, decomposition ensues within 0.5 h and formamides (22–86%) and amines (0–24%) corresponding to the starting azides can be isolated. The formation of diazomethane was also demonstrated and in two cases (viz., 2-Me- and 2-$EtSO_2C_6H_4N_3$) this may be of synthetic utility (70% yield).

Tosyl azide is the most commonly employed azide but *p*-dodecylbenzenesulfonyl azide,[461] *p*-carboxybenzenesulfonyl azide,[456] polymer-bound tosyl azide,[462] triflyl azide,[463] (azidochloromethylene)dimethylammonium chloride,[464] trisyl azide,[465] and 4-nitrophenyl azide[466] have found some use. 4-Cyclopentene-1,3-dione was converted to the diazo congener with 2-azido-3-ethyl-1,3-benzothiazolium tetrafluoroborate in an alkaline medium.[467] The same reagent and 1-ethyl-2-azidopyridinium tetrafluoroborate have been reported previously.[468]

A major factor in the continued search for new diazo transfer reagents has been the difficulty encountered in the separation of the diazo product from excess reagent and 4-toluenesulfonamide following diazo transfer with tosyl azide. Accordingly, 4-carboxybenzenesulfonyl azide has been recommended as a replacement for the latter since it is soluble in base. Recently,[469] the much less expensive but still base-soluble reagent mesyl azide[470] was shown to be an excellent alternative.

The diazo compounds resulting from these procedures have enjoyed extensive exploitation as carbene or carbenoid precursors.[471] Thus, the diazo esters **661–664** form the corresponding cyclopropanes **665–668**, respectively, in 46–84% yield on treatment with $CuSO_4$ and $Cu(acac)_2$ in refluxing benzene.[472]



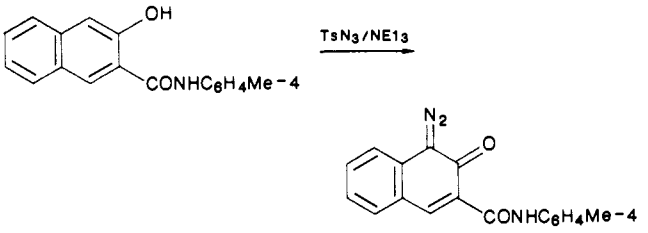
661. R = CO_2Me
662. R = Me

665. R^2 = CO_2Me; R^3 = vinyl
666. R^2 = Me; R^3 = vinyl
667. R^2 = CO_2Me; R^3 = allyl
668. R^2 = H; R^3 = allyl

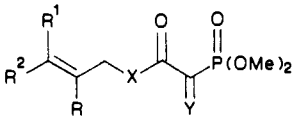
663. R^1 = CO_2Me
664. R^1 = H

Intramolecular cyclopropanation of α-diazo-β-ketophosphonates (cf. **670**) using copper powder has also been reported.[473] Formation of the diazo compounds **670** from the corresponding activated methylene compounds **669** was effected in 80–96% yield by using tosyl

SCHEME 30

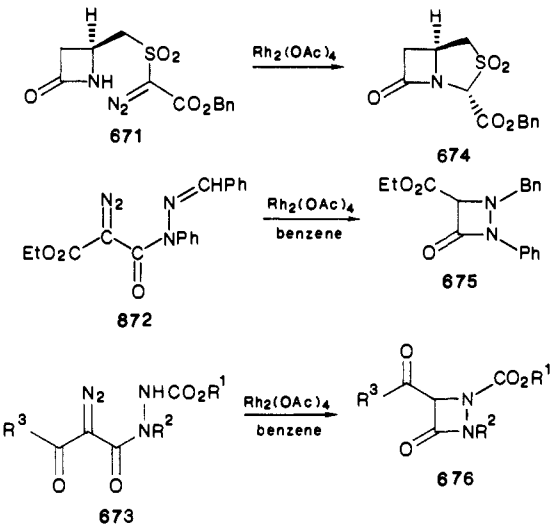


azide and sodium hydride. The yields were considerably lower when triethylamine was used as base.



889, R, R^2 = cyclic; R^1 = H; X = CH_2, O; Y = H_2
R = H; R^1 = R^2 = H; X = CH_2, O; Y = H_2
670, Y = N_2, rest as above

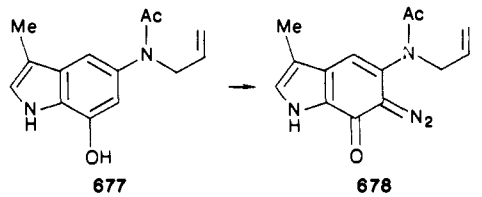
Diazo compound cyclization reactions have been considerably enhanced by the use of rhodium(II) acetate as catalyst. Thus, the novel β-lactam **674** and aza β-lactam analogues **675** and **676** were prepared in ex-



cellent yield (75–100%) by heating the corresponding diazo compounds **671–673** with a catalytic quantity of rhodium(II) acetate.[474-476] A cephalosporin analogue has been prepared similarly.[477] The diazo compounds were in turn synthesized in variable yield by diazo transfer to the activated methylene precursors. Tosyl azide was the reagent of choice for this process except for in the case of **671**, where *p*-carboxybenzenesulfonyl azide was employed.

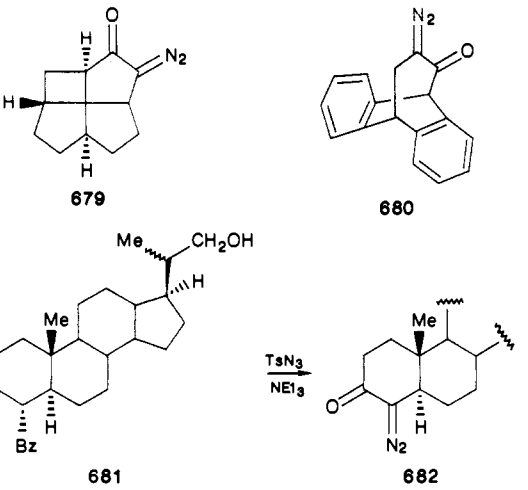
Diazo transfer to phenols has also been reported,[478] and recently this process was used to prepare 3-(*p*-tolylcarbamoyl)-1,2-naphthoquinone 1-diazide (Scheme 30).[479]

An attempt to convert phenol **677** to the corresponding quinone diazide **678** using tosyl azide was unsuccessful; the product mixture consisted primarily



of materials containing two *p*-toluenesulfonamide groups.[430] These compounds were not characterized but were suggested to be of the same type as those obtained from reaction of alkylindoles and tosyl azide.[481] Successful conversion of **677** to **678** was realized in 45% yield by using *m*-nitrobenzenesulfonyl azide and trifluoroethanol as solvent. The latter had been reported to be an excellent solvent for the diazo transfer reaction between β-naphthol and tosyl azide.[482]

As briefly mentioned previously, α-formyl ketones can be directly converted to the corresponding α-diazo ketones by treatment with tosyl azide and triethylamine. In this manner Dauben and Walker[483] prepared the fenestrane derivative **679** and Banciu[484] synthesized **680**. Some modifications on this process have been reported. Thus, the benzoyl group can perform the same function as the formyl moiety (cf. **681** → **682**).[485]

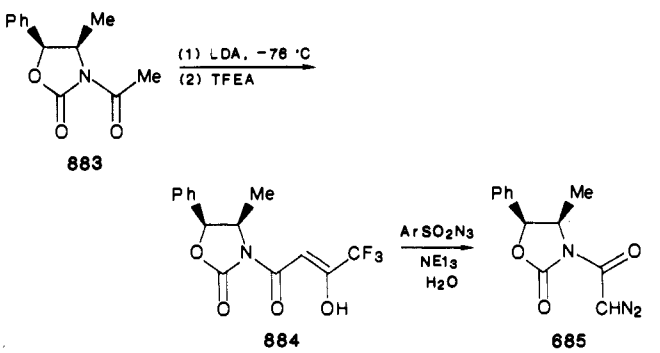


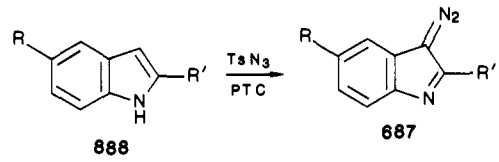
The trifluoroacetyl group has been utilized similarly, with the advantage that its removal is more facile.[486] Thus, *N*-acetyloxazolidone **683** was converted to **684** with LDA and 2,2,2-trifluoroethyl trifluoroacetate (TFEA) (Scheme 31). Subsequent diazo transfer in the presence of no more than 1 equiv of water gave **685** directly. Direct diazo transfer with **683** was not successful.

Diazo transfer to heterocyclic systems has also been reported. Thus, 2-arylindoles **686** (R = H, F, Cl; R′ = Ph, 2-pyridyl, 2-thienyl) react with tosyl azide under phase-transfer conditions (benzyltriethylammonium chloride) to give the corresponding 3-diazo-3*H*-indoles **687**.[487]

Treatment of diketopiperazine derivative **688** (X = H_2) with *n*-butyllithium and tosyl azide gave the cor-

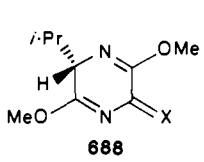
SCHEME 31



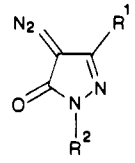


688 687

responding diazo compound 688 (X = N_2), which was



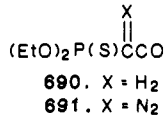
688



689, R^1 = Ph, Me; R^2 = H, Ph

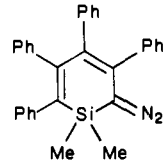
used in situ as a synthetic equivalent of aminocarboxycarbene.[488] More routinely, diazopyrazolinones 689 have been prepared by treatment of the parent pyrazolinones with tosyl azide/triethylamine.[489]

Ethyl (diethoxythiophosphoryl)diazoacetate (691), the first thiophosphoryl diazocarbonyl compound, was prepared in 22% yield by treating 690 with potassium *tert*-butoxide followed by tosyl azide.[490]



690, X = H_2
691, X = N_2

692



693

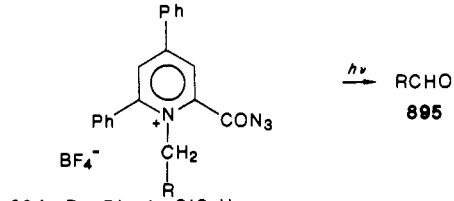
In a variation of the standard diazo transfer process, (trimethylsilyl)diazomethane (692) was prepared in 78.6% yield by reaction of [(trimethylsilyl)methyl]-magnesium chloride with diphenylphosphoroazidate [$(PhO)_2P(O)N_3$].[491] The first example of a 6-diazosilacyclohexa-2,4-diene (693) was also prepared by diazo transfer (*n*-BuLi/tosyl azide).[492]

Diazo transfer to amines affords azides and this is covered in section II.J.

J. Other Reactions

A few azide transformations have been reported that do not fit into the categories described so far.

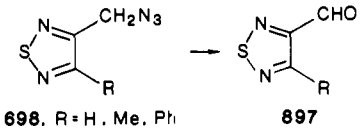
Thus, irradiation of 1-substituted 2-(azidocarbonyl)-4,6-diphenylpyridinium tetrafluoroborates 694 gave the aldehydes 695 (60–76%) expected from cleavage of the R group except for 694 (R = $PhCH_2$) and 694 (R = $CH_2C_6H_4Cl$-*p*), where benzaldehyde and phenylacetaldehyde (2:1) and *p*-chlorobenzaldehyde, respectively, were formed.[493]



694, R = Ph, 4-ClC_6H_4, 4-MeC_6H_4, *n*-Pr, $PhCH_2$, 4-$ClC_6H_4CH_2$

695

Aldehydes 697 (68–83%) also result from the dropwise addition of thiadiazolylalkyl azides 696 to concentrated sulfuric acid at −5 to 0 °C.[494]

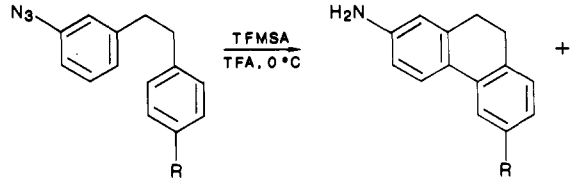


698, R = H, Me, Ph 697

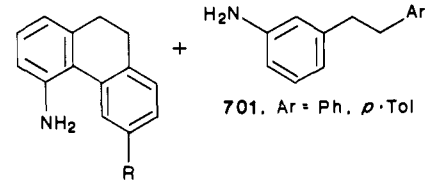
IV. Applications in Alicyclic Chemistry

A. Cyclizations

Bibenzyl derivatives 698 react with trifluoromethanesulfonic acid (TFMSA) at 0 °C to give the cyclized species 699 (major) and 700 and small quantities of the hydrogen abstraction products 701.[495] The process can be extended to *trans*-*m*-azidocinnamate.

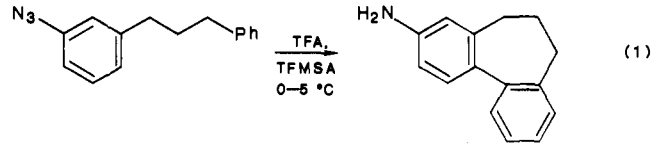


698, R = H, Me 699



700 701, Ar = Ph, *p*-Tol

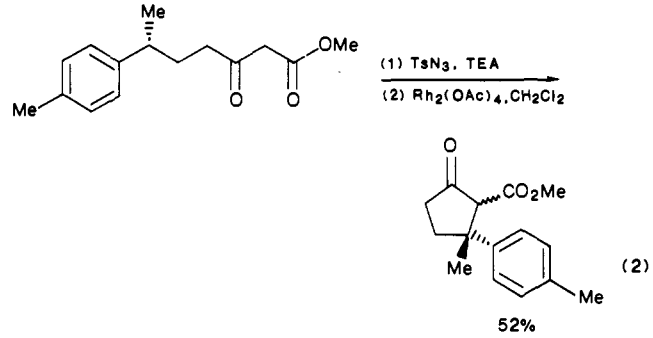
Similar treatment of 3′-azido-1,3-diphenylpropane results in a high-yield cyclization to a seven-membered ring (eq 1).[496]



(1)

80%

Reaction of tosyl azide with active methylene compounds gives diazo compounds which subsequently may be converted to carbenes with rhodium diacetate (see section III.I for other examples). Recently, this methodology has been extended to provide a generally applicable strategy for the enantioselective construction of a chiral quaternary center (eq 2).[497]

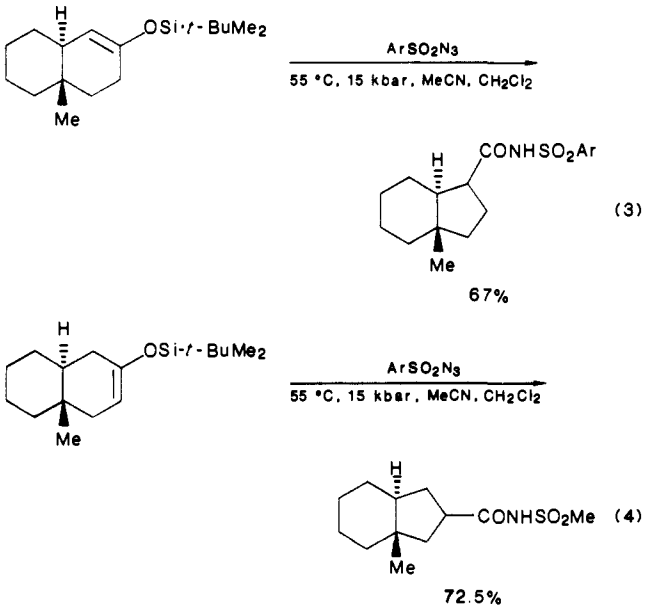


(2)

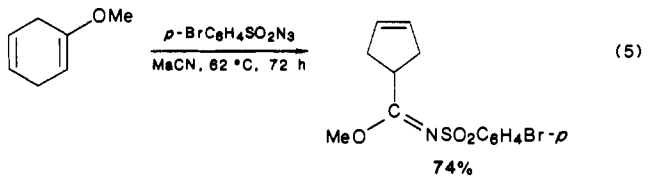
52%

B. Ring Contractions

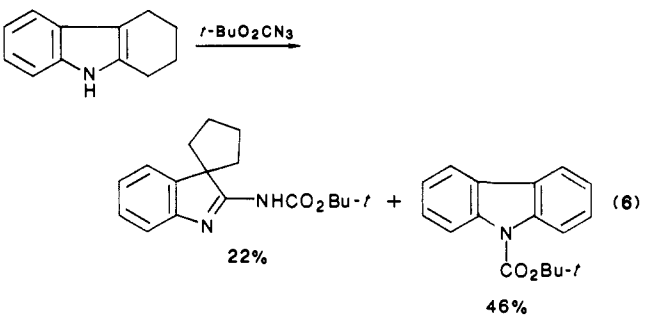
Hindered silyl enol ethers undergo ring contraction via triazolines when allowed to react with arylsulfonyl azides under pressure.[498] Enol ethers give cleaner products with greater regiospecificity than do enamines (eq 3 and 4).



Methyl enol ethers produced by Birch reduction of anisoles have been found to undergo reaction at ambient pressure and moderate temperature (eq 5).[499]



Recently, phosphoryl azides have been used to effect the ring contraction of cyclic enamines in moderate to good yield.[500] An interesting variation of this ring contraction, which leads to a spiro product, involves initial addition of *tert*-butyl azidoformate to a tetrahydrocarbazole (eq 6).[501]



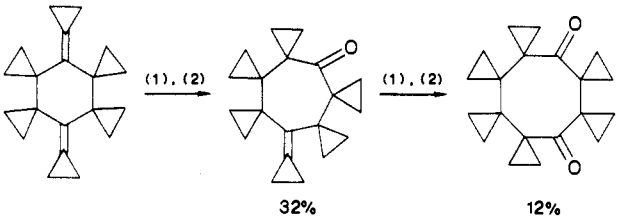
C. Ring Expansions

An interesting ring expansion of alicycles with an exocyclic methylene group involves an azide cycloaddition followed by treatment with base (Scheme 32).[502]

D. Rearrangements

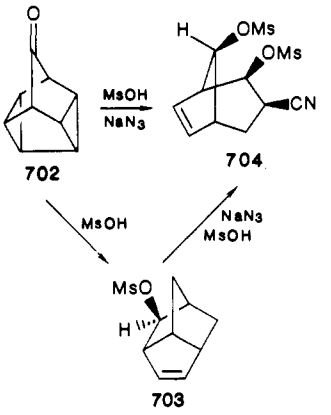
On occasion interesting rearrangements occur under Schmidt conditions. Thus, homocuneone (**702**) reacts with sodium azide in methanesulfonic acid at 0–5 °C (20 min) to yield the unusual cyano dimesylate **704** in ca. 20% yield.[503] It was surmised that acid-catalyzed rearrangement of **702** preceded Schmidt fragmentation and this premise was confirmed by isolation of **703** on treatment of **702** with methanesulfonic acid alone.

SCHEME 32[a]



[a] (1) p-$NO_2C_6H_4SO_2N_3$; (2) KOH, MeOH.

Subsequent conversion of **703** to **704** could then be effected in ca. 40% yield. The homocuneone (**702**) → 8-ketobrendane (**703**) transformation appears to be fairly general and occurs with a variety of acids and electrophiles. Other rearrangements of alicyclics have been reported by the same research group.[504]

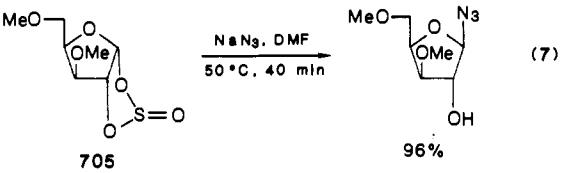


V. Applications in Carbohydrate Chemistry

A. Synthesis

Methods for the introduction of the azido group into sugars have been well studied, as the azido group can be reduced easily under a variety of conditions to afford amino sugars[505] (see also section III.A). Preparations of azido carbohydrates are discussed here, rather than in section II, where considerations of carbohydrate chemistry are paramount.

Cyclic sulfate **705** undergoes regioselective ring opening to give the trans alcohol (eq 7).[506]

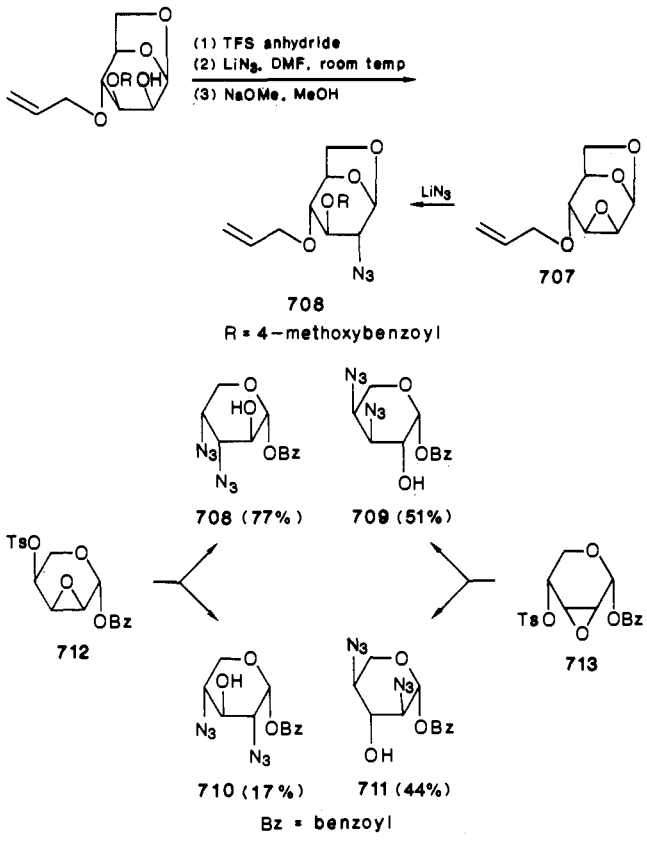


Azide **706** may be prepared in four steps from 1,6-anhydro-β-D-mannopyranose (Scheme 33).[507] The last three steps occur in good overall yield. This contrasts with the former method, which involves treatment of **707** under vigorous conditions[508] (see section II.B for another example of triflate replacement).

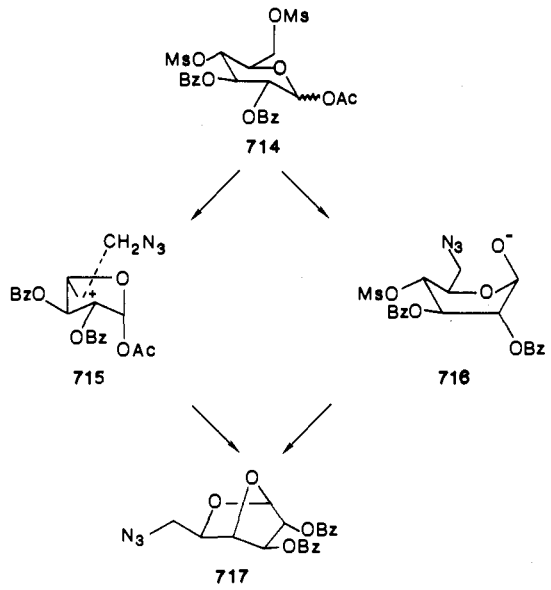
Four new diazido sugars (**708–711**) have been made by treatment of the anhydro tosylribopyranosides **712** and **713** with sodium azide.[509]

Mesylate **714** reacts with sodium azide to give the azidogalactopyranose derivative **717**.[510] Oxygen-17 NMR and oxygen-18 induced shifts in carbon-13 NMR support the intermediacy of azido mesylate **716** rather than the alternative carbenium ion **715**[510] (see section

SCHEME 33



II.B for tosylate replacement).

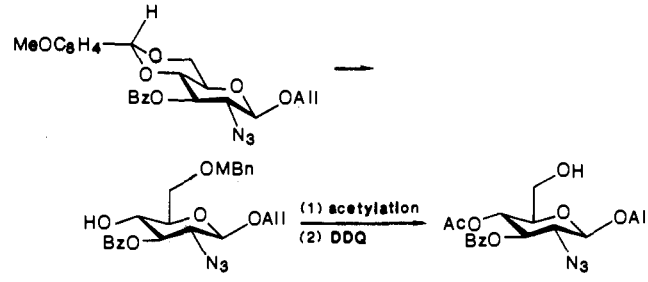


The synthesis of chemically modified cyclodextrins has been reviewed, and this review contains a section on azido derivatives.[511] Azido carbohydrates are discussed in another general review of hydrazine derivatives of carbohydrates.[512]

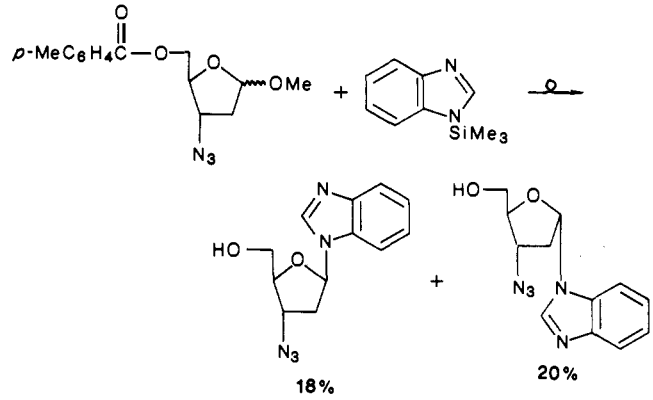
B. Survival of Azido Groups during Other Manipulations

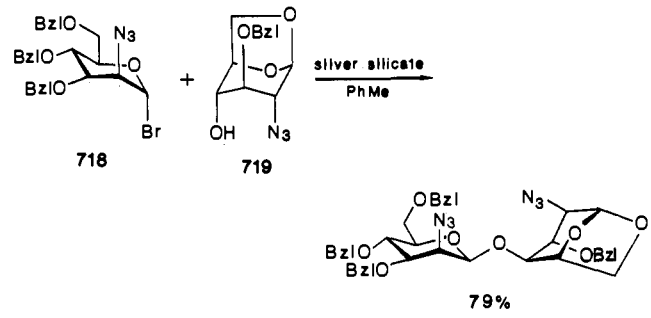
Apart from ease of reduction, the presence of an azido group at C-2 in a sugar has the advantage of nonparticipation during the formation of α- and/or β-glycosidic linkages[513] (for other examples of azide survival, see section II.L). For example, glycosyl bromide 718 has been condensed with the 4-hydroxy group of the glycosyl acceptor 719.[514]

SCHEME 34



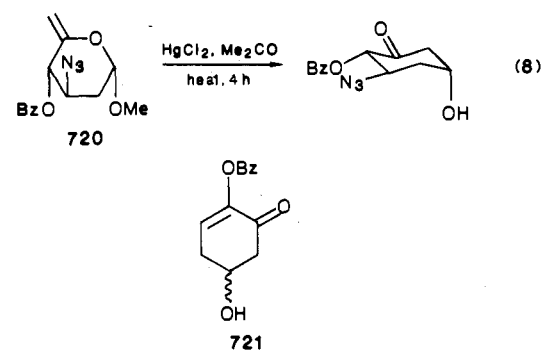
SCHEME 35





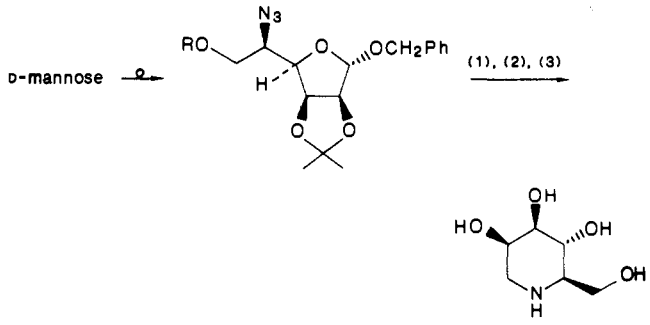
In another paper, the effect of a C-2 azido substituent on the β/α ratio in glycosidic bond formation relative to 4-*O*-alkyl functions has been studied.[515] Recently, it was found that a 4-methoxybenzylidene acetal could be opened reductively and the so formed 4-methoxybenzyl ether removed by oxidation with DDQ without affecting the C-2 azido function (Scheme 34).[505] No acetyl ester migration from C-4 was noted.

The azido functionality can survive the Ferrier transformation to provide a 1,3-diaminocyclitol precursor (eq 8).[516] However, the erythro analogue of **720** undergoes elimination of hydrazoic acid to give **721**.



(8)

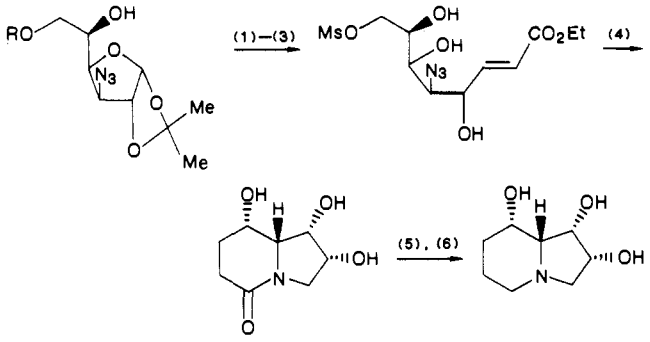
SCHEME 36[a]



R = $SiPh_2Bu$-*t*

[a] (1) Bu_4NF, THF, room temperature; (2) CF_3CO_2H, dioxane, H_2O; (3) palladium hydroxide, H_2, MeOH.

SCHEME 37[a]



[a] (1) MsCl, pyridine; (2) CF_3CO_2H, H_2O (9:1); (3) Ph_3P=$CHCO_2Et$, THF; (4) H_2, 10% Pd/C, MeOH; (5) $(Me_3Si)_2NH$, Me_3SiCl; (6) BH_3·Me_2S, THF.

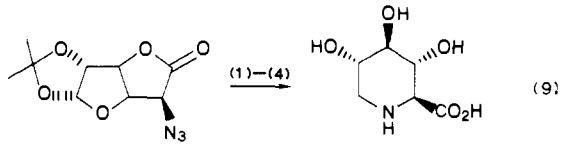
Azides survive glycosidation with 1-(trimethylsilyl)-benzimidazole (Scheme 35).[517]

C. Reductive Cyclizations (See Also Section III.C)

1,5-Dideoxy-1,5-imino-D-mannitol can be synthesized from D-mannose via hydrogenation of a 5-azido-5-deoxymannose (Scheme 36). A route from D-glucose has also been described.[518]

Two stereoisomers of swainsonine have been synthesized by similar sequences (Scheme 37).[519]

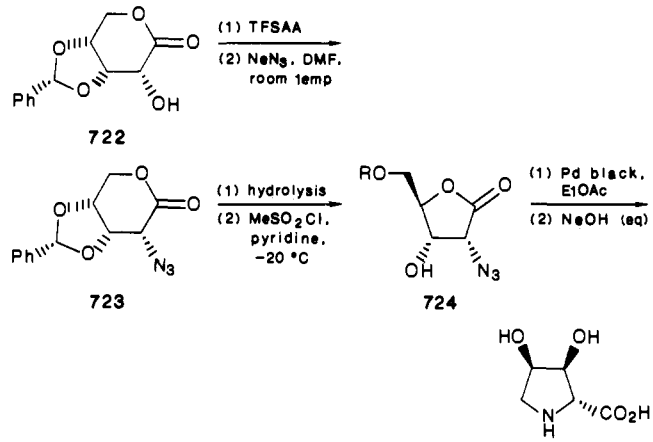
Reductive cyclization of the isopropylidene derivatives of D-glucuronolactone gives a trihydroxypipecolic acid (eq 9).[520]



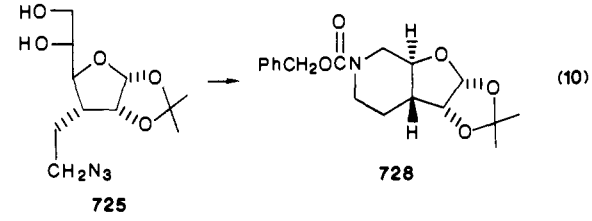
(1) H_2, 10% Pd/C, EtOAc; (2) $PhCH_2OCOCl$, $NaHCO_3$, EtOAc, H_2O; (3) CF_3CO_2H, H_2O, room temperture; (4) H_2, Pd black, H_2O, HOAc (9:1), 4 days

Treatment of D-ribonolactone with benzaldehyde in concentrated hydrochloric acid gives Zinner's lactone (**722**), the triflate of which rather surprisingly gives azide **723** with retention of configuration.[521] Conversion to 1,4-lactone **724** and reduction affords 2(*R*),3(*S*),4-(*R*)-dihydroxyproline (Scheme 38) (see ref 522 for another example of hydroxypyrrolidine synthesis).

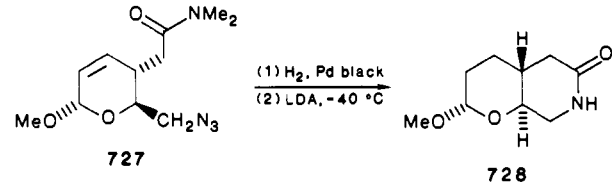
SCHEME 38



Successive treatment of **725** with sodium iodate, hydrogen/palladium black, and $PhCH_2OCOCl$ provides benzyl carbamate **726** in 66% overall yield.[523]



Hydrogenation of azido amide **727** in the presence of palladium black in ethanol reduces both the double bond and the azide to an amine, which can be cyclized to lactam **728** with LDA.[524]

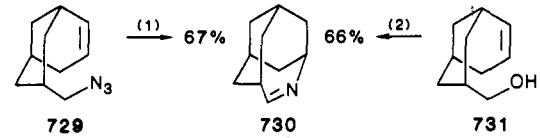


VI. Heterocyclic Synthesis

A. Cyclizations

1. Alkyl Azides

Azide **729** cyclizes to 4-azahomoadamant-4-ene (**730**) in the presence of methanesulfonic acid; **730** is obtained also from alcohol **731**.[525]



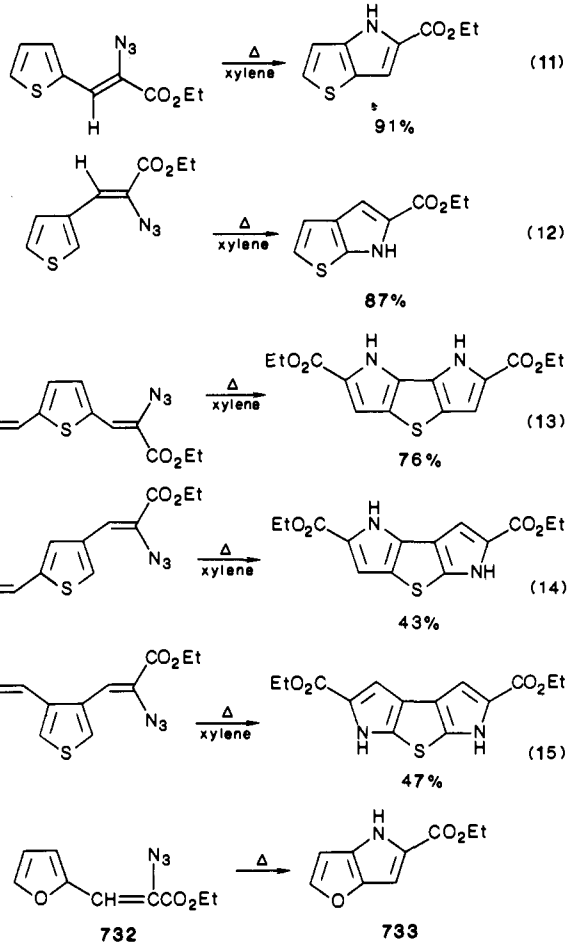
(1) $MeSO_3H$, CH_2Cl_2, room temperature, 30 min; (2) NaN_3, $MeSO_3H$, CH_2Cl_2

2. Vinyl Azides

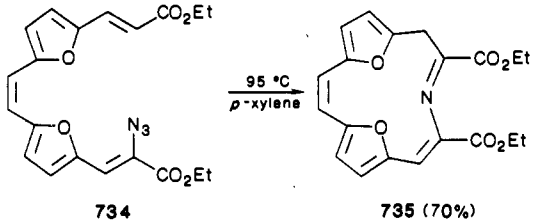
An important method for the construction of five-, six-, and seven-membered fused nitrogen heterocycles, based on the cyclization of azidoacrylate has been developed into a powerful synthetic method by Moody and Rees. Hemetsberger and co-workers[526,527] found that azidocinnamates, which are readily prepared from the corresponding benzaldehyde, ethyl azidoacetate,

and sodium ethoxide, undergo ring closure to indoles. The intermediate azirine can be observed by NMR when the thermolysis is carried out at 80 °C. Recently, Knittel[528] obtained indoles in virtually quantitative yields at 140 °C and azirines at 80 °C (Scheme 39).

Monovinyl (eq 11 and 12)[529] and divinyl (eq 13–15) azido thiophenes[530] have proved to be useful precursors for the annulation of pyrroles to thiophenes.



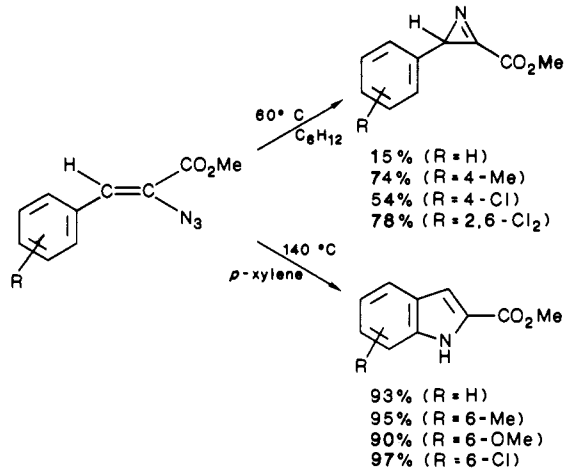
Azido furan **732** predictably undergoes cyclization to furopyrrole **733**.[531] However, **734** gives the azaannulene **735** by intramolecular cycloaddition without any furopyrrole formation, thus providing a convenient high-yield azaannulene synthesis.[531]



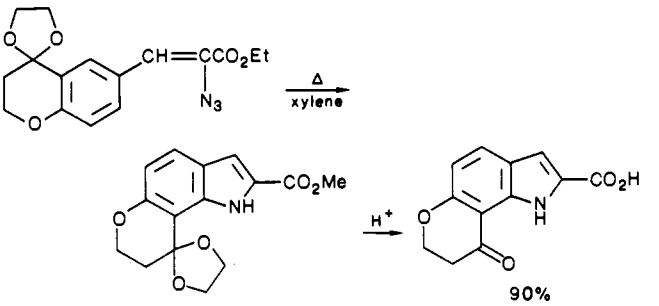
The preparation of acryl azides under strongly basic conditions is confined to aldehydes that cannot undergo competitive condensations. Remote carbonyl groups may be protected to avoid this disadvantage, as for example in the synthesis of oxopyrano[*g*]indoles (Scheme 40).[532]

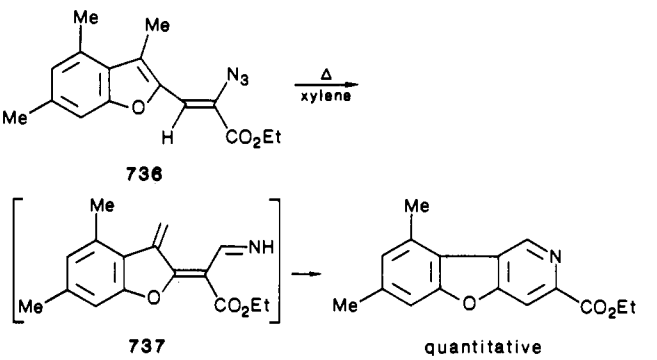
Where cyclization to a five-membered ring is blocked, closure can take place at an *o*-methyl group to give a pyridine ring. (2-Azidoacrylyl)benzofuran **736** undergoes cyclization in quantitative yield to a benzofuran[3,2-*c*]pyridine via an enamine (**737**) rather than by direct insertion.[533]

SCHEME 39



SCHEME 40

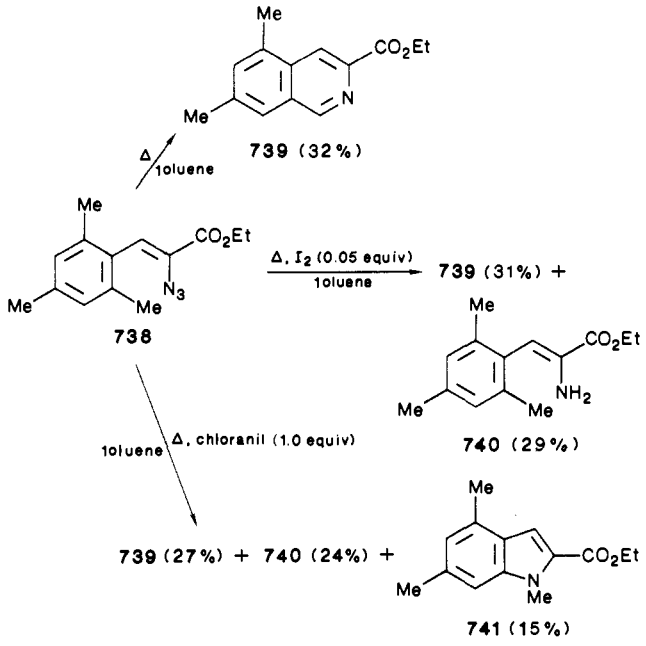




Rees, Moody, and co-workers have studied these reactions extensively from both a mechanistic and a synthetic viewpoint. They have found that decomposition of an azidocinnamate (**738**) with blocked ortho positions in the presence of an oxidant profoundly affects the nature of the products (Scheme 41).[534]

It was hoped that added iodine would oxidize the intermediate dihydropyridine to **739** before H abstraction by nitrene occurred to give enamine **740**. Formation of **741** in the presence of chloranil is interesting as it provides the first instance of indole formation by cyclization to a "blocked" ortho position followed by a methyl shift. The requirement of two ortho blocking groups would limit this as a general isoquinoline synthesis to isoquinolines with a 5-substituent. Therefore, the same workers[534] studied the effect of oxidants on indole versus isoquinoline formation for a series of azidocinnamates bearing only one substituent ortho to the azidoacrylyl group (Scheme 42). Isoquinoline yield increased from 2 to 52%, and indole

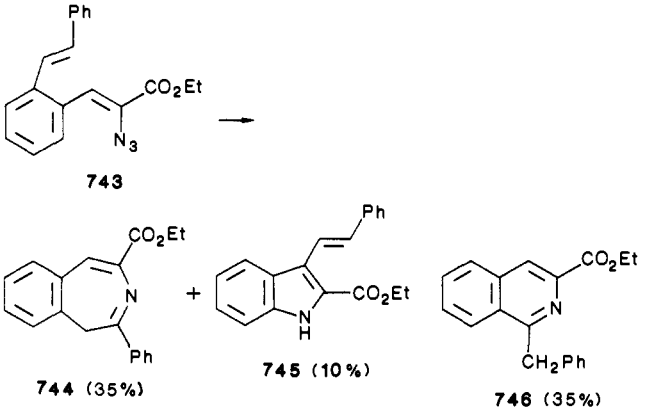
SCHEME 41



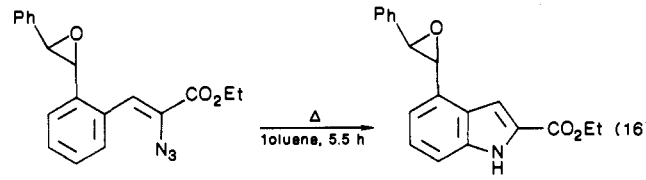
yield fell when thermolysis of **742** was carried out in the presence of iodine and potassium acetate.

The above difficulties were avoided by using azidocinnamates with an ortho carbonyl substituent which on treatment with TEP undergo intramolecular aza-Wittig reaction to give isoquinolines in very high yield (Scheme 43).[535] This procedure has the advantage of high-yield, mild conditions, and it offers an alternative to the more common isoquinoline syntheses which require at least one electron-donating substituent in the benzene ring to promote an electrophilic ring closure.

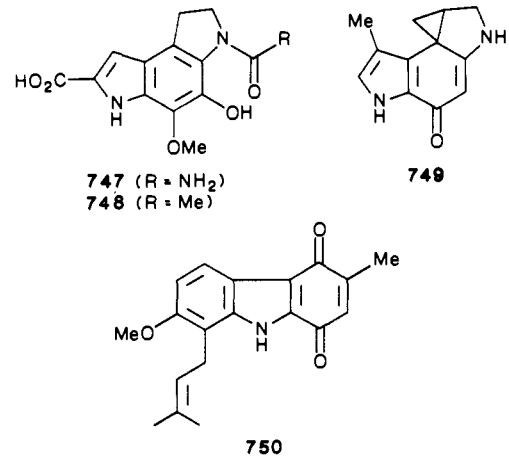
Decomposition of *o*-styrylazidocinnamate **743** in boiling toluene affords benzazepine **744** as well as the anticipated indole **745** and isoquinoline **746**.[536]



Exclusive indole formation can be achieved in good yield by protecting the ortho olefinic substituent as the epoxide (eq 16).[537]



Azidocinnamate cyclizations provide the key steps (i.e., construction of both pyrrole rings) in the synthesis of the phosphodiesterase inhibitors PDE-I (**747**) and PDE-II (**748**),[538] the left-hand unit of the potent antitumor agent CC-1065 (**749**),[539] and the pyrrole ring of murrayaquinone-B (**750**).[540]



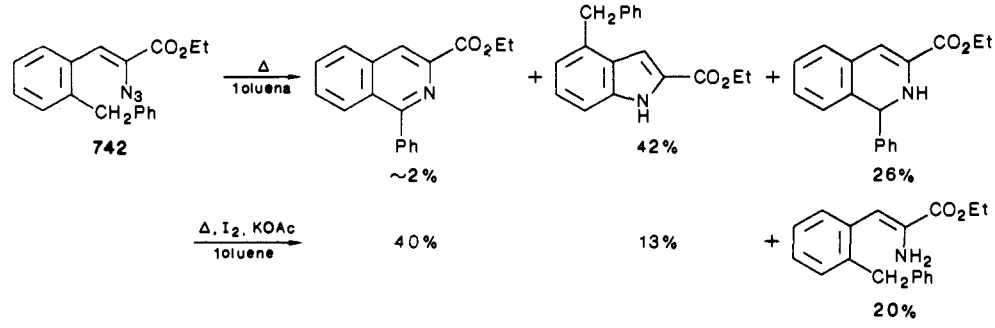
Azepines can be the preferred products of decomposition of azidocinnamates bearing an ortho cycloalkenyl substituent of appropriate ring size.[541] Here intramolecular cycloaddition via a dihydrotriazole intermediate is proposed (Scheme 44).

Moody has annulated pyrroles,[542] pyridines, and azepines[543] to the 2,3-positions of suitably substituted indoles (Scheme 45).

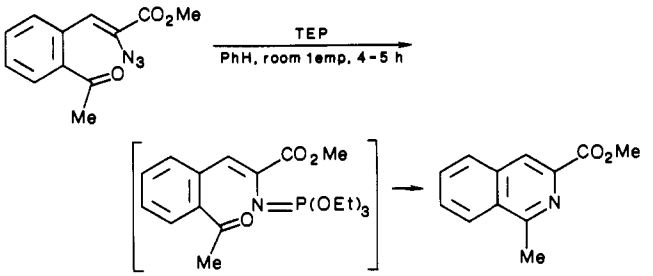
The presence of an *o*-thiophenoxy group in the azidocinnamate results in the formation of a benzothiazine on thermolysis (Scheme 46).[544]

2,5-Diarylpyrroles have been prepared in quite good yields by the hexacarbonylmolybdenum-mediated dimerization of arylvinyl azides. Two possible reaction pathways have been suggested (Scheme 47).[545]

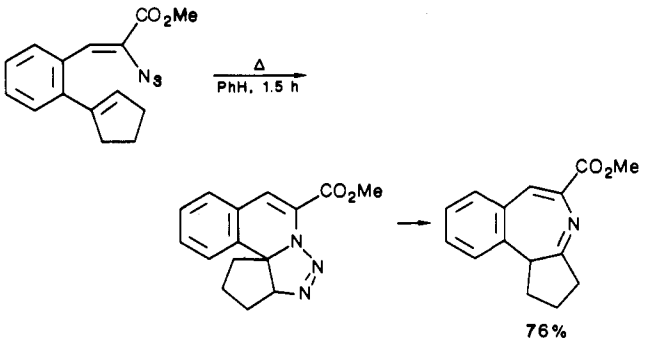
SCHEME 42



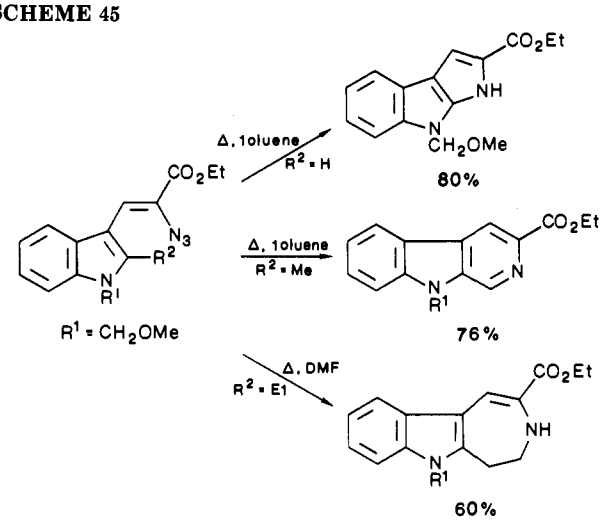
SCHEME 43



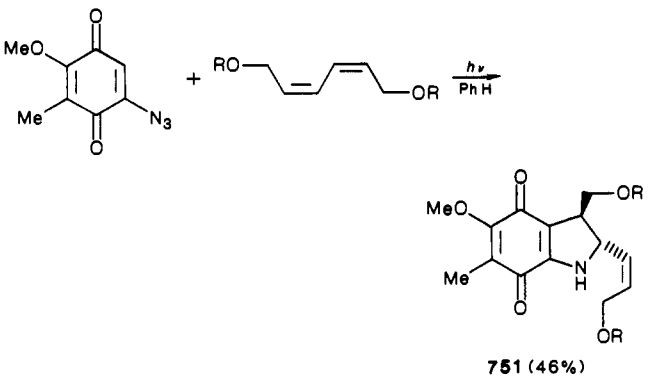
SCHEME 44



SCHEME 45



A mitomycin precursor (751) has been prepared with high stereoselectivity by photolysis of an azidoquinone and a *cis,cis*-diene.[546]

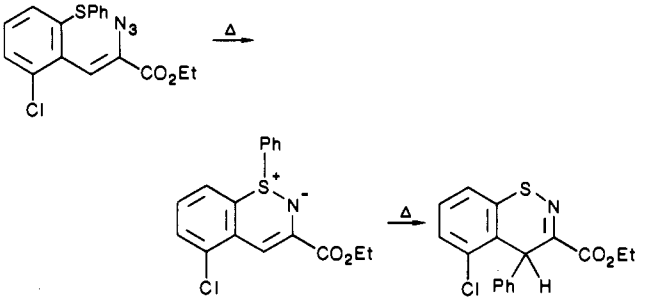


751 (46%)

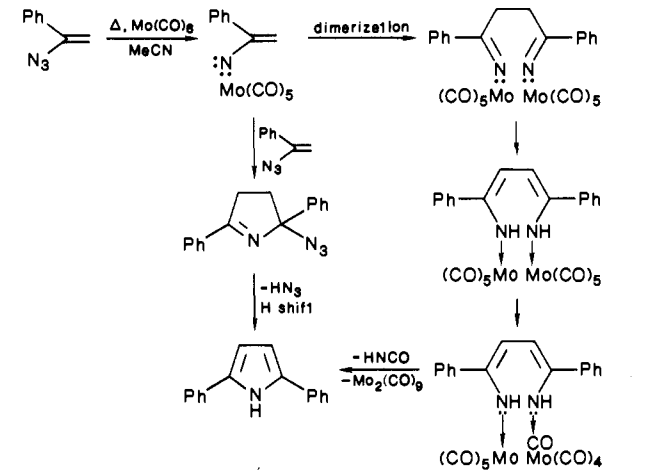
3. Aryl and Heteroaryl Azides

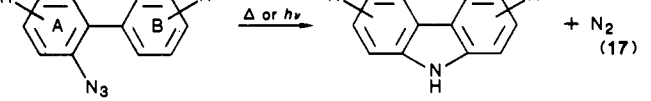
Intramolecular cyclizations of aryl and heteroaryl azides to form five-, six-, and seven-membered rings are well-known general high yield processes. They have been reviewed several times recently; therefore older work will not be discussed in detail here. The prototype of these reactions, the cyclization of *o*-azidobiphenyl to carbazole, was reported by Smith and Brown in 1951 (eq 17).[547]

SCHEME 46



SCHEME 47

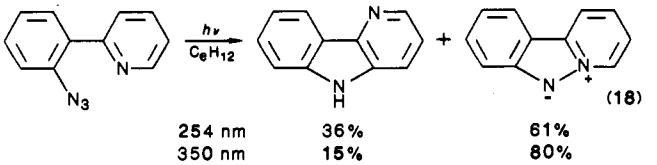




(17)

The reaction is typically carried out thermolytically at 150–200 °C in, for example, di- or 1,2,4-trichlorobenzenes or by photolysis.[548] Yields are usually excellent[549] regardless of the nature of the substituents attached to rings A and B. However, attachment of ortho substituents (e.g., nitro) that provide the opportunity for a competing non-nitrene reaction does prevent carbazole formation via a singlet nitrene process.

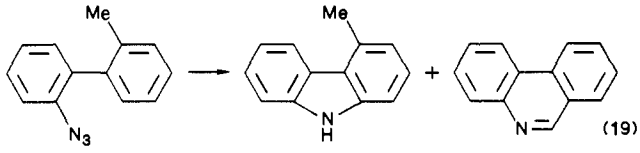
Replacement of ring A or B of the azidobiphenyl by various heterocyclic systems (e.g., thienyl and pyridyl)[550] also usually leads to good-yield cyclizations on decomposition. The wavelength chosen for photolysis can have a significant effect upon the yields of products formed (eq 18).[551]



(18)

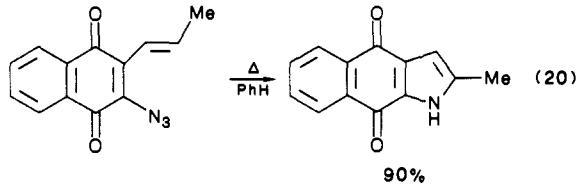
Cyclization onto a suitably placed methyl group is promoted under triplet nitrene forming conditions (eq 19), although carbazole formation is still significant.[552] However, this process is not as efficient as carbazole

formation under "singlet conditions".

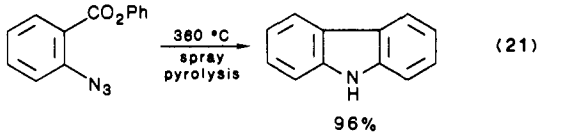


The report of the thermolysis of an azido-1,2-quinone is of interest as it results in the formation of an indoloquinone rather than zwittazido cleavage (Scheme 48).[553a]

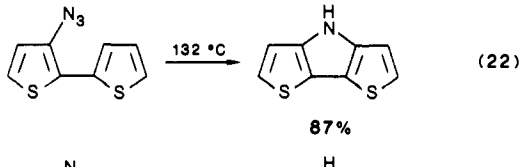
This offers an alternative to the other azide ring closure route to indoloquinone (eq 20),[553b] and it promises to have generality.

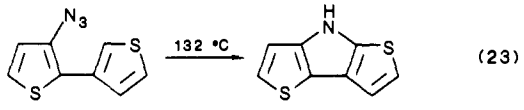


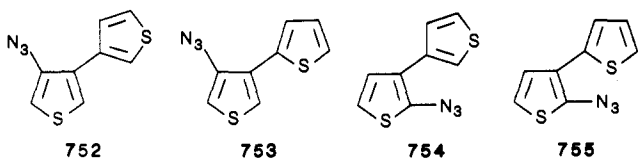
o-Azidobenzoates yield carbazoles on spray pyrolysis with loss of carbon dioxide (eq 21).[554] This is the first example of the successful decomposition of an azido aromatic having two atoms between the rings. On solution thermolysis this reaction is not observed.



In contrast to the extensive work on carbazole synthesis, little was known of the cyclization of *o*-azidobithienyls to dithienopyrroles. Now an extensive study has appeared,[555] employing *o*-azidobithienyls newly available by treatment of lithiobithienyls with tosyl azide and subsequent fragmentation of the intermediate lithium triazene salts.[228] Both 3-azido-2,2′-bithienyl and 3-azido-2,3′-bithienyl undergo cyclization readily in high yield in boiling chlorobenzene (eq 22 and 23), but the

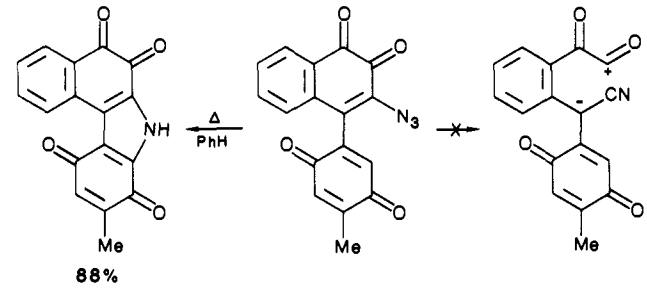




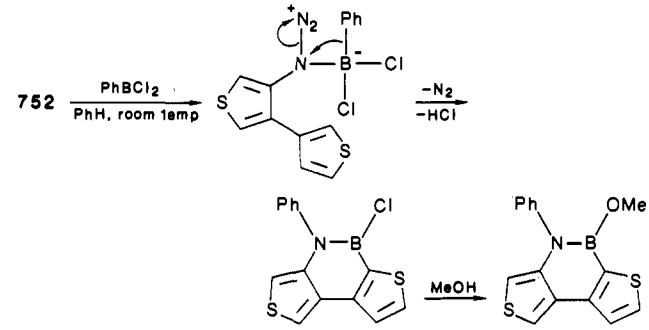


other four isomers **752–755** do not give the analogous cyclic products. Isomers **752** and **753** give polymeric materials, **754** undergoes ring opening, and **755** gives intractable products. These failures were attributed to the lack of availability of low-energy concerted pathways for reaction in these isomers, as has been found in related 2-azidophenyl heterocycles.[552]

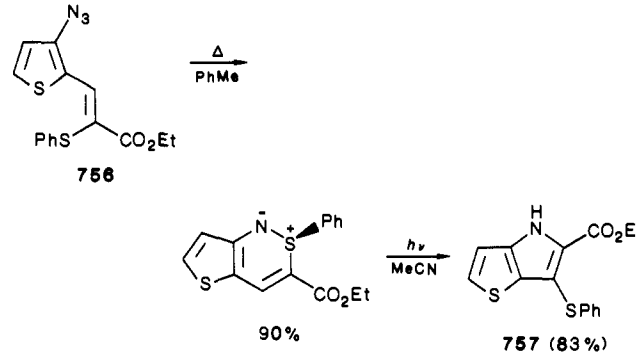
SCHEME 48



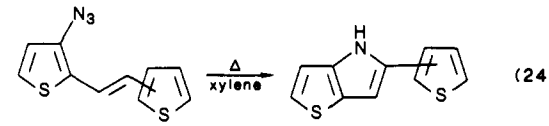
SCHEME 49



Ortho-substituted 3-azidothiophene **756** undergoes cyclization in boiling toluene to afford an azathiabenzene derivative in 90% yield.[555] On photolysis in acetonitrile the azathiabenzene rearranges to a thienopyrrole (**757**).[557-559]



Thermal decomposition of azidodithienylethenes gives thienyl-4*H*-thieno[3,2-*b*]- or -[3,4-*b*]pyrroles in good yield (eq 24).[560,561]

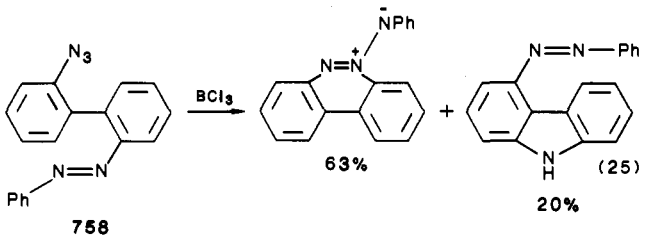


Azide **752** readily cyclizes to a 1,2-dihydro-1-aza-2-borabenzene on standing with phenyldichloroborane at room temperature (Scheme 49).[564]

However, treatment of *o*-azidobiphenyl with boron trichloride in benzene at room temperature gives carbazole in 91% yield.[564]

Substituted *o*-azidobiphenyl **758** gives the *N*-phenylimide of benzo[*c*]cinnoline as the main product on similar treatment (eq 25).[564]

Biaryl azides of the type **759** cyclize initially on decomposition to five-membered rings which undergo a Smiles-like rearrangement to six-membered rings (Scheme 50). The synthetic importance of this method (particularly in phenothiazine synthesis) and its mechanism were delineated chiefly by Cadogan and his

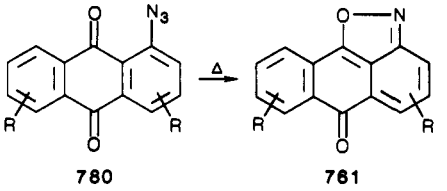


group working on both azide decomposition and phosphorus-mediated deoxygenations of nitro and nitroso compounds.[565]

Thiazepines are the major product when the B ring contains two methyl groups ortho to the ring junction (Scheme 51).[550]

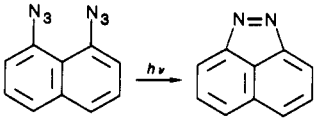
Azepinobenzothiazoles formed via ring expansion of the azanorcaradiene tautomer of the spiro intermediate are more commonly encountered in systems where X = CH_2. Jones' group[566] has compared the effect of thermolysis temperature on solution and flash vacuum thermolysis of *o*-azidodiphenylmethanes. Acridines and acridans are favored at higher temperatures using flash vacuum pyrolysis whereas at lower temperature on solution thermolysis azepinoindoles are the main product (Scheme 52).

Azides of the type **760** undergo cyclization to anthraisoxazolones **761** on heating.[223]



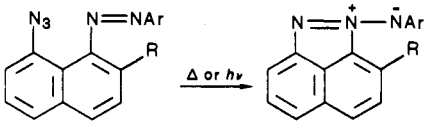
780 761

Benzo[*c*,*d*]indazole has been formed by the photolysis of *peri*-diazidonaphthalene in a rigid matrix at low temperature (eq 26).[567]



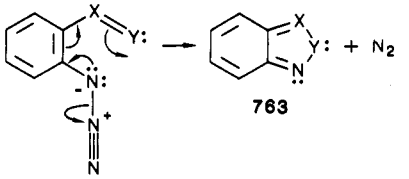
(26)

The *N*-arylimine derivative of this ring system, which contains the rare 1,3-dipolar azimine system, has been isolated for the first time (eq 27).[241a]



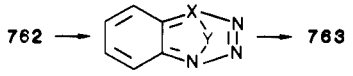
(27)

Ring closures of an azido group to an ortho substituent that do not involve an intermediate nitrene have interested azide chemists for some years.[568] Two mechanisms (one based on a concerted reaction (eq 28),[569] the other on 1,3-dipolar cyclization (eq 29)[570])



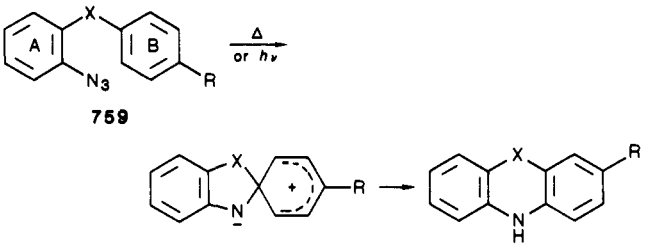
(28)

762



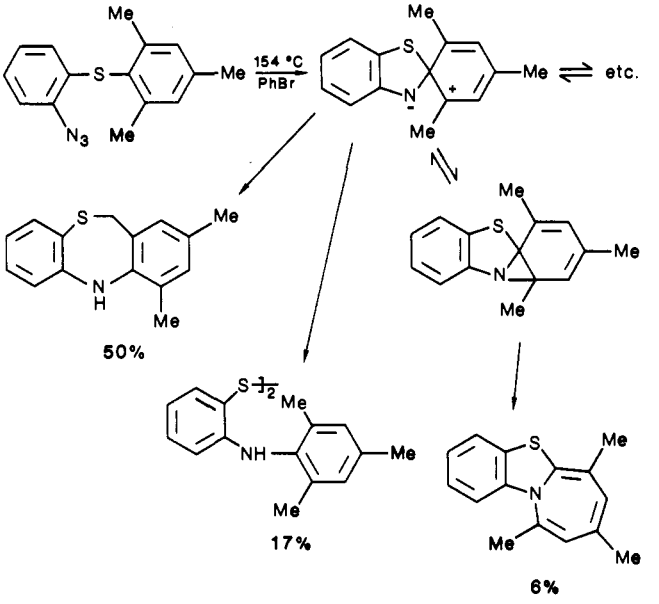
(29)

SCHEME 50

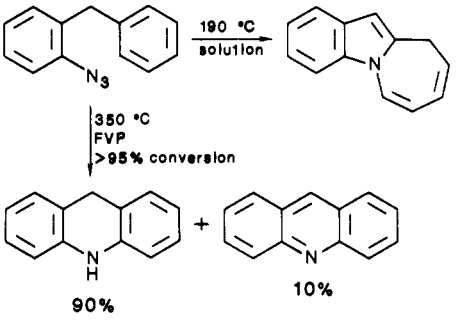


X = CH_2, CO, NAc, O, S, SO_2

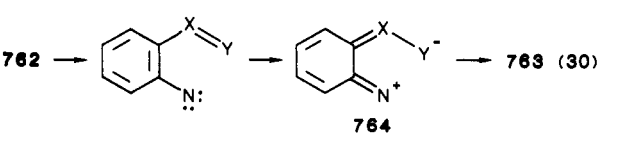
SCHEME 51



SCHEME 52



have been proposed based on experimental observations. Now a third mechanism has appeared[571] that, unlike the other two, accounts for the observed order of accelerating effects on azide fragmentation with different ortho substituents, viz., ArN=N- > O=N(O)- > O=C(R)- > RN=C(R)- > R_2C=C(R)-. This new mechanism is based on the notion that charge separation contributes more to the structure of the arylnitrene than it does to the corresponding azide (eq 30). The

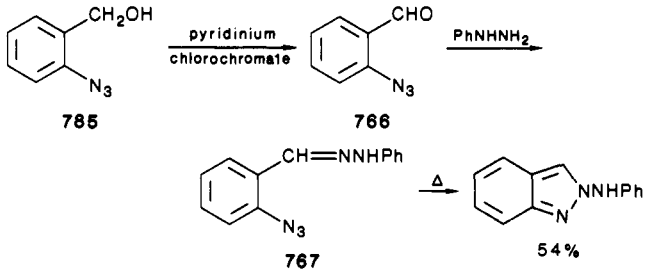


(30)

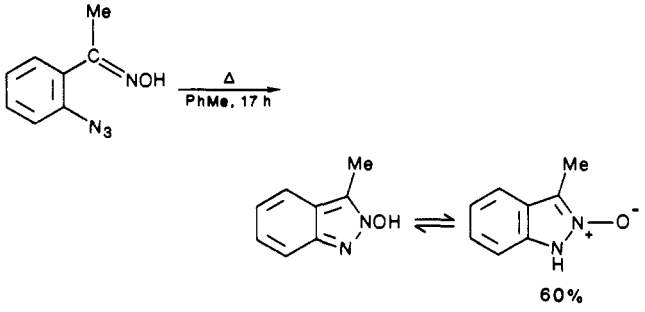
764

more the transition state resembles the charge-separated structure **764**, the easier is ring closure. Furthermore, this process unlike an electrocyclic one does not require the delocalization energy of the new heterocycle that is being formed in the transition state to

SCHEME 53



SCHEME 54



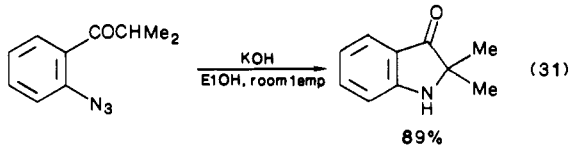
provide the driving force for reaction. These mechanistic considerations should be useful for selecting reaction conditions for synthetic endeavors.

Routes to several hitherto somewhat elusive indazole derivatives have appeared recently.[262,572-571] One[572] is based on the cyclization of the anils of *o*-azidobenzaldehyde, an established method (Scheme 53).[575] The synthetically important point here is the conversion of the benzyl alcohol (**765**) to aldehyde (**766**) in 90% yield using Corey's reagent, without detriment to the ortho azido group (see section II.L.1 for other examples). Previous routes to the azidoanils of the type **767** gave much lower yields.[576]

o-Azidoacetophenone oxime cyclizes on reflux in toluene to give a tautomeric 2-hydroxyindazole (Scheme 54).[263]

3-Chloroindazole has been made in 91% yield, merely by heating *o*-azidobenzanilide with thionyl chloride (Scheme 55).[577] This method has recently been extended to give a benzimidazole synthesis (Scheme 56).[574]

In contrast, treatment of *o*-azidobenzanilide with sodium hydride in DMF gives an indazol-3-one by base-catalyzed cyclization (Scheme 57).[573,578] A similar base-catalyzed closure, involving a carbanion, yields indoxyls (eq 31).[579,580] Note that low temperature is



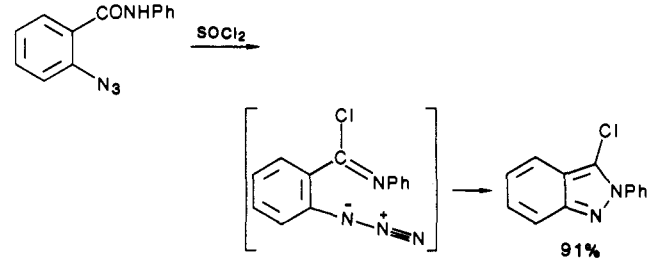
(31)

necessary to avoid formation of a benzisoxazole by azide fragmentation. These azide cyclizations offer potentially general routes to several less readily available simple heterocycles.

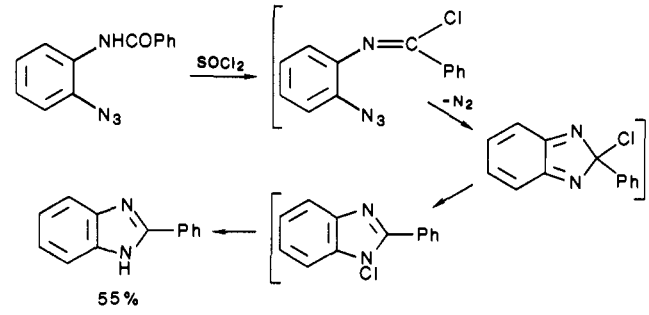
Intermolecular electrophilic attack at ring positions in arylnitrenium ions is well-known.[581] Now attack at nitrogen by alkenes followed by Friedel–Crafts reaction has been used to prepare *trans*-[5]para-1-azacyclophanes (Scheme 58).[582]

Abramovitch has trapped arylnitrenium ions intramolecularly to provide a potentially general approach

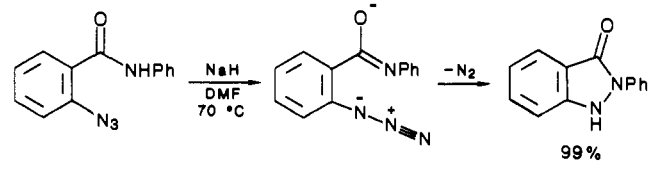
SCHEME 55



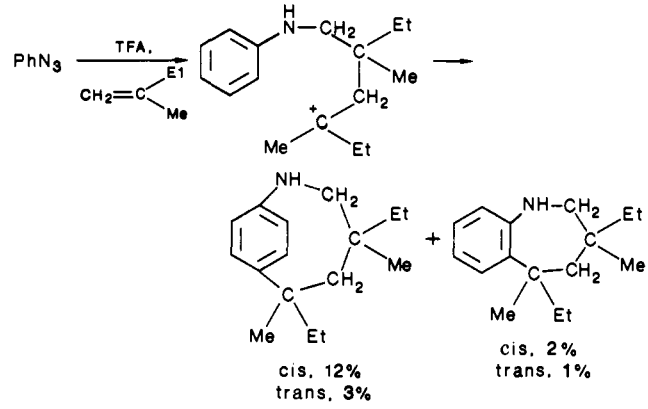
SCHEME 56



SCHEME 57



SCHEME 58



to a number of heterocycles that have amino groups β to the ring junction (Scheme 59).[495]

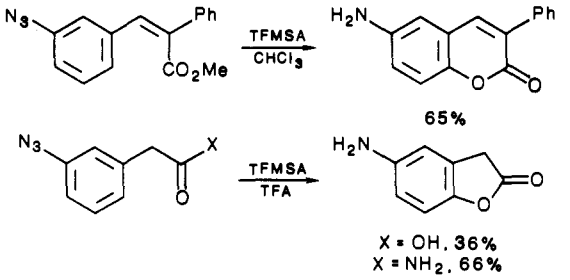
More recently, this lactone synthesis has been extended to the preparation of spirolactones (Scheme 60).[583]

4. Acyl Azides

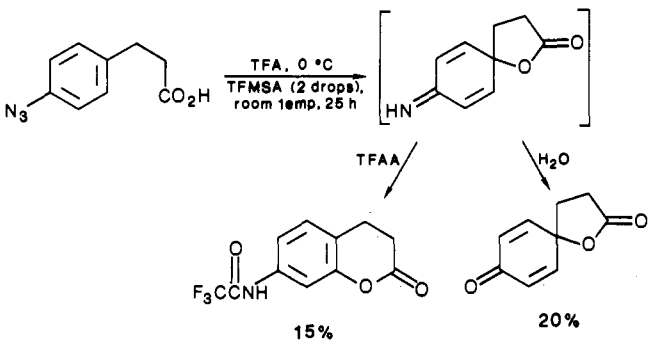
Cyclization of isocyanates, formed by Curtius rearrangement of acyl azides (see section III.D for a further treatment of the Curtius reaction), is a well-established method for the synthesis of heterocycles.[3] Therefore, only a few examples will be given. The parent furo[2,3-*c*]pyridine system has been made for the first time by annulation of a pyridine to furan (Scheme 61).[160b]

A pyrazinone ring system was formed by reaction of pyrrole and an isocyanate (Scheme 62).[584] Note that these acyl azides are best prepared from mixed anhydrides.

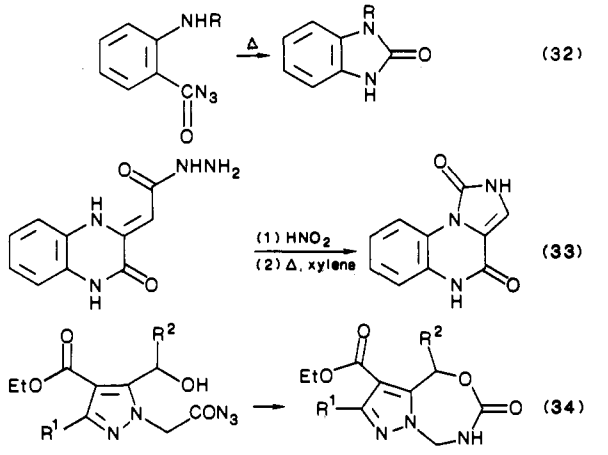
SCHEME 59



SCHEME 60

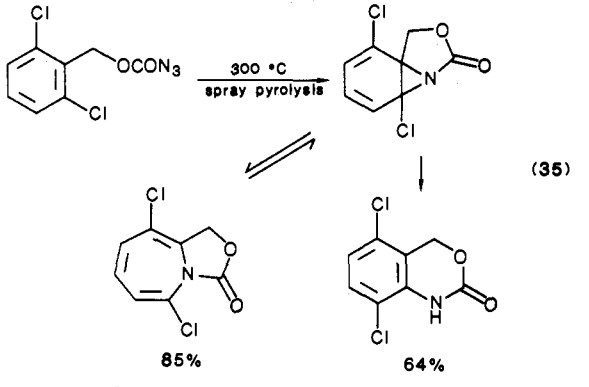


Acyl azide cyclizations via isocyanates may also be used to prepare five-membered (eq 32 and 33)[585] and seven-membered (eq 34)[586] rings.



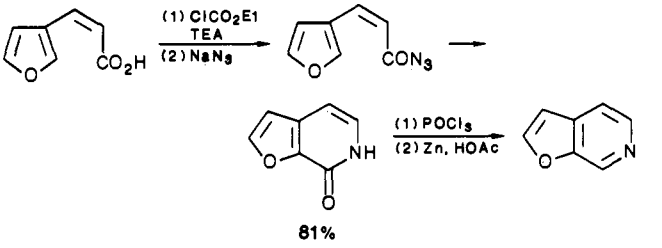
The Meth-Cohn spray pyrolysis technique has been applied successfully to the synthesis of several heterocycles. 4-Azaazulene was obtained in 56% overall yield from the chlorohydrin 768 (Scheme 63).[587]

Spray pyrolysis of benzyl azidoformate at 330 °C gives oxazoloazepines, or their dimers, which on further heating rearrange to benzoxazines (eq 35).[588]

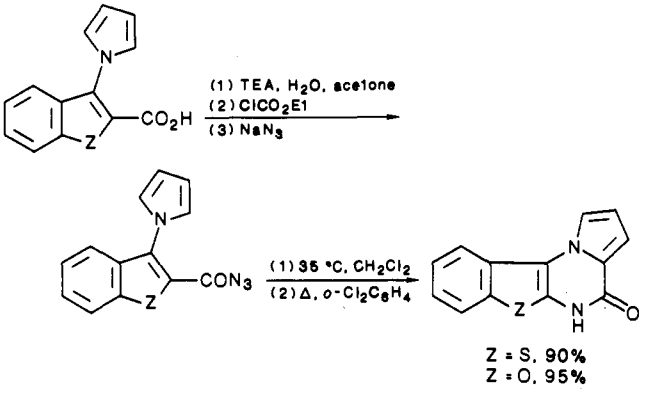


Lwowski and co-workers have studied the reactions of carbamoyl azides extensively.[589] Some recent work

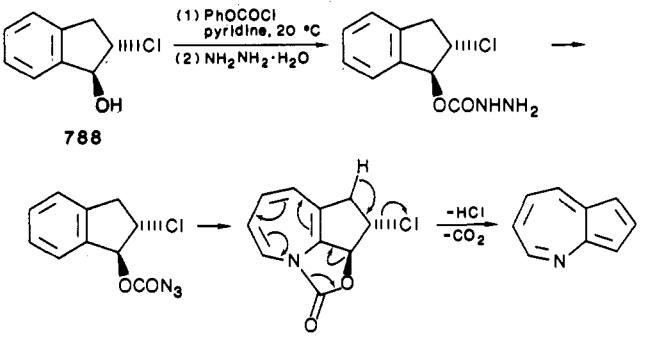
SCHEME 61



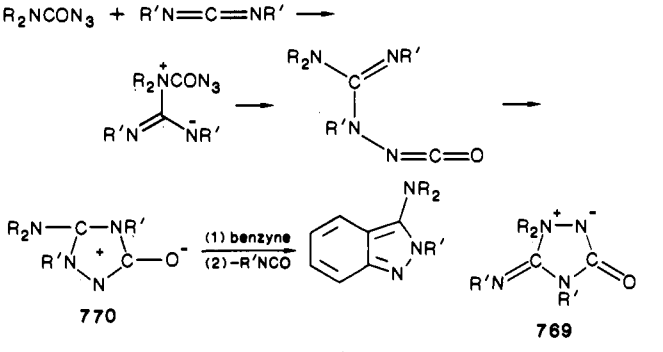
SCHEME 62



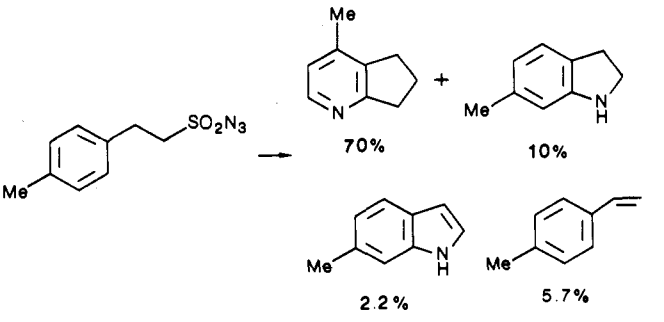
SCHEME 63



SCHEME 64

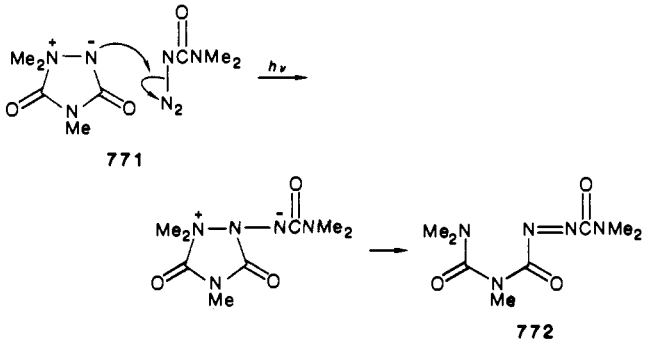


SCHEME 65



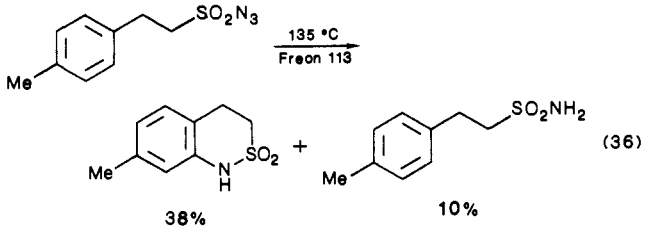
has concerned the photolysis of dialkylcarbamoyl azides in the presence of carbodiimides which yields **769** and **770**,[590] the latter by a novel process (Scheme 64). An indazole may be obtained by reacting **770** with benzyne.

Dimethylcarbamoyl azide has been photolyzed in the presence of methyl isocyanate to give the ylide **771** and an azo compound **772**. The latter is formed by photoreaction of **771** with more azide,[591] which provides the first instance of an intermolecular-assisted loss of nitrogen from a carbamoyl azide.



5. Sulfonyl Azides

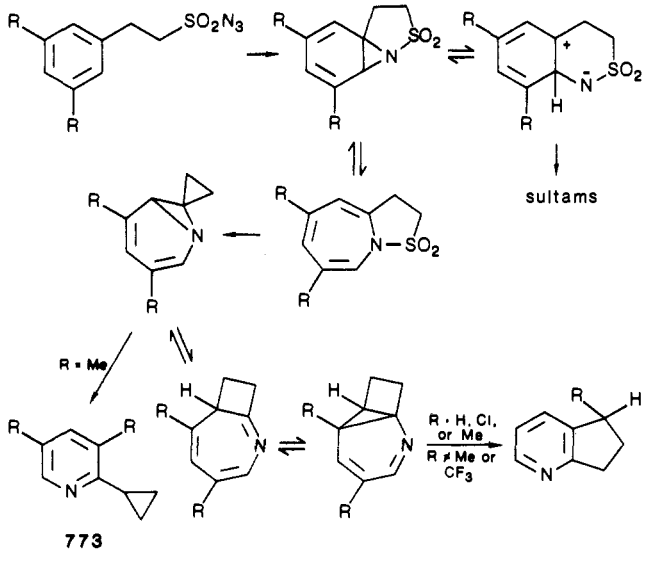
Abramovitch has made a fundamental study of the intermolecular reactions of arylsulfonyl azides.[592] The intramolecular reactions of substituted arylethanesulfonyl, arylpropanesulfonyl, and other sulfonyl azides have now been carried out to investigate the corresponding intramolecular reactions. β-Arylethanesulfonyl azides, when thermolyzed in inert solvents such as Freon 113, cyclize to sultams (eq 36).[83,593] Corresponding sulfonamides, the triplet nitrene hydrogen abstraction products, are also formed.



(36)

Dihydropyrindines rather than sultams become the main products of FVP of arylethanesulfonyl azides at the appropriate temperature (Scheme 65). The nature of products formed varies greatly with the FVP temperature.

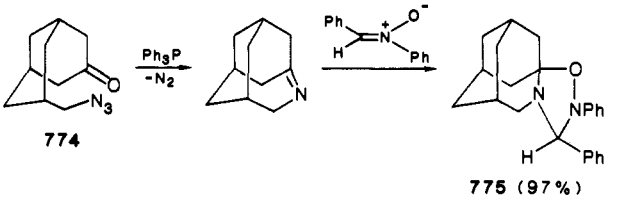
SCHEME 66



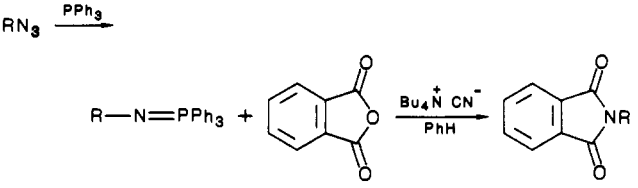
A mechanism that accounts for the formation of dihydropyrindine and other interesting products (e.g., **773**) has been established by using variously substituted arylethanesulfonyl azides (Scheme 66).[594]

Solution and flash vacuum pyrolysis of 3-arylpropanesulfonyl azides give seven-membered sultams. Best yields are obtained on solution decomposition in Freon 113.[595]

SCHEME 67

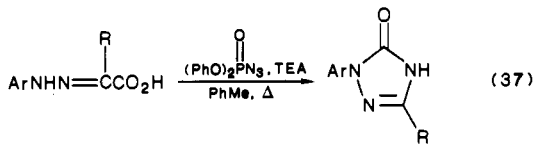


SCHEME 68



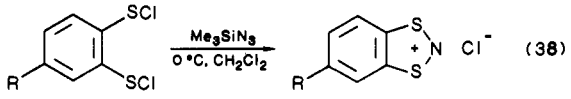
6. Other Azides

1-Aryl-1,2,4-triazolin-5-ones may be prepared from arylhydrazones of α-keto acids by reaction with diphenylphosphoryl azide (eq 37).[596]



(37)

Treatment of benzene-1,2-disulfenyl chlorides with trimethylsilyl azide at 0 °C affords benzo-1,3,2-dithiazolium chlorides almost quantitatively (eq 38).[597]



(38)

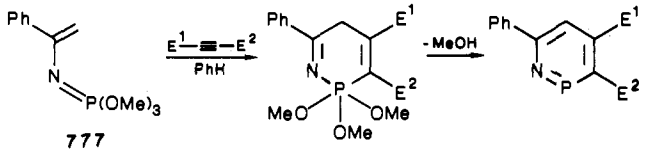
7. Staudinger Reaction and Related Processes

Azides react readily with trivalent phosphorus compounds to give phosphine imines (Staudinger reaction), which can undergo further reaction with, for instance, a carbonyl group (aza-Wittig reaction) (for reduction, see section III.A).[598] This section contains examples of cyclizations that produce nitrogen and phosphorus heterocycles (see section VI.A.2 for other examples).

Bridgehead imines are most often prepared from bridgehead azides, but unsymmetrical bridgehead azides give mixtures of imines. A new sequence starting with the azido ketone **774** and involving Staudinger and aza-Wittig reactions followed by trapping affords the bridgehead imine adduct **775** in nearly quantitative yield (Scheme 67).[599]

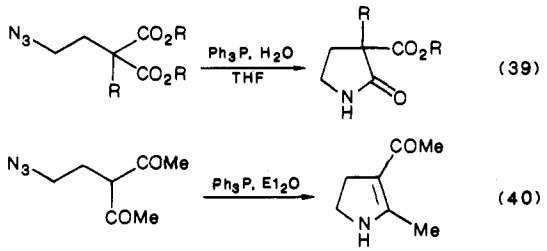
ω-Azido ketones react with triphenylphosphine under anhydrous conditions to yield five-, six-, or seven-

SCHEME 69



777

membered cyclic imines.[600] Azido esters cyclize in good yield to amides under aqueous conditions (eq 39)[601] whereas an azido ketone forms a β-keto ester on reaction with triphenylphosphine under anhydrous conditions (eq 40).[601]

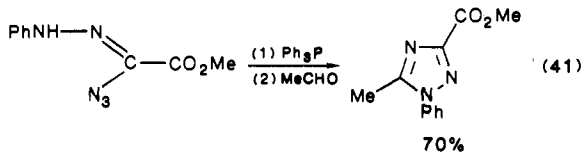


(39)

(40)

Phthalimido derivatives may be prepared by treatment of the appropriate azide with triphenylphosphine and phthalic anhydride (Scheme 68).[602] This provides another method for protecting amines and is of great potential for amino carbohydrates.

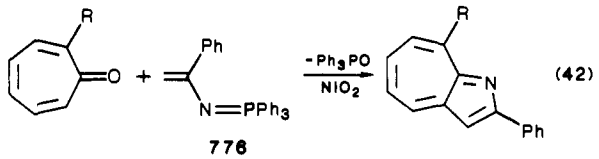
Hydrazonyl azides have been cyclized via an aza-Wittig reaction (eq 41).[603]



(41)

70%

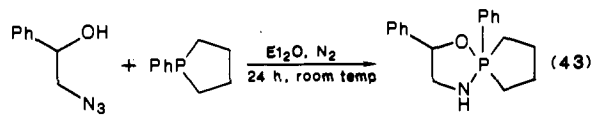
α-Azidostyrene readily forms iminophosphoranes **776** and **777** on reaction with triphenylphosphine or trimethyl phosphite, respectively. These have been used in the synthesis of azaazulenes (eq 42)[604] and the 1,2-λ^5-azaphosphorine ring system (Scheme 69).[605]



(42)

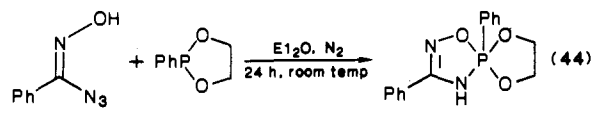
776

Cadogen and co-workers have shown that treatment of hydroxyalkyl and hydroximic azides with phosphorus(III) reagents provides a general route to penta-coordinate phosphoranes (eq 43 and 44).[606]



(43)

84%

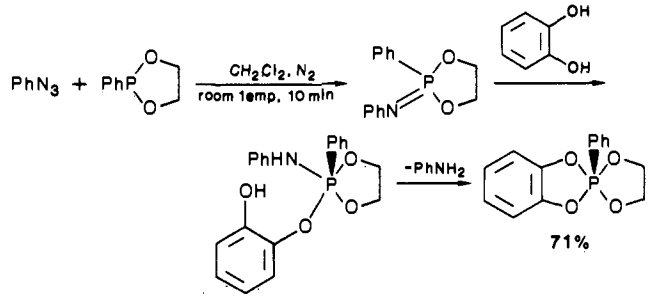


(44)

91%

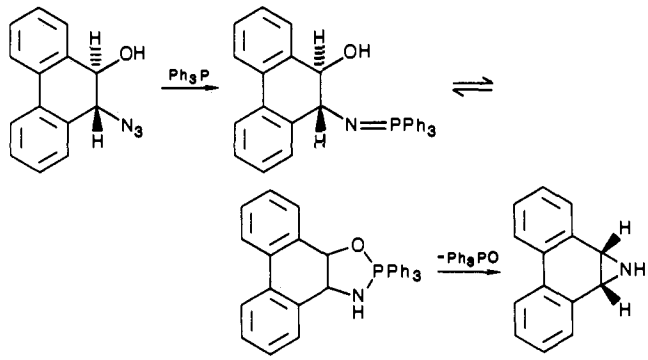
An intermolecular version of the above reaction, involving phenyl azide, has also been described (Scheme 70).[607]

SCHEME 70

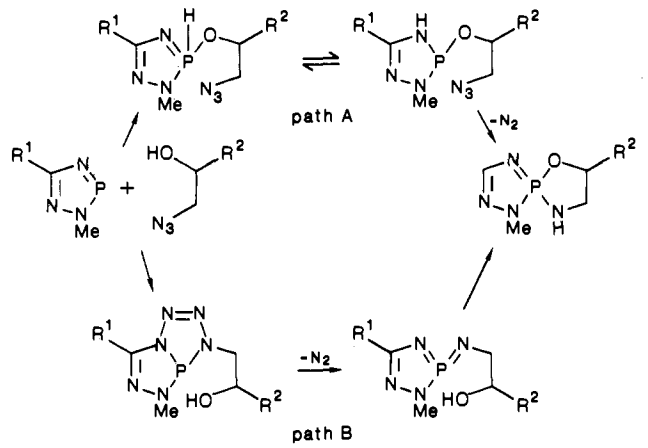


71%

SCHEME 71



SCHEME 72



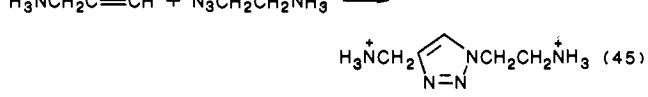
Fused azirines may be obtained via oxazaphospholidines by loss of phosphine oxide (Scheme 71).[608]

Spirophosphazenes have been prepared by the reaction of azido alcohols with triazaphospholes; however, path A is favored over path B (Scheme 72).[609]

B. Cycloadditions

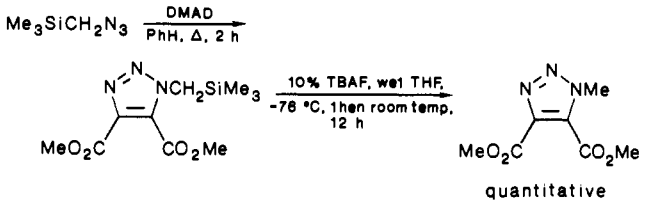
1. Formation of Stable Triazoles

Addition of azides to acetylenes or activated methylene compounds offers two well-established methods for the synthesis of 1,2,3-triazoles.[610-612] Recent work has been concerned with mechanistic examination and synthetic extensions of these reactions. The rather slow cyclization (eq 45) is speeded up when carried out in the presence of cucurbitural (a nonadecacyclic cage compound that can encapsulate substituted ammonium ions).[613]

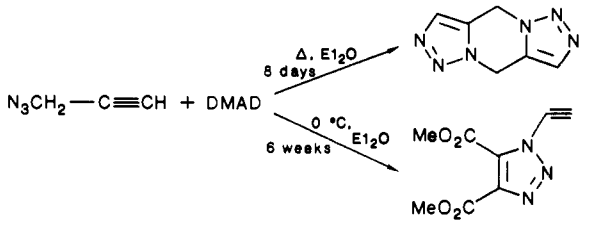


(45)

SCHEME 73



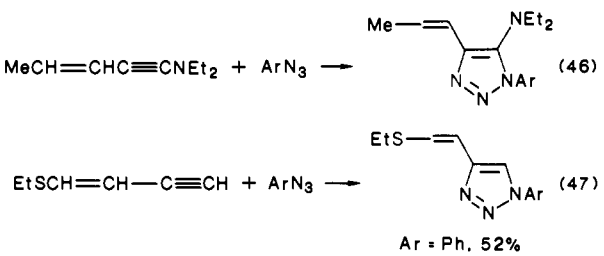
SCHEME 74



Synthesis of N-unsubstituted triazoles usually entails the selection of an azide (RN_3) that adds easily to an alkyne and has an R group that is easily removable. Benzyl is a favorite group for this purpose but it requires forcing conditions for its removal. 4-Methoxybenzyl azide is reasonably stable and undergoes additions smoothly, and the 4-methoxybenzyl group may be removed relatively easily.[614] (Trimethylsilyl)methyl azide, made from (chloromethyl)trimethylsilane and sodium azide has been used as a methyl azide equivalent (Scheme 73).[615]

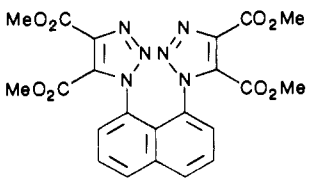
3-Azido-1-propyne adds to DMAD in the cold, but dimerizes on heating in ether (Scheme 74).[53]

Suitably substituted enynes undergo addition with azides at the triple rather than the double bond as had been observed previously (eq 46 and 47).[616]



Cycloaddition and substitution by azide ion have proved valuable in triazolobenzazepine synthesis (Scheme 75).[617]

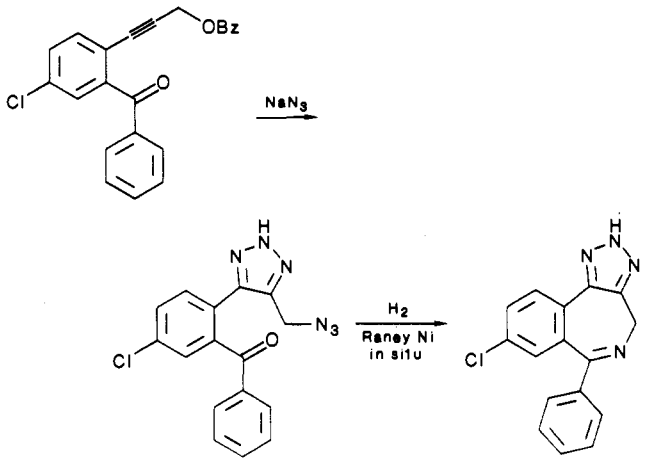
Addition of DMAD, its congeners, or enolates of acetoacetic esters to 1,8-diazidonaphthalene gives, e.g., the strained 1,8-bis(triazolyl)naphthalene **778** in high yield.[618]



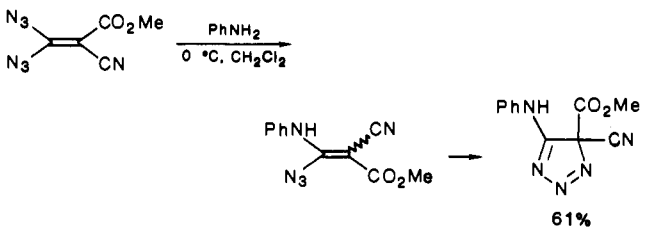
778

Addition of azides to phosphonium ylides,[619] which proceeds under mild conditions, has been used for the formation of triazoles at a 4-substituent in sydnones,

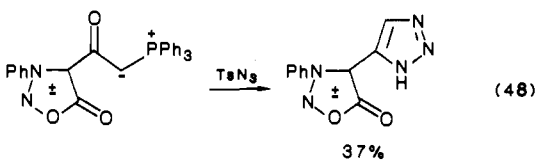
SCHEME 75



SCHEME 76



which are very sensitive to acid, base, and heat (eq 48).[620]



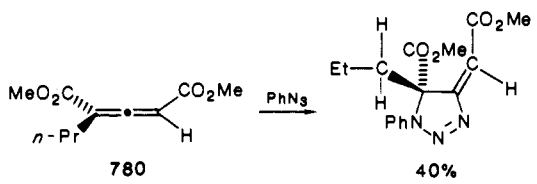
Phenyl azide adds to perfluoropropyne to give mainly **779**,[621] whereas phenyl azide gives an equimolar amount of both regioisomers on addition to phenylpropyne.[622]

779

Vinyl azides usually eliminate nitrogen readily to form 2*H*-azirines rather than cyclize to 4*H*-triazoles. However, when suitably substituted, they spontaneously cyclize to 4*H*-triazoles (Scheme 76).[623]

2. Formation of Stable Triazolines

Addition of phenyl, *p*-nitrophenyl, and *o*-methoxyphenyl azides to the allene **780** takes place in a regio- and directiospecific manner.[624]

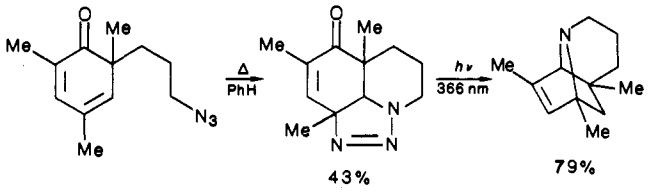


780 40%

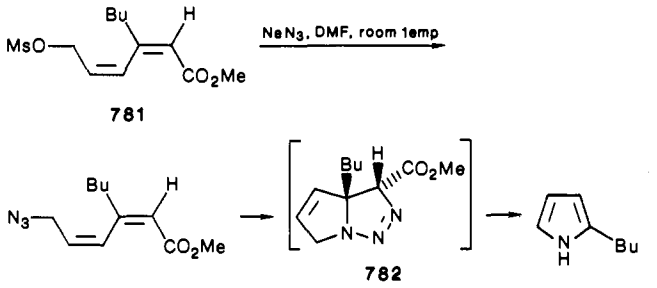
3. Triazolines as Intermediates

(a) Intramolecular Cycloadditions. Intramolecular azide cycloadditions involving triazolines are playing an

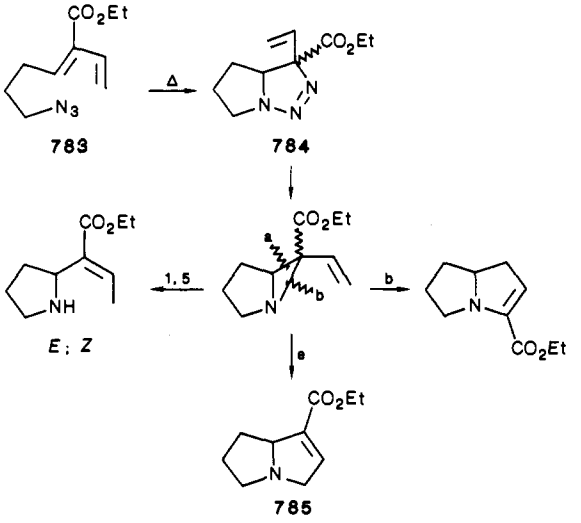
SCHEME 77



SCHEME 78



SCHEME 79

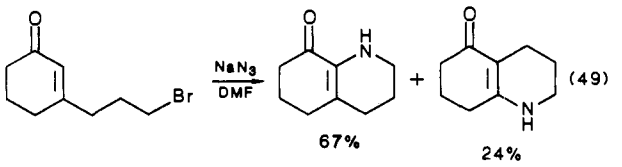


increasingly important part in heterocyclic synthesis,[625,626] often without the isolation of the azide. A new synthesis of the 2-azatricyclo[4.4.0.0^{2,8}]decenone system has been achieved (Scheme 77).[107]

Treatment of mesylate **781** with sodium azide in DMF at room temperature gave 2-butylpyrrole in high yield; presumably the azide undergoes intramolecular cycloaddition via **782** (Scheme 78).[111]

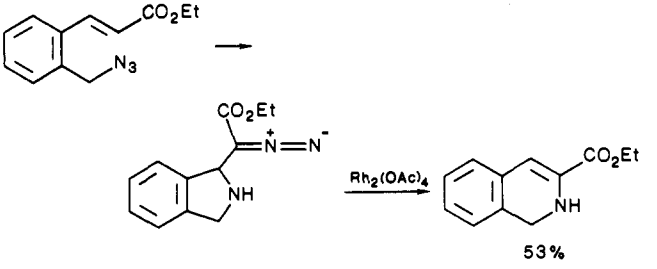
Two groups of workers[237,627] have found that decomposition of azido diene **783** (Scheme 79) gives access to the pyrrolizidine alkaloids probably via **784**, which is similar to **782**, providing a formal total synthesis of supinidine (**785**).

Cycloadditions of alkyl azides, generated in situ, to enones (eq 49)[630] and cinnamate esters (Scheme 80)[628-630] afford a variety of heterocycles via triazole intermediates.

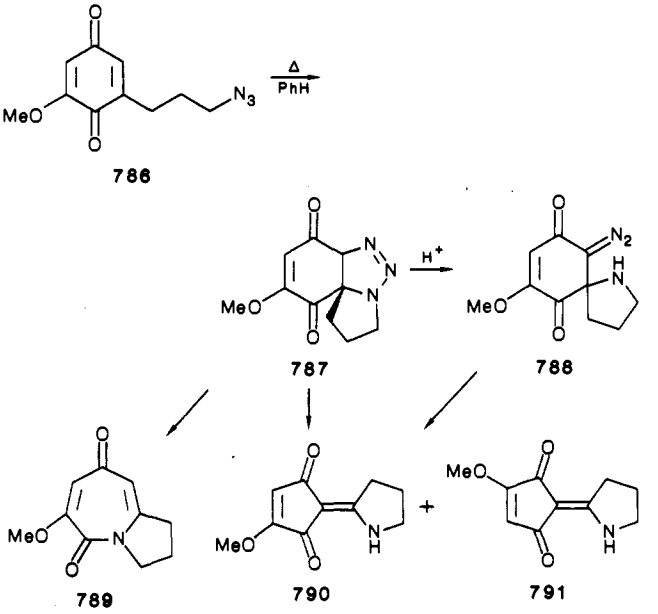


1,4-Benzoquinone azide **786** undergoes intramolecular cycloaddition to give triazoline **787**, which has been

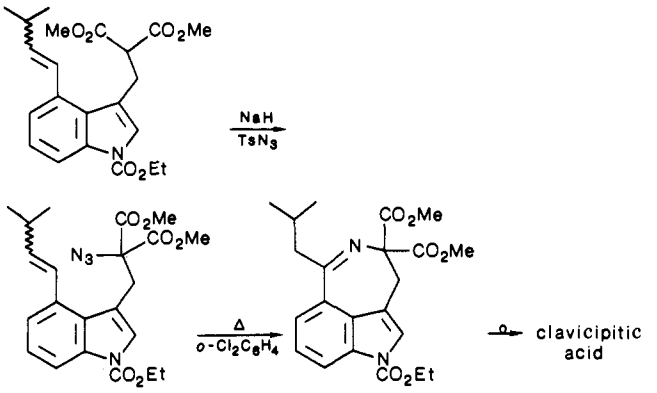
SCHEME 80



SCHEME 81



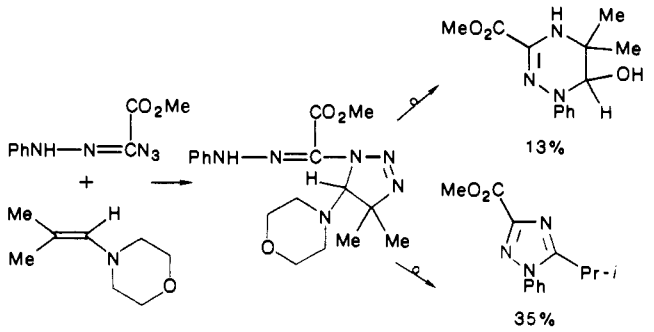
SCHEME 82



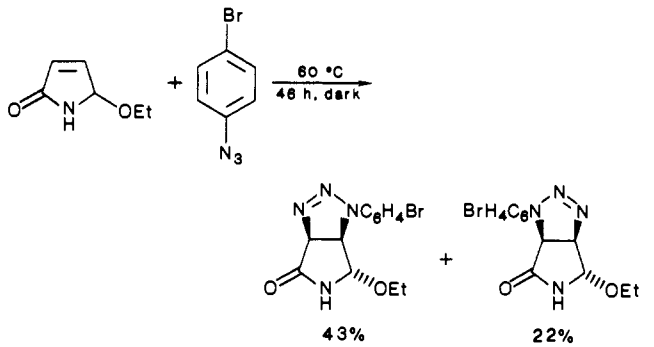
observed directly by ^{1}H NMR (Scheme 81).[631,632] Formation of the triazoline can be followed by NMR; after 2.5 h of reaction a trace of **788** and the products **789–791** appear, with 50% triazoline and 25% starting azide. Continued heating at 40 °C results in formation of a 1:1 mixture of azepinedione and the 4-cyclopentene-1,3-diones **790** and **791**. If a trace of acid is added, or on silica gel chromatography, the triazoline is quickly converted to **788**. The diazo enedione **788** is stable at 40 °C in benzene for 21 h, but may be quantitatively converted to a mixture of **790** and **791** in toluene at reflux, without any azepinedione being detected among the products.

Another total synthesis, that of clavicipitic acids, has been described in which the key feature is the formation of the seven-membered ring via a triazoline (Scheme

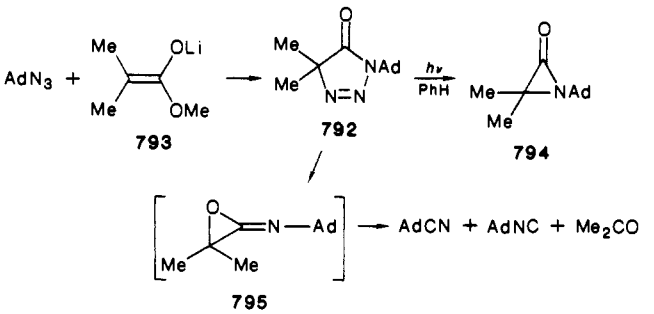
SCHEME 83



SCHEME 84



SCHEME 85



82).[226] The use of the azide transfer reaction (II.J.) for making the starting azide is also noteworthy.

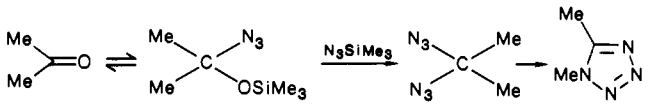
(b) Intermolecular Reactions. Methyl azido(phenylhydrazono)acetate undergoes 1,3-dipolar cycloaddition reactions with various substituted enamines to give ultimately 1,2,4-triazines and 1,2,4-triazoles, probably via triazoline intermediates (Scheme 83).[633]

1,3-Dipolar cycloaddition of a series of azides to 1-methyl-1,2,5,6-tetrahydropyridine yields pharmaceutically interesting 1-methylpiperidylidene-2-sulfon(cyan)amides via initially formed triazolines.[634] *p*-Bromophenyl azide adds to 5-ethoxy-3-pyrrolin-2-one to give a mixture of regioisomeric triazolines (Scheme 84).[635]

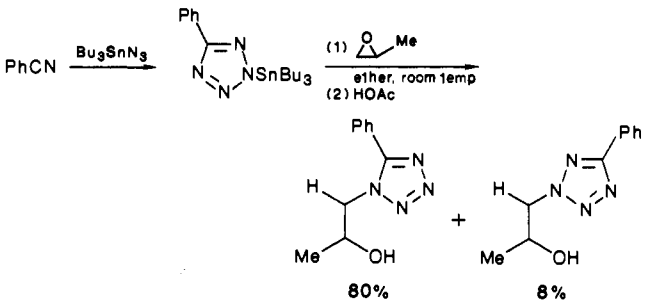
Alkyl azides are known to add to ketone enolates.[636,637] Therefore, formation of triazol-4-one **792** when adamantyl azide was added to a suspension of **793** in hexane at −78 °C and the mixture was allowed to stand at room temperature for 3 h was no surprise (Scheme 85).[638] However, **792** on irradiation in dry benzene gave **794**, accompanied by adamantyl isocyanide, a small amount of adamantyl cyanide, and acetone. These other products were accounted for by reaction through **795**.

Treatment of tetracyclone with sodium azide under acidic conditions affords tetraphenylpyridone in 90%

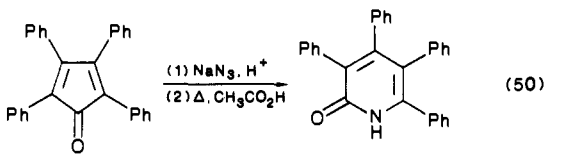
SCHEME 86



SCHEME 87



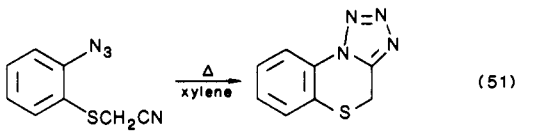
yield. The reaction involves a cycloaddition to a triazole intermediate rather than Schmidt reaction (eq 50).[639]



(50)

4. Tetrazoles

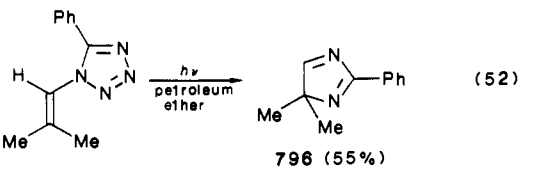
(a) Intramolecular Formation. Tetrazolo[5,1-*c*]-[1,4]benzothiazines, of pharmaceutical interest, have been synthesized by intramolecular azide cycloaddition to a nitrile (eq 51).[640] This method is analogous to one described previously,[641] the mechanism of which has been studied recently.[642]



(51)

Imidoyl azides, usually generated in situ by treatment of the chloride with azide, spontaneously cyclize to tetrazoles (the von Braun–Rudolf reaction), unless they contain a stabilizing moiety. Factors that affect such cyclizations have been studied recently,[64] and reactions of tetrazoles have been reviewed.[643]

The first report of the synthesis of a 5-unsubstituted 4*H*-imidazole **796** by photolysis of an alkenyltetrazole has appeared (eq 52).[644] The tetrazole was prepared by azide treatment of an imidoyl chloride obtained by chlorination of an enamide. Mild photolysis conditions are essential as **796** is a most unstable and volatile compound.

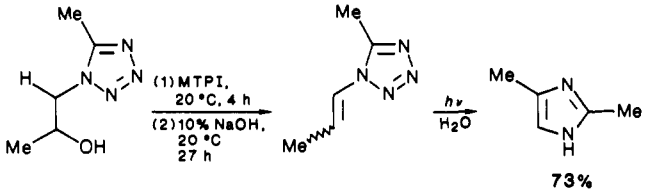


(52)

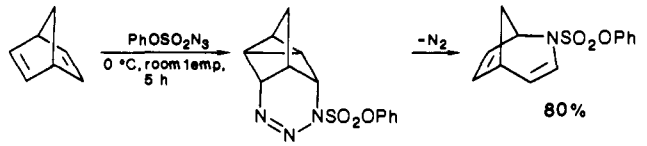
A quantitative yield of 1,5-dimethyltetrazole is formed when a mixture of acetone, 3 equiv of trimethylsilyl azide, and 0.1 equiv of $SnCl_2 \cdot 2H_2O$ is heated at 55 °C for 20 h (Scheme 86)[645] (see section II.D for azide synthesis from ketals).

(b) Intermolecular Reactions. Addition of tributylstannyl azide to nitriles gives 2-(tributylstannyl)tetra-

SCHEME 88



SCHEME 89

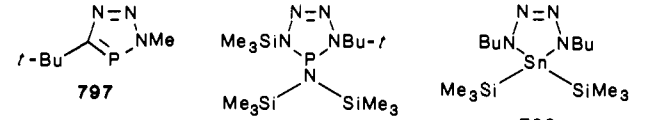


zoles, which react with epoxides to form alcohols with destannylation (Scheme 87). These alcohols may be readily dehydrated; the resulting alkenes give imidazoles on photolysis (Scheme 88).[646]

5. Other Cycloadditions

Aryl azidosulfonates add to norbornadiene to provide a new synthesis of the 2-azabicyclo[3.2.1]octadiene system (Scheme 89).[647]

Azide cycloaddition reactions continue to be employed for the synthesis of uncommon heterocycles **797**,[648] **798**,[649] **799**[650]

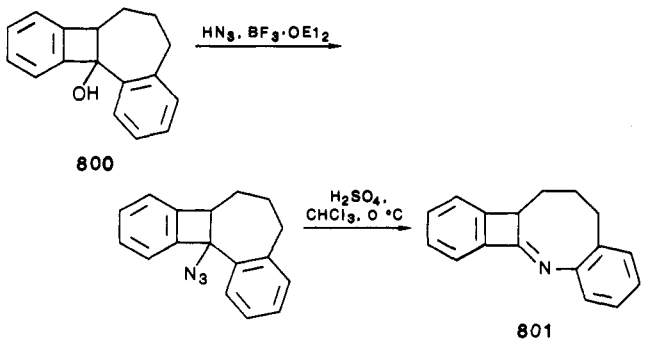


C. Ring Expansions and Contractions

1. Schmidt Reaction and Related Processes

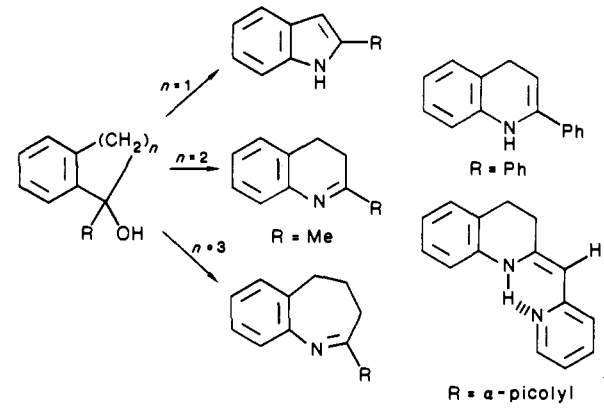
The term Schmidt reaction has come to cover a number of interconversions[13] brought about by hydrazoic acid under strongly acidic conditions. Here only cyclic examples are considered. Andrieux and coworkers have treated a series (n = 1,[651] n = 2,[652] n = 3[653]) of benzocycloalkanols with HN_3–BF_3 and have obtained ring-expanded products (Scheme 90). The position of the isolated double bond in the dihydroquinolines depends upon the nature of R.

Reaction of alcohol **800** with $HN_3/BF_3{\cdot}OEt_2$ unexpectedly gave benzazocine (**801**) rather than an indole.[654]

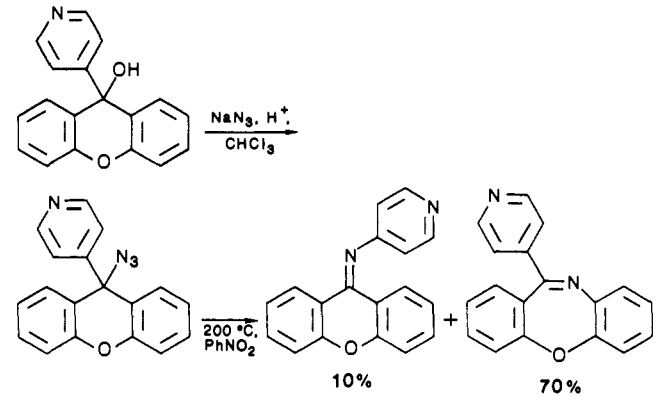


Ring expansion of 9-aryl-9-azidothioxanthenes, first described independently by Loudon[655] and Coombs,[656] now has been developed as a general synthetic method

SCHEME 90

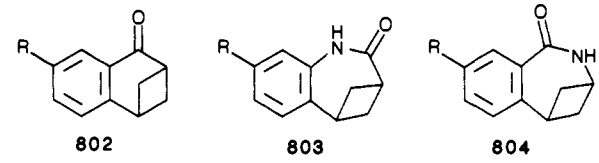


SCHEME 91



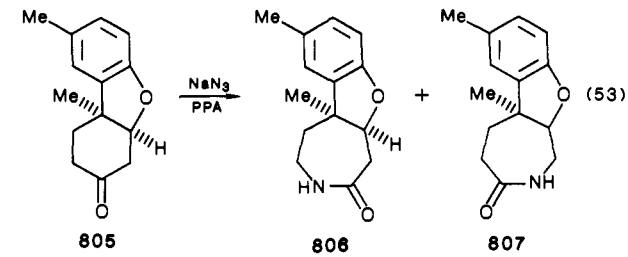
by Desbene and co-workers for dibenzo[*b*,*f*][1,4]-thiazepines and -oxazepines (cf. Scheme 91).[657]

Preference for aryl migration (over secondary alkyl) was observed in the reactions of ketones **802** with sulfuric acid/sodium azide at 64 °C to give cyclic amides **803** and **804** in 80–91% yield.[658] The percentage of the

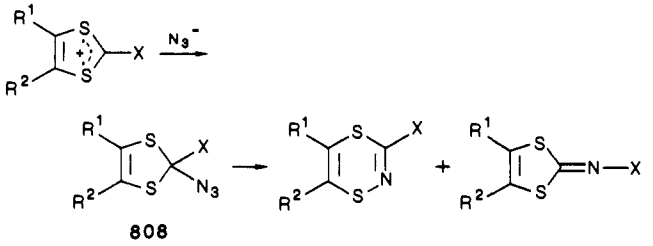


product mixture constituted by the "aryl migration" product **803** (75%, R = H) was increased by the presence of a nitro group at the 7-position in the ketone (80%, **803**, R = NO_2) and decreased by a similarly positioned amino function (70%, **803**, R = NH_2).

A mixture of products (viz., **806** and **807**) also resulted from treatment of **805** with sodium azide in poly(phosphoric acid).[659] 1,5- and 1,8-dichloroanthraquinones react with hydrazoic acid to give, in each case, both of the theoretically possible lactams.[660] For the corresponding reactions with 1- and 2-chloroanthraquinones, two of the four theoretically possible lactams were identified.

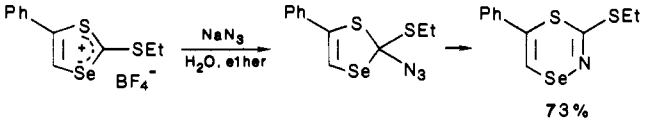


SCHEME 92



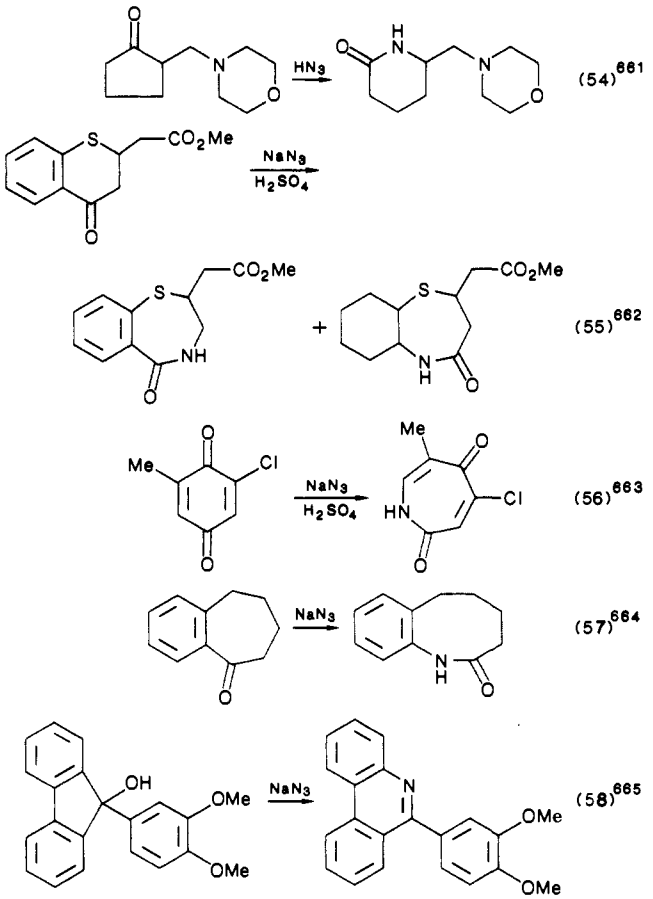
808

SCHEME 93



73%

Some other recent applications of the Schmidt reaction in heterocyclic chemistry appear in (eq 54–58).



(54)[661]

(55)[662]

(56)[663]

(57)[664]

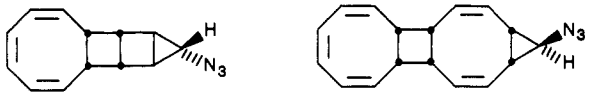
(58)[665]

Treatment of 1,3-dithiolium salts (X = halogen) with azide ion gives thermally unstable 2-azido-1,3-dithioles (**808**),[666] which rearrange with loss of nitrogen to give 1,4,2-dithiazines and N-substituted 2-imino-1,3-dithioles (Scheme 92). When X = SAr, the (thioimino)-1,3-dithioles are formed in good yields, e.g., 77% when R^1, R^2 = $-(CH_2)_4-$, and X = *p*-nitrophenylthio.[667] ((Benzenesulfonyl)imino)dithiole may be produced similarly.[668]

The method described above has recently been extended to afford 1,4,3-thiaselenazines (Scheme 93).[669]

Nakayama and co-workers also have carried out the decomposition of dithiolyl azides[670] and their benzo analogues.[671,672] They found that certain 1,4,2-dithiazines extrude sulfur to give isothiazoles (Scheme 94).

Azides **809** and **810** have been ring expanded to aza[14]annulenes[673] and aza[18]annulenes[674] by photolysis at low temperature.



809 **810**

Ring expansion of azido perfluorohydrocarbons is rare;[675] however, **811** undergoes ring expansion readily on flow pyrolysis at 380 °C (Scheme 95).[676]

2. *Via Ylide Intermediates*

Trithiapentalene **812** reacts with ethyl azidoformate to give dithiazine **813**. A mechanism that involves attack by a nitrene to give an ylide was proposed (Scheme 96).[677]

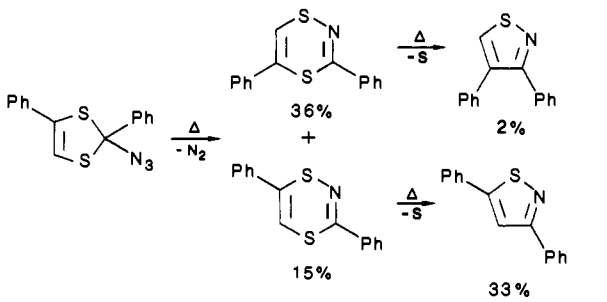
3. *By Epoxide Ring Opening*

Epoxide ring opening by azide ion plays an important part in the synthesis of the 1,3-diimino[14]annulene **814** (Scheme 97)[678] (see section II.C.).

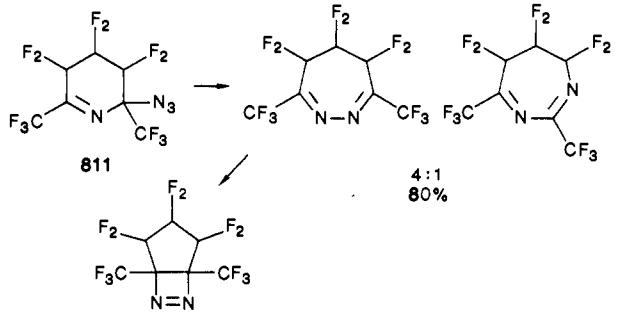
4. *Washburne Procedure*

Washburne found that certain cyclic anhydrides react with trimethylsilyl azide to give ring expansion via an isocyanate formed by Curtius rearrangement (Scheme 98).[679]

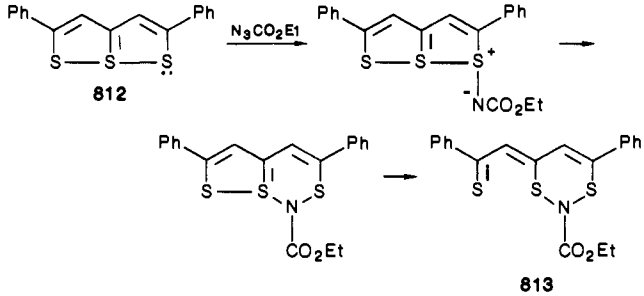
SCHEME 94



SCHEME 95

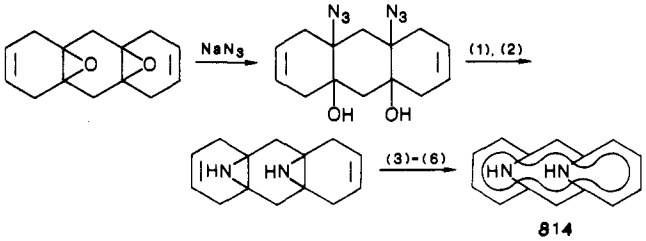


SCHEME 96



813

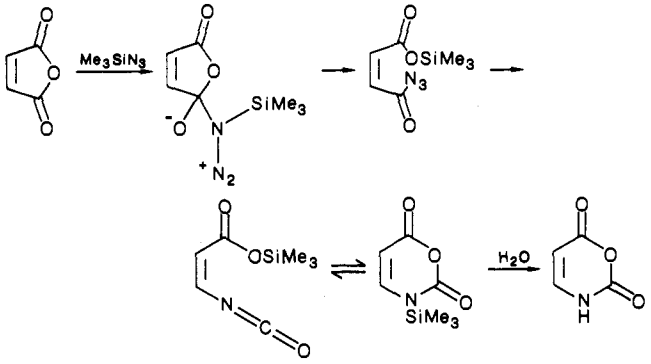
SCHEME 97[a]



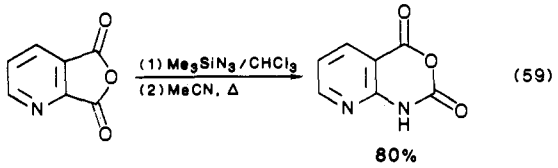
814

[a] (1) oleum; (2) LAH; °C (3) $SOCl_2$, TEA, 0 °C; (4) Br_2, CH_2Cl_2, −78 °C, then DBN, THF, −10 °C; (5) DDQ, PhH, Δ; (6) HOAc, HCl.

SCHEME 98



This procedure has recently been extended to permit the expansion of 2,3-pyridinedicarboxylic anhydride to provide a superior route to azaisatoic anhydride (eq 59).[680]



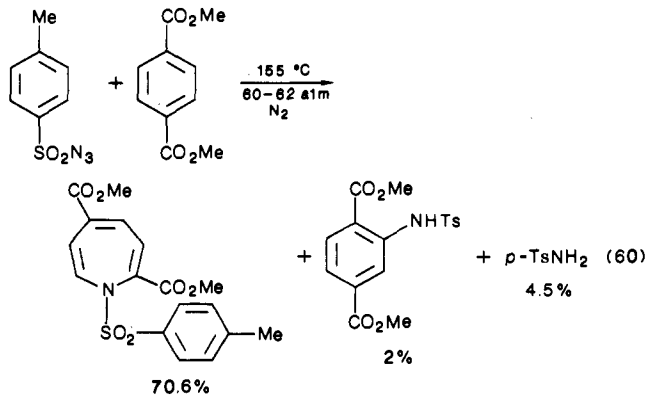
(59)

80%

Treatment of isoimidium perchlorates with sodium azide gives acyl azides which undergo Curtius rearrangement and electrocyclic closure to novel 2*H*-1,3-oxazin-2-ones on heating (Scheme 99).[681]

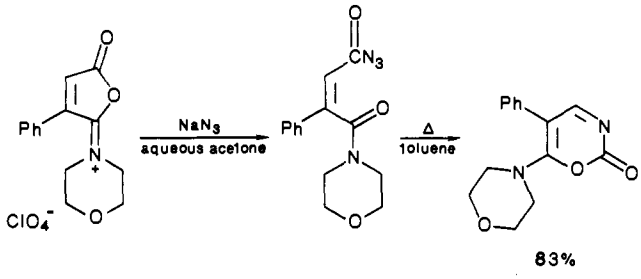
5. Nitrene Insertion into Aromatics

The reaction of sulfonyl azides with aromatics was first described by Curtius[682] and has been thoroughly investigated by Abramovitch.[592,593,683,684] Recently, the optimum conditions for azepine formation were described (eq 60) and the operative mechanism under



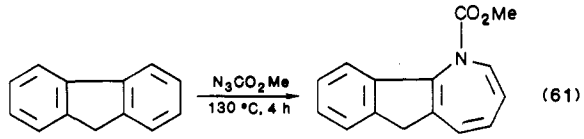
these conditions was discussed.[685] Control of temperature (between 155 and 160 °C) is a crucial factor for

SCHEME 99



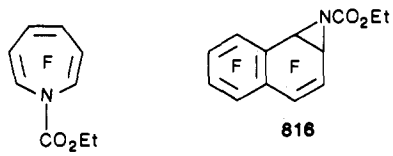
successful ring expansion. The generality of this reaction, however, is limited by the nature of the substituents in the aromatic substrate. Aryl sulfonamides are the main products when aromatic solvents bearing electron-donating groups are used.

Fluorene undergoes expansion to an indenoazepine when it is heated with methyl azidoformate (eq 61).[686]



(61)

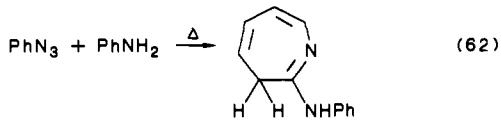
Hexafluorobenzene has been used as an inert solvent for the study of (ethoxycarbonyl)nitrene insertions into C–H bonds; however, thermolysis of ethyl azidoformate in excess hexafluorobenzene at 90 °C for 72 h gives azepine **815**. Ring expansion is also observed on photolysis.[687] On the other hand, photolysis of ethyl azidoformate in PFN gives adduct **816**, which does not undergo subsequent ring expansion.



815 816

6. Decomposition of Azides in the Presence of Nucleophiles

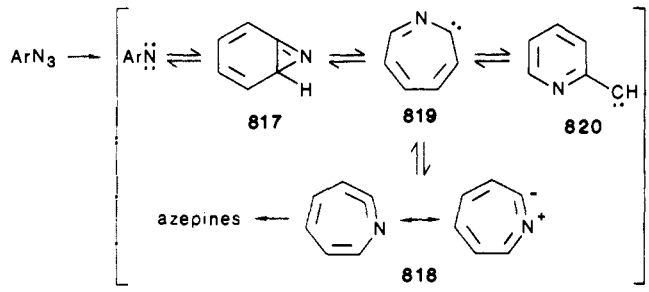
Wolff[688] was the first to describe the ring expansion of an aryl azide to an azepine on thermolysis in a nucleophilic solvent (eq 62).



(62)

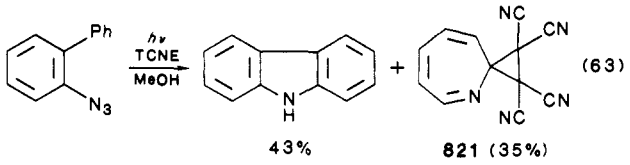
This reaction has been developed a great deal since 1912. Much of this work has been discussed in several detailed reviews.[550,568,690,691] Therefore, only major points of recent developments will be discussed here.

The mechanism of this reaction has posed a fascinating puzzle over the years. Currently, the precise nature of the intermediate [(**817**, **818**) or other (**819**, **820**)] that undergoes nucleophilic attack is the subject of investigation by several research groups. The latest results indicate that on phenyl azide photolysis didehydroazepine (**818**) is the intermediate formed that undergoes reaction with nucleophiles to ultimately yield 3*H*-azepines. The nature of the products formed has been found to depend dramatically upon azide concentration and the power of the light source[692] as well as the temperature[693] at which the photolysis is carried



out. Several substituted monocyclic aryl azides also have been studied by IR spectroscopy of low-temperature matrices. Series of five meta (F, Cl, CN, Me, MeO) and para (F, Cl, CN, Me, MeO) phenyl azides all yield didehydroazepines on irradiation regardless of the position or nature of the substituent.[694]

However, photolysis of 2,6-dimethylphenyl azide in the presence of CO in an N_2 matrix at 12 K gives the isocyanate by trapping of the nitrene as rearrangement to didehydroazepine is very inefficient. Pentafluorophenyl azide on irradiation in a matrix at 12 K gives no didehydroazepine formation; however, in the presence of CO, isocyanates are formed. Irradiation (at 254 nm) of *o*-azidobiphenyl and TCNE in acetonitrile gives two products, one of which (**821**) is consistent with the trapping of a 2-azacyclohepta-2,4,6-trienylidene intermediate (eq 63).[695]



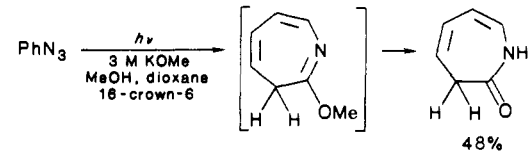
In none of the above work has evidence for involvement of a benzazirine intermediate been obtained. Evidence for azirine formation in the photolysis of bi- and polycyclic aryl azides, however, has been adduced.[696,697]

Ring expansion of monocyclic aryl azides occurs, on thermolysis or photolysis in an excess of primary or secondary aliphatic amines as solvents, to give fair to good yields of azepines. However, azides that carry an ortho substituent suitable for participation in an assisted cyclization usually do not yield azepines. The cyclization reaction is preferred. Aromatic azides with *p*-methoxy, *o*-nitro, or *p*-nitro substituents usually do not give azepines in synthetically useful yields. However, it should be noted that a *m*-methoxy group has a yield-enhancing effect on azepine formation in the photolysis of *m*-anisyl azide in ethylamine solution.[698]

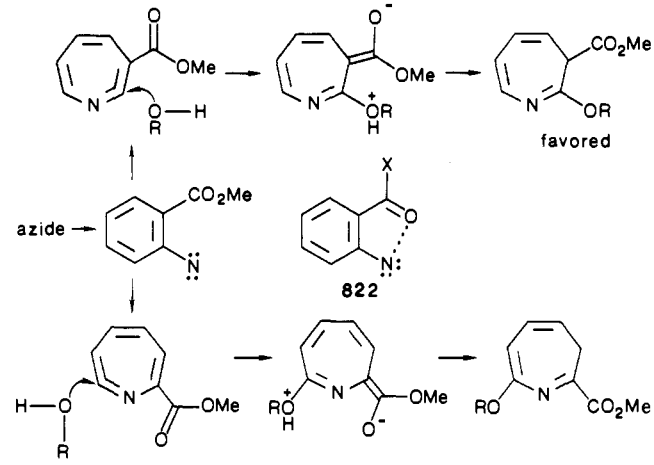
There is only one report of phenyl azide itself undergoing ring expansion on photolysis in methanol to give a methoxyazepine, but in only 10% yield.[699] Photolysis of the same azide in the presence of methoxide affords 3*H*-azepin-2-one, presumably via the methoxyazepine (Scheme 100).[700]

However, aryl azides that have a carbonyl-containing ortho substituent undergo ring expansion to azepines in good yield on photolysis in methanol.[701,702] More recently, azides bearing certain para and meta electron-withdrawing groups also have been found to yield azepines.[234,703-705] These observations, plus the fact that aryl azides with *o*-CN and *o*-CF_3 groups form azepines, indicate that electronic effects of substituents rather than a special stabilization by an ortho carbonyl group

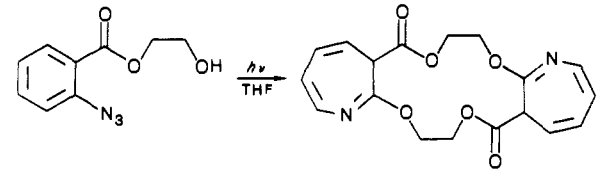
SCHEME 100



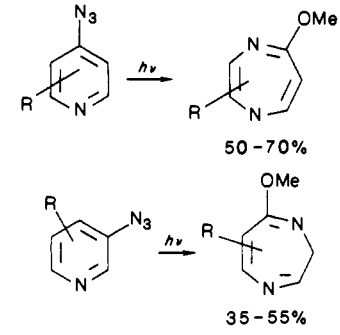
SCHEME 101



SCHEME 102



SCHEME 103



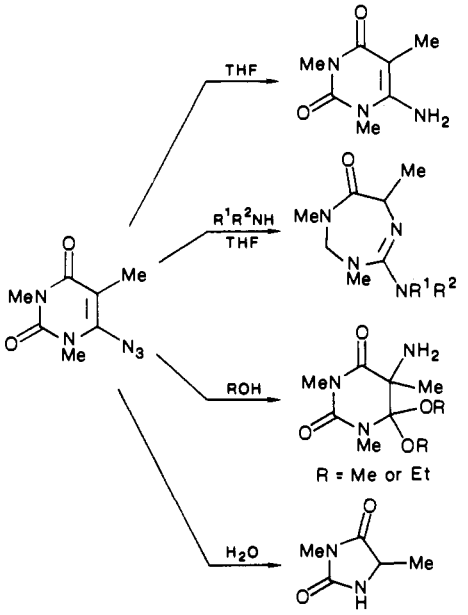
(e.g., **822**) dictate the course of these reactions. A mechanism involving nucleophilic attack on a didehydroazepine rather than a benzazirine intermediate has been proposed (Scheme 101).[234]

This ring expansion, therefore, promises to have a more general synthetic application than previously thought.[706] One such extension to the synthesis of a diazepino-14-crown-4 has been reported by Smalley and co-workers (Scheme 102).[707]

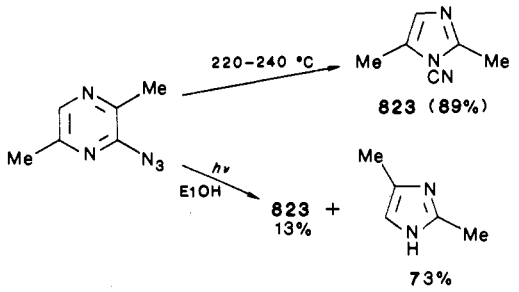
Photolysis of 3- and 4-azidopyridine and some of their methyl derivatives in the presence of methoxide ion yields 1,3- and 1,4-diazepines, respectively (Scheme 103).[708] Ring expansion of 4-azidopyridines to 5-methoxy 6*H*-1,4-diazepines has been achieved also by thermolysis.[709] The authors noted that heating conditions (200 °C for 8 min) are fairly critical.

Full details of the work of Hirota's group on the photolytic reactions of substituted azidouracils with nucleophiles have appeared.[710] Some of the wide div-

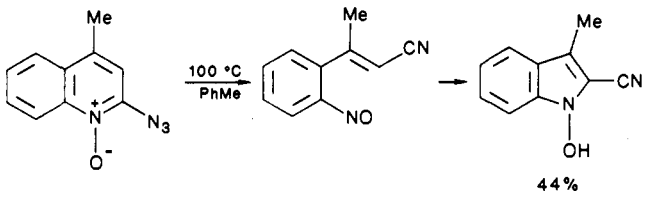
SCHEME 104



SCHEME 105



SCHEME 106



ersity of products is summarized (Scheme 104).

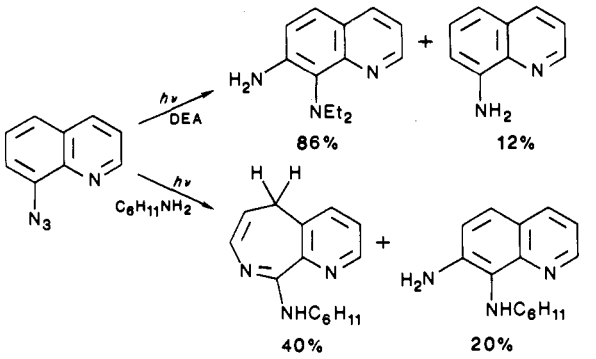
Azidopyrazines undergo ring contraction to imidazoles on pyrolysis or photolysis (Scheme 105).[711]

2-Azido-4-methylquinoline 1-oxide undergoes ring contraction on decomposition at 100 °C, probably via an *o*-nitrosocinnamonitrile (Scheme 106).[712] 3- and 4-pyridine 1-oxides give complex mixtures on thermal or photochemical decomposition in the presence of amines. No products of ring contraction were detected.[713]

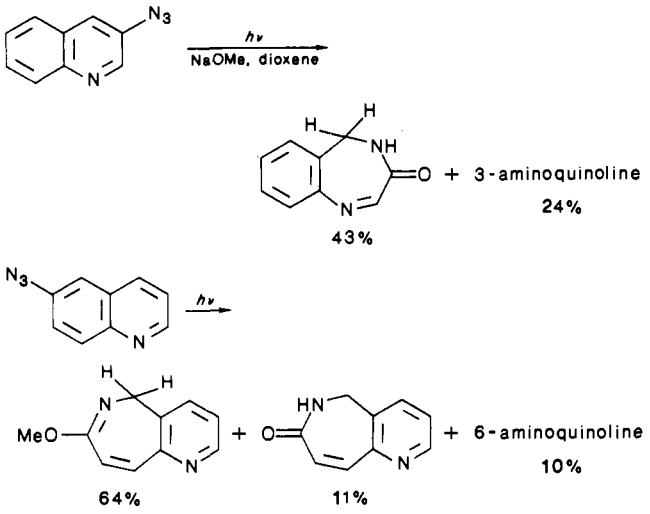
Photolysis of bicyclic aromatic and heterocyclic azides in the presence of amines as a general synthetic route to bicyclic azepines and diazepines is limited by competitive formation of *o*-diamines, which depends upon the position of the azide group and the nature of the amine (Scheme 107).[714-716] The rearomatization reaction is discussed in section III.B.

Studies of the product distribution from the photolysis of several types of [6,6]-bicyclic aromatic azides in various amines have led to the following synthetically useful generalizations.[714] Reaction of primary amines with α-nitrenes (naphthalene nomenclature) tends to

SCHEME 107



SCHEME 108



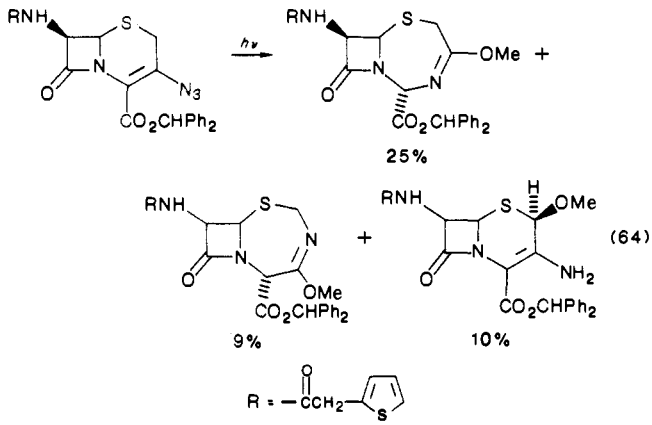
give mainly azepines, occasionally with minor amounts of *o*-diamines. Secondary amines usually afford the parent amine from the α-nitrene (triplet product), unless the starting azide bears a *m*-methoxy substituent, in which case ring expansion to azepines is observed.[715] With β-bicyclic nitrenes *o*-diamines have been obtained from both primary and secondary amines.

Formation of azepines by the photolysis of bicyclic azides in the presence of methoxide ions is a much more general reaction than that in amines.[716] Both α- and β-azides undergo ring expansion to give methoxyazepines or azepinones, and furthermore, the methoxy substituents may be replaced by nucleophiles (Scheme 108).[717]

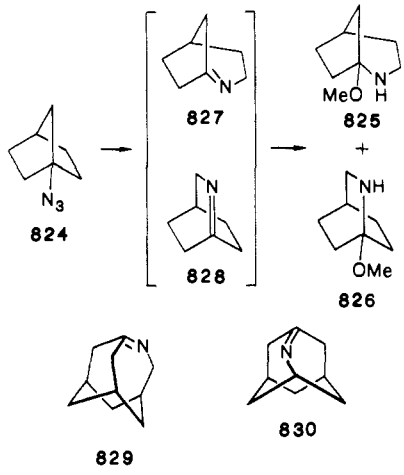
The presence of a methoxy group meta to the azide has an even greater enhancing effect on azepine yield[715] than in the monocyclic series.[698] Mono- and bicyclic azides also have been decomposed in the presence of alkyl mercaptans to afford *o*-((aminoalkyl)thio) derivatives in modest yields.[718]

C(3)-Azidocephams undergo ring expansion on photolysis (eq 64).[719]

Some time ago Lwowski and Reed[720] found that irradiation of 1-azidobicyclo[2.2.1]heptane (**824**) in methanol gave **825** and **826** by trapping of the anti-Bredt imines **827** and **828**. More recently, the study of bridgehead imines has been given great impetus by the belief that the thermal and photochemical syn–anti and cis–trans isomerization of strained CN double bonds might be involved in vision.[721] The direct observation of matrix-isolated 4-azahomoadamant-3-ene (**829**) (formed on matrix photolysis of 1-azidoadamantane)



and 2-azaadamant-1-ene (**830**) (matrix photolysis of 3-azidonoradamantane) has been reported.[722]



VII. Azides as Reagents

The two most commonly used azides are sodium azide and hydrazoic acid (usually generated from sodium azide and an acid). This section serves to cross reference the three leading organic azide reagents in which the azide group is attached to a sulfur (principally *p*-toluenesulfonyl azide), phosphorus (diphenyl phosphorazidate (DPPA)), or silicon (trimethylsilyl azide (TMSA)).

A. *p*-Toluenesulfonyl Azide

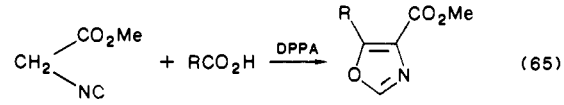
p-Toluenesulfonyl azide is probably the most versatile of the three reagents mentioned above and it participates in most azide reactions.[723] These include amination (sections III.G and VI.C.5), diazo transfer (sections III.I and IV.A.1), azide transfer (sections II.J, VI.A.3, and VI.B.3.a), cycloaddition (section VI.B.1), cycloaddition–ring expansion (section IV.A.3), cycloaddition–ring contraction (section IV.A.2), and ring expansion (section VI.C.5). *p*-Tosyl azide is a shock-sensitive reagent;[420,421] therefore modified reagents have been developed to avoid this disadvantage. Thus, a polymeric sulfonyl azide has been used for the diazo transfer process.[462] This approach holds considerable promise for the future.

B. Diphenyl Phosphorazidate

The diversity of reactivity exhibited by DPPA has made this a particularly attractive reagent and its utility has been reviewed.[724,725]

Recently, it has been employed for the conversion of carboxylic acids to amines (see section III.D) or acyl azides (see section II.F) and enamines to amidines (see section III.H.1). Additionally, DPPA has been used for diazo transfer[726] (see section III.I) and as a peptide coupling reagent for the synthesis of several cytotoxic cyclic peptides[727-731] and a straight-chain peptide precursor to an indole alkaloid.[731]

4-(Methoxycarbonyl)oxazoles can be formed in 57–95% yield by DPPA-mediated C-acylation of methyl isocyanoacetate with carboxylic acids (eq 65).[733]



C. Trimethylsilyl Azide

The use of TMSA as a reagent has been reviewed.[734,735] In the present review, TMSA has been discussed as an azide source for the preparation of azides from halides (section II.A), alkenes (section II.G), epoxides (section II.C), and ketals (section (II.D) among others and for cyclizations (section VI.A.6), cycloadditions (section VI.B), and the Washburne procedure (section VI.C.4).

VIII. Prospects

The increasing number of mild methods available for azide synthesis make azides more accessible than ever for synthetic work. One can expect to see techniques like PTC and ultrasonication (section II.A.1) more generally applied in azide synthesis. The scope of some of the newer reactions mentioned in this review will be extended and milder conditions will be found for them. The remarkable stability of the azide group, particularly under oxidative conditions, commends it as a protective group during multistage synthetic sequences (section V.B.).

Before azides are generally accepted as reagents for large-scale synthetic work, an improvement in their stability is required. This would seem to provide an ideal opportunity for the development of polymer-bound reagents. It would add increased safety to all the other advantages offered by such reagents.[735] Indeed, polymer-bound tosyl azide has been used for diazo transfer.[462] Such a reagent also may well be suitable for aminations (section III.G.1) and azide transfer (section II.J.) reactions. In a different way, Hassner has used a polymeric quaternary ammonium azide[47] for alkyl azide synthesis, and polymeric phosphines have been employed in the Staudinger reaction.[407]

We expect to see an increasing use of azides under all the main headings in this review. If one were asked to select areas for particular attention, those of stereoselective synthesis, reductive cyclization, and metal-assisted azide decomposition applied especially to natural product synthesis would spring to mind.

IX. References

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