strong bands at 1250, 950–1000, and 2400 cm^{-1}, characteristic of P–O, P–O–C, and P–H absorptions, respectively. In the event that cleavage is incomplete, the ether solution is treated with dry HBr at room temperature until the monitored bands above disappear (usually 15 min). The loss of optical purity in this operation is ca. 5% (Table I).

(10) As noted by others,[12] 1-phenylethyl bromide is readily prone toward racemization. For instance, at 27 °C in a 1:1 mixture of HMPT and pentane the optical half-life is only ca. 8 h. When pure, the neat bromide has an optical half-life of about 125 days but racemization seems to be catalyzed by impurities.

(11) In the event that the chiral bromo derivative is part of the synthetic sequence, it is often profitable to use it without purification in order to minimize racemization. If necessary, the optical purity of the produced bromo compound may be obtained by conversion to the corresponding methylsulfide (with inversion) via treatment with sodium methylsulfide–HMPT (see Experimental Section). The methylsulfide derivatives are formed in nearly quantitative yields and can be purified by distillation without fear of racemization. The maximum rotations for a number of such methylsulfides are available[1,12,13a] for evaluation of the optical purities of the bromides.

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Role of Protic and Dipolar Aprotic Solvents in Cycloaddition Reactions Involving Anionic 1,3-Dipoles. Action of Inorganic Azides on Imidoyl Chlorides[1]

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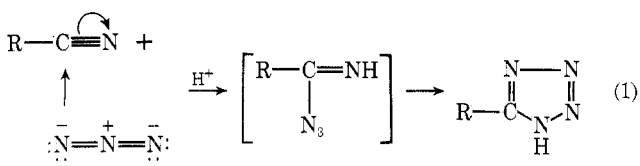
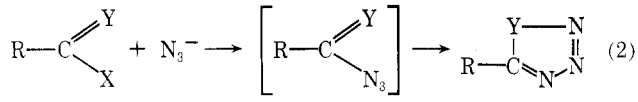
While conventional 1,3-cycloaddition reactions involve the participation of 1,3 dipoles that are polar molecules, cycloadditions of anionic dipoles constitute reactions of an anionic 1,3-dipolar system, such as an azide ion, with a multiple bond.[2] The anionic dipole can undergo either a "direct" or "indirect" cycloaddition. The reaction of the azide ion with nitriles[3] provides an example of "direct" addition (eq 1). The action of inorganic azides on imidoyl chlorides and related compounds[3] may be considered to be an example of "indirect" addition (eq 2).



(1)

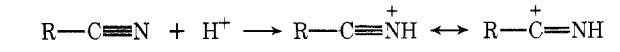


(2)

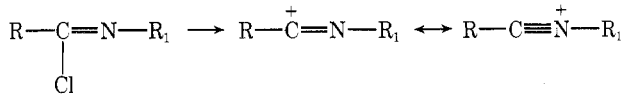
X = halogen, alkoxyl, or other displaceable group and Y = a C unit or a substituted or unsubstituted heteroatom which may or may not, together with R, be part of a cyclic system. Imidoyl chlorides, X = Cl and Y = N–R′

Although reactions of the azide ion with multiple bonds are very useful in heterocyclic synthesis,[3–5] no kinetic or other mechanistic studies exist on many of these reactions. Azide addition may be conceived to occur in a single step following a 1,3-cycloaddition pathway or in a two-step reaction via an azido intermediate. In the reaction of hydrazoic acid with alkynes leading to triazoles, a synchronous 1,3-cycloaddition mechanism is considered more probable.[6] Kinetic data for the addition of azide ion to aromatic diazonium chlorides indicate that the reaction follows a concerted course.[7] Few anionic 1,3 cycloadditions have been proven to proceed in a stepwise manner;[8] in fact, the addition of 2-(*N*,*N*-diisopropylcarbamoyl)allyllithium to the –N=N– bond appears to be the first instance where experimental evidence exists for an anionic 1,3 cycloaddition occurring in a nonconcerted manner.[8]

No kinetic studies are available for the reaction of the azide ion with nitriles (eq 1) or with imidoyl chlorides (eq 2). In the azide–nitrile reaction, an azocarbonium ion appears to be formed first, followed by azide addition.[9] The

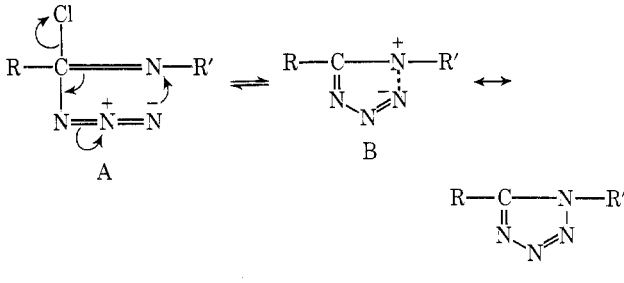


facts, that the reaction is subject to general acid catalysis and that electronegative substituents on the nitrile facilitate addition, are in support of this mechanism.[9]



A very similar mechanism could be conceived for the azide–imidoyl chloride reactions as well. Very recent studies on the rates of solvolysis of substituted imidoyl chlorides indicate that a unimolecular mechanism involving the formation of an azocarbonium ion intermediate is in operation.[10] However, the possibility of an addition–elimination mechanism for chloride displacement should not be ignored. Such a mechanism is known to be involved in the reaction of azide ion with a number of alkyl- and aryl-substituted β-chlorovinyl ketones[11] [eq 2, X = Cl and Y = C–C(=O)–R_1]. Also, there is evidence that anionic nucleophiles, such as the azide ion, react with acyl halides (eq 2, X = Cl and Y = O) via an addition–elimination reaction.[12] Kinetic studies on chloride substitution with amines in diarylimidoyl chlorides have indicated that an addition–elimination mechanism, where bond forming is important, predominates when $\sigma_{N\text{-Ph-substituent}} > 0.3$, while an azocarbonium ion mechanism, where bond breaking is important, prevails when $\sigma_{N\text{-Ph-substituent}} < 0.3$.[13]

Azide addition to the imidoyl chloride (in the addition–elimination mechanism), may be conceived to proceed in a two-step reaction via an azidoazomethine (imidoyl azide) intermediate, or in a single step concerted cycloaddition.[14] The linear azido group must adopt a "bent" configuration[15,16] for cyclization, and as it bends, the resonance form B becomes increasingly important, until cyclization occurs, when the terminal azide nitrogen comes within bonding distance of the azomethine nitrogen.[17] A concerted 1,3-anionic addition is quite likely when a bent transition state similar to B becomes energetically favorable.



In view of the important role of solvents in determining chemical reactivity,[18] recently a program was initiated in our laboratories to understand the true role of protic and dipolar aprotic solvents in 1,3-cycloaddition reactions and how it could be utilized to advantage in heterocyclic synthesis.[19] In the normal 1,3 cycloadditions where no discrete ions are involved, solvent effects, although definite, have been found to be of a small order and to arise mainly from

solvation of the partially charged transition state.[19] In the anionic cycloadditions, on the other hand, solvent effects of a much higher order may be expected, and solvation of the anionic dipole would be contributing largely toward these effects.

Small anions are known to be much less solvated in dipolar aprotic than in protic solvents;[18] hence, anionic cycloadditions will be greatly retarded and will occur with difficulty in protic solvents. Indeed, the poor results recorded in the great majority of reactions where inorganic azides are involved[3-5] appear to be a direct outcome of the solvation effects in the solvent media used. In these reactions, it has been customary to use as the source of the anionic dipole solutions of hydrazoic acid in hydrocarbon solvents such as benzene, toluene, or xylene or to use sodium azide, either alone or mixed with acetic acid, in protic solvents such as ethanol–water mixture, 2-propanol, or butanol. These reactions usually require the use of high pressures and temperatures and extended reaction periods; often, in addition to the main products, other undesirable side products are also formed.[3-5]

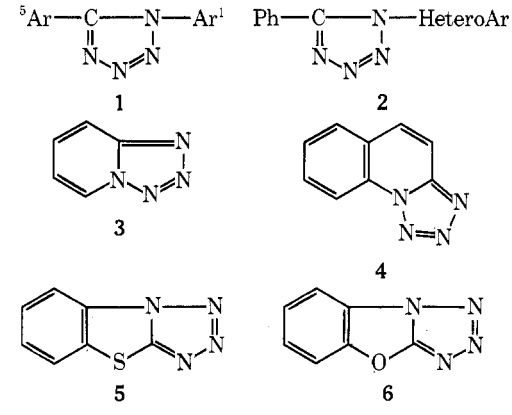
In dipolar aprotic solvents, on the other hand, the greater reactivity of the anion, poorly solvated relative to the transition state, will greatly facilitate the reaction. Also, dipolar aprotic solvents solvate cations strongly and since they have high dielectric constants, electrolytes are strong in these solvents; the anions are thus free to actively participate in the reaction without the stabilizing influence of ion-pair formation.[18] It should thus be possible to perform 1,3-cycloaddition reactions involving the azide anion much more advantageously in dipolar aprotic than in protic or hydrocarbon solvents. Indeed, this has been found to be the case, as reported here.

Although DMF and Me_2SO have been found to facilitate the addition of inorganic azides to nitriles (eq 1) in one isolated study,[9] as the mechanism of action of these solvents was not known at that time, it prevented further studies in this direction. Thus the scope and utility of solvation effects in anionic 1,3 cycloadditions have not been explored to any extent. This paper reports studies on the action of inorganic azides on imidoyl chlorides.

This reaction constitutes a general method for the synthesis of 1-mono- and 1,5-disubstituted tetrazoles. However, the nonaqueous medium in which it is normally carried out, using hydrazoic acid, requires high temperatures and pressures, and the tetrazoles formed are often accompanied by products derived from carbodiimides such as ureas, not to mention the disadvantages involved in handling anhydrous hydrazoic acid.[20] The use of buffered aqueous sodium azide solutions makes it convenient to handle the azide and eliminates rearrangement products. However, nucleophilic displacement of chloride by both azide and water occurs, producing, in addition to the tetrazoles, large amounts of the starting amides;[21] this entails tedious fractionations and an appreciable loss in yield.

By carrying out the reaction in a dipolar aprotic solvent such as DMF, it is possible to use solid sodium azide and achieve anhydrous reaction conditions as well as convenience in handling the azide. The action of DMF as a solvent is twofold; while it provides for greater reactivity of the azide anion, which is poorly solvated, it ensures greater stability of the large polarizable transition state (having properties similar to B), well solvated in this solvent. Thus DMF helps to attain mild reaction conditions and very short reaction periods. It is also possible that DMF might contribute significantly toward shifting the azidoazomethine–tetrazole equilibrium in the direction of the latter.[22] Reactions using DMF proceed smoothly and exclusively to give tetrazoles in high yield and purity; there is no formation of any undesirable side products. Both open and cyclic imidoyl chlorides react in this manner; the latter, however, are less reactive and require the use of ammonium azide. The best sources of anions for reactions in dipolar aprotic solvents are lithium or ammonium salts, since these are very soluble.[18] The reaction works equally well for aromatic as well as heterocyclic substituted imidoyl chlorides.

The superior versatility of this reaction procedure becomes well apparent when compared with results obtained in conventional solvents. While phenyl-4-nitrobenzimidoyl chloride reacts with sodium azide in DMF to give 90% pure tetrazole 1 in 1 h, in acetone–water mixture,[21] after an extended reaction period followed by numerous fractionations for product purification, the yield of tetrazole drops down to 62%. 2-Bromopyridine reacts with ammonium azide in DMF to give 75% tetrazole in 21 h, but in ethanol–water mixture, only 20% product is obtained.[23] 2-Chloropyridine is less reactive in DMF as expected.[18] 2-Chlorobenzo-1,3-thiazole yields 91% pure tetrazole 5 in 30 min by reaction with ammonium azide in DMF; in ethanol–water mixture, the yield is reduced to a mere 3%, and if ammonium azide is replaced by sodium azide, there is no reaction whatsoever in the protic solvent.[23]



1 2 3 4 5 6

Experimental Section[25]

Synthesis of 1,5-Substituted Tetrazoles in DMF. The open-chain imidoyl chlorides required for the preparation of 1 and 2 were obtained by heating a mixture of the appropriate amide (0.04 mol) and PCl_5 (0.04 mol) in a round-bottom flask connected to a water aspirator through a drying tube, so that the HCl and $POCl_3$ formed during the reaction were removed continuously from the system as they originated. The entire operation took less than 20 min. The imidoyl chloride residues were then dissolved in DMF with minimum exposure to air and used immediately in tetrazole synthesis.

In a typical reaction, a mixture of commercial NaN_3 (0.075 mol) and DMF (25–50 ml) (Eastman White Label) was placed in a two-necked flask attached with drying tube and adding funnel, and immersed in a water bath maintained at 20–25 °C throughout the reaction. The solution of the imidoyl chloride (0.04 mol) in DMF (50–75 ml) (the amount of DMF varied according to the solubility of the imidoyl chloride, but the total volume in the overall reaction mixture always remained at 100 ml) was then added dropwise with stirring (a magnetic stirrer was found most convenient for this purpose) to the suspension of NaN_3 in DMF over a period of 45 min. After the addition was completed, the stirring was continued for an additional 15–30 min. The reaction mixture was treated with water, just enough to produce a cloudiness, and then cooled, when the 1,5-substituted tetrazoles (1 and 2) separated out as shining, crystalline compounds. Often, a similar treatment of the filtrate yielded an additional amount of tetrazole.

The products were filtered, washed with a few milliliters of EtOH–H_2O mixture, and pressed dry. The crystalline material was then washed well with water to remove inorganic matter such as NaCl and unreacted NaN_3. The tetrazoles thus obtained were pure and had the same melting points and NMR spectra before and after crystallization from appropriate solvents.

The aryl-substituted tetrazoles (1) prepared in this manner,

along with yield, melting point, and NMR in $CDCl_3$ with Me_4Si as internal standard, included 1,5-diphenyl-, 84, 145–146 °C, δ 7.49 (m, 10, ArH); 1-phenyl-5-*p*-nitrophenyl-, 90, 182–183 °C, δ 8.32 (d, 2, ArH), 7.80 (d, 2, ArH), 7.58 (m, 5, ArH); 1-phenyl-5-*o*-nitrophenyl-, 70, 179–181 °C, δ 8.28–8.05 (m, 1, ArH), 7.88–7.42 (m, 3, ArH), 7.35 (m, 5, ArH); 1-phenyl-5-*p*-anisyl-, 70, 114–116 °C, δ 7.18–7.78 (m, 7, ArH), 6.88 (d, 2, ArH), 3.77 (s, 3, OCH_3); 1-*p*-nitrophenyl-5-phenyl-, 72, 155–157 °C, δ 8.45 (d, 2, ArH), 7.70 (d, 2, ArH), 7.57 (s, 5, ArH); 1-*p*-chlorophenyl-5-phenyl-, 87, 113–114 °C, δ 7.52 (m, 9, ArH); 1-*p*-tolyl-5-phenyl-, 70, 130–132 °C, δ 7.51 (m, 5, ArH), 7.31 (s, 4, ArH), 2.37 (s, 3, CH_3); 1-*p*-anisyl-5-phenyl-, 84, 130–132 °C, δ 7.55 (m, 5, ArH), 7.36 (d, 2, ArH), 7.04 (d, 2, ArH), 3.83 (s, 3, OCH_3); 1-α-naphthyl-5-phenyl-, 70, 129–131 °C, δ 8.07 (m, 3, ArH), 7.80–7.10 (m, 9, ArH); 1-*o*-nitrophenyl-5-phenyl-, 94, 166–168 °C, δ 8.40–8.02 (m, 1, ArH), 7.93–7.50 (m, 3, ArH), 7.45 (m, 5, ArH); 1-(2-methyl-4-nitrophenyl)-5-phenyl-, 93, 153–154 °C, δ 8.40–8.07 (m, 2, ArH), 7.60 (s, 1, ArH), 7.48 (m, 5, ArH), 2.20 (s, 3, CH_3).

The heteroaryl substituted tetrazoles (**2**) included 1-4-pyridyl-5-phenyl-, 75, 167–168 °C, δ ($CDCl_3$) 8.85 (d, 2, PyH), 7.57 (s, 5, ArH), 7.42 (d, 2, PyH); 1-(4,6-dimethyl-2-pyridyl)-5-phenyl-, 70, 94–96 °C.

Anal. Calcd for $C_{12}H_9N_5$: C, 64.57; H, 4.04; N, 31.39. Found: C, 64.44; H, 4.03; N, 31.40. Calcd for $C_{14}H_{13}N_5$: C, 66.93; H, 5.18; N, 27.89. Found: C, 66.88; H, 5.10; N, 27.78.

The cyclic imidoyl chlorides were obtained commercially. The tetrazoles **4–6** were prepared by heating on a steam bath a mixture of the imidoyl chloride (0.02 mol) and NH_4N_3 (0.03 mol, generated in situ from equivalent amounts of NaN_3 and NH_4Cl) in DMF (20 ml). While **4** required 2 h of heating, 30 min was sufficient for **5** and **6**. The reaction mixture, when diluted with water and cooled, yielded the tetrazoles as a clean, crystalline mass: **4**, 94%, mp 155–156 °C, δ ($CDCl_3$) 8.62 (dd, 1, H), 8.15–7.55 (m, 5, H); **5**, 91%, mp 108–109 °C, δ (Me_2SO-d_6) 8.23 (m, 2, H), 7.65 (m, 2, H); **6**, 85%, mp 69–71 °C.

Replacement of NH_4N_3 by NaN_3 caused the yield of **4** to drop to 14%, mp 148–152 °C.

When the reaction was performed in EtOH–H_2O mixture (14 ml of EtOH + 6 ml of H_2O) using NH_4N_3, **5** was obtained in 2.9% yield, mp 108–109.5 °C. In EtOH–H_2O, when NaN_3 was used, no reaction occurred, and the imidoyl chloride was recovered unchanged. The reactions were repeated, heating for a period of 2 h. NH_4N_3 in EtOH–H_2O gave 29% **5**, while NaN_3 in the same solvent yielded 2.1% **5**, mp 100–104 °C.

The mixture of 2-chloropyridine (0.02 mol) and NH_4N_3 (0.03 mol) in DMF (20 ml) was heated in an oil bath at 115–118° for 30 h. The reaction mixture was then made basic with NaOH (10% solution), evaporated to dryness under reduced pressure, and extracted with $CHCl_3$. Evaporation of the solvent yielded tetrazole **3**: yield 80%; mp 158–159 °C, δ ($CDCl_3$) 8.86 (deg. ddd, 1, H_5), 7.98 (deg. ddd, 1, H_8), 7.74 (deg. ddd, 1, H_7), 7.29 (deg. ddd, 1, H_6).

2-Bromopyridine under identical reaction conditions gave a 75% yield of **3** in 21 h. In refluxing EtOH–H_2O (14 ml of EtOH + 6 ml of H_2O), the yield of **3** was reduced to 20%. When the heating period was reduced to 7 h, in DMF using NH_4N_3, the tetrazole was obtained in 45 and 53% yields from the 2-chloro- and 2-bromopyridines, respectively.

Acknowledgment. The author thanks Miss Lini S. Kadaba for technical assistance.

Registry No.—**1** (Ar^1 = Ar^5 = Ph), 7477-73-8; **1** (Ar^1 = Ph; Ar^5 = *p*-NO_2Ph), 14213-27-5; **1** (Ar^1 = Ph; Ar^5 = *o*-NO_2Ph), 57761-69-0; **1** (Ar^1 = Ph; Ar^5 = *p*-anisyl), 57761-70-3; **1** (Ar^1 = *p*-NO_2Ph; Ar^5 = Ph), 57761-71-4; **1** (Ar^1 = *p*-ClPh; Ar^5 = Ph), 57761-72-5; **1** (Ar^1 = *p*-tolyl; Ar^5 = Ph), 52411-70-8; **1** (Ar^1 = *p*-anisyl; Ar^5 = Ph), 57761-73-6; **1** (Ar^1 = α-naphthyl; Ar^5 = Ph), 57761-74-7; **1** (Ar^1 = *o*-NO_2Ph; Ar^5 = Ph), 57761-75-8; **1** (Ar^1 = 2-Me-4-NO_2Ph; Ar^5 = Ph), 57761-76-9; **2** (Ar = 4-pyridyl), 57761-77-0; **2** (Ar = 4,6-dimethyl-2-pyridyl), 57761-78-1; **3**, 274-87-3; **4**, 235-25-6; **5**, 248-02-2; **6**, 57761-79-2; NaN_3, 26628-22-8; *N*-phenylbenzimidoyl chloride, 4903-36-0; *N*-phenyl-*p*-nitrobenzimidoyl chloride, 5466-94-4; *N*-phenyl-*o*-nitrobenzimidoyl chloride, 57761-80-5; *N*-phenyl-*p*-methoxybenzimidoyl chloride, 38968-72-8; *N*-*p*-nitrophenylbenzimidoyl chloride, 34918-79-1; *N*-*p*-chlorophenylbenzimidoyl chloride, 34918-76-8; *N*-*p*-tolylbenzimidoyl chloride, 15999-95-8; *N*-*p*-anisylbenzimidoyl chloride, 34918-74-6; *N*-α-naphthylbenzimidoyl chloride, 57353-87-4; *N*-*o*-nitrophenylbenzimidoyl chloride, 3493-72-9; *N*-(2-methyl-4-nitrophenyl)benzimidoyl chloride, 57761-81-6; *N*-4-pyridylbenzimidoyl chloride, 57761-82-7; 2-chloroquinoline, 614-62-4; 2-chlorobenzothiazole, 615-20-3; 2-chlorobenzoxazole, 615-18-9; NH_4N_3, 12164-94-2; 2-chloropyridine, 109-09-1; 2-bromopyridine, 109-04-6; *N*-(4,6-dimethyl-2-pyridyl)benzimidoyl chloride, 57761-83-8.

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(23) In view of the fact that data reported in the literature do not seem convincing, we chose to perform the experiments under identical conditions in protic and dipolar aprotic solvents, so that the advantages of using the latter as the solvent medium can be brought out clearly and candidly. For example, it is reported[24] that 2-chlorobenzo-1,3-thiazole yields 74% of the tetrazole derivative when refluxed for 8 h with sodium azide in ethanol–water mixture. Repeating the reaction in a like manner, we found it is impossible to obtain the tetrazole in an yield greater than 3%.
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