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THE RAPID SYNTHESIS OF 1-SUBSTITUTED TETRAZOLES

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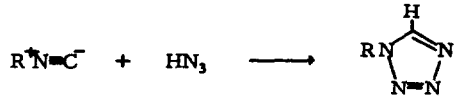
For almost sixty years chemists have used the reaction of isocyanides with hydrazoic acid as the method of choice for the preparation of 1-substituted tetrazoles (I).[1]



I

Today isocyanides are readily and cheaply available[2] and HN_3 solutions in inert solvents are easily made by extracting an acidified solution of NaN_3 in water, but there are still two disadvantages to the synthesis. First, low yields especially in the formation of aryltetrazoles† are often obtained and, second, the patience of a Job is sometimes required to survive the long reaction times which can run into weeks. In this communication we show that both these handicaps are simple and direct consequences of the fact that the reaction as reported in published procedures, has been carried out under the wrong conditions.

Recently we needed a large quantity of 1-vinyltetrazole (II) as a precursor to a series of vinyl carbodiimides.[3] Since the literature synthesis of II[4] involves a tedious, low overall yield, several step process beginning with 5-aminotetrazole, we decided to attempt its preparation by the classical scheme above from vinyl isocyanide (III) and HN_3. III can be made rapidly and conveniently from ethanolamine[5] and we were pleased to discover that on treatment with HN_3 in ether it is cleanly converted to II. This result, though very satisfactory in its practical aspects, involved us in a mechanistic quandry, since in other reactions of III with 1,3-dipoles[5] the ethylenic bond is the reactive (though not very reactive) site; for example:[5]

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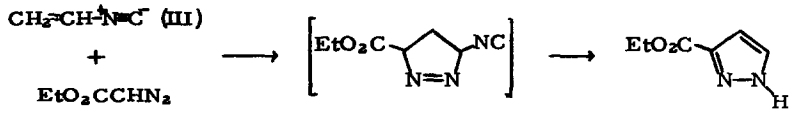
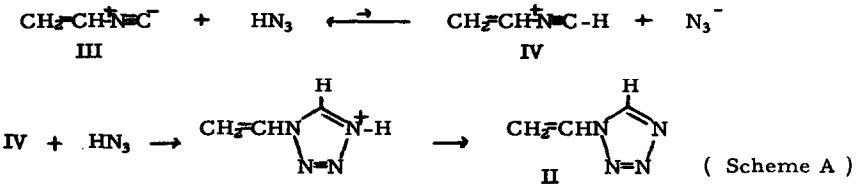
†These low yields seem to be primarily a result of researcher impatience. In order to speed up product formation some experimenters have carried out the reaction in refluxing benzene or toluene. Under these conditions we have found the HN_3 slowly distills away. When the reaction is run in refluxing ether for several days, aryltetrazoles are obtained in high yield.



The general theory of 1,3-dipolar cycloadditions[6] would seem to require that those factors which enhance the dipolarophile properties of a particular multiple bond to one 1,3-dipole would carry over and induce reactions at the same site with other 1,3-dipoles - a result obviously not true here.

In our solution to this dilemma we postulate that, in its 1,3-dipolar cycloaddition with HN_3, III itself is not the reactive species, but that instead the key intermediate is protonated vinyl isocyanide (IV) which then undergoes the cycloaddition:

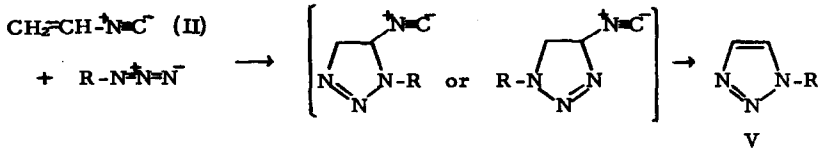


(Scheme A)

Since IV has very different electronic characteristics than vinyl isocyanide it would not be surprising if the molecule had changed enough to make the isocyanide function the new reaction site. In accord with this hypothesis is the fact that nitrilium cations ($RC\equiv\overset{+}{N}-R$) react very rapidly with HN_3 to yield 1,5-disubstituted tetrazoles.[7]

The mechanism outlined above leads to two important predictions.

First, the reaction of substituted azides with vinyl isocyanide should afford triazoles (V):



This has been verified: 1-methyl-1,2,3-triazole is obtained from II and MeN_3 though only in 16% yield.

Second, in general, the classical synthesis of 1-substituted tetrazoles from isocyanides and hydrazoic acid should be acid catalyzed. The validity of this prediction is forcefully demonstrated in Table I. It is seen that in the absence of added catalyst the reaction is usually very slow, even when a large excess of HN_3 is used(pseudo first order conditions). In the presence of large quantities of BF_3·etherate as the acid catalyst, the reaction rate increases tremendously but a byproduct (the formamide formally derived by hydrolysis of the isocyanide) is also found in low yield. An adequate rate enhancement without the byproduct complication can be accomplished just by adding a drop of concentrated sulfuric acid to the reaction mixture.

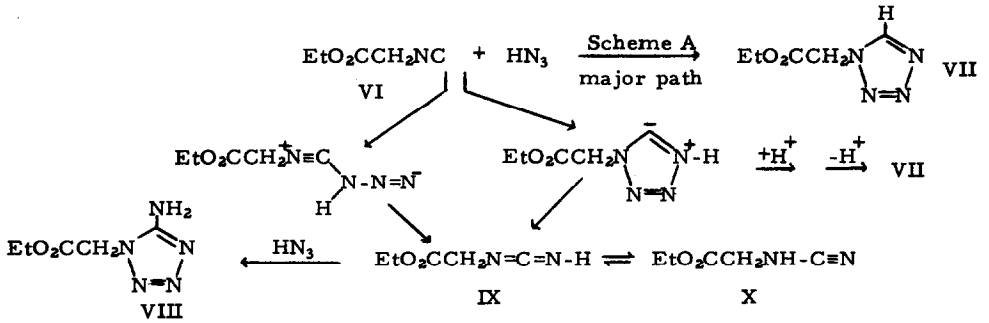
Sometimes even smaller amounts of strong acid are sufficient as is apparent from the following experiment. The ethereal HN_3 solution is normally prepared in a separatory funnel by slowly adding a large excess of conc H_2SO_4 with shaking to a cold aqueous solution of NaN_3 under a layer of ether. During this process a trace amount of H_2SO_4 is also extracted into the ether. This is removed by neutralization during the standard drying procedure with Na_2SO_4 but can be left in the ether by drying instead with $CaCl_2$ (note the large rate increases in Table I).

Table I. Synthesis of 1-Substituted Tetrazoles (I) from RNC and HN_3 in Ether[a]

Tetrazole R=	Reaction Description[b]	Rxn Time	Rxn Temp	Product Yield	Leftover Isocyanide[c]	Byproduct Formamide[c]
pCl-Phenyl	No added catalyst	24 hrs	33°	20%	75%	None
"	No added catalyst	57 hrs	32°	35%	49%	None
"	HN_3-ether is $CaCl_2$ dried	24 hrs	33°	32%	66%	None
"	1 drop conc H_2SO_4 added	24 hrs	35°	95%	None	None
Benzyl[d]	No added catalyst	24 hrs	33°	25%	64%	None
"	HN_3-ether is $CaCl_2$ dried	24 hrs	36°	95%	None	None
"	0.25 eq BF_3 ether added	1 hr	0°	74%	16%	10%
"	0.5 eq BF_3-ether added	1 hr	0°	83%	None	12%
Cyclohexyl[d]	No added catalyst	24 hrs	35°	33%	62%	None
"	HN_3-ether is $CaCl_2$ dried	24 hrs	35°	41%	54%	None
"	1.0 eq BF_3· ether added	30 min	0°	84%	None	12%
"	1 drop conc H_2SO_4 added	24 hrs	35°	93%	None	Trace
Vinyl	No added catalyst	24 hrs	33°	22%	e	f
"	No added catalyst	48 hrs	33°	39%	e	f
"	HN_3-ether is $CaCl_2$ dried	24 hrs	33°	92%	e	f
EtO_2CCH_2[d]	No added catalyst	24 hrs	36°	41%	48%	None
"	No added catalyst	2 wks	35°	85%[g]	Trace	None
"	HN_3-ether is $CaCl_2$ dried	24 hrs	33°	85%	10%	None
"	HN_3-ether is $CaCl_2$ dried	30 hrs	36°	94%	Trace	None
"	1.0 eq BF_3-ether added	30 min	0°	70%	None	15%

[a]All rxns. at same concentrations; ratio HN_3:RNC is 6:1; this ratio is used in order to obtain significant product yields in a reasonable time period in the uncatalyzed rxns; with less HN_3 the same yields can be obtained using a longer rxn. time or more catalyst. [b]The ethereal HN_3 extract is dried with Na_2SO_4 unless otherwise specified. [c]Determined by NMR analysis (for maximum yields when the rxn. is run in the presence of acid special care should be taken to be certain the medium is anhydrous). [d]New compound; satisfactory analytical and spectroscopic data obtained: 1-benzyltetrazole m.p. 59-60°, 1-cyclohexyltetrazole m.p. 48-49°, 1-carbethoxymethyltetrazole (VII) m.p. 32-34°. [e]Too volatile to assay. [f]Not assayed for. [g]Plus 11% isomer (VIII) m.p. 145-146°; see text; VIII has also been synthesized by an independent route.

It is possible that a minor pathway in the formation of I involves a direct reaction of RNC with HN_3. Supporting this is the fact that the 5-aminotetrazole derivative (VIII 11%) and the expected tetrazole (VII 85%) are both obtained on treatment of the isocyanide (VI) with HN_3. We suggest the following mechanisms or prototropic variants for the generation of VIII.



In support of this mechanism is the fact that: 1) 1,4-disubstituted tetrazolium salts cleave to carbodiimides on titration with triethylamine,[3,8] 2) cyanamides (X) react with HN_3 to yield 5-aminotetrazoles as if they had the carbodiimide structure (IX),[9] and 3) no aminotetrazole (VIII) is obtained when VI is treated with HN_3 in the presence of BF_3·etherate.

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