Cu^I-Catalyzed Cycloadditions

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$Cu_2(OTf)_2$-Catalyzed and Microwave-Controlled Preparation of Tetrazoles from Nitriles and Organic Azides under Mild, Safe Conditions**

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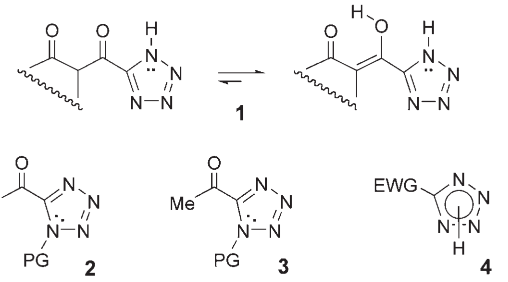
Dedicated to Professor Rolf Huisgen and Professor K. Barry Sharpless

In connection with a project aimed at preparing new series of diketotetrazoles (see compound **1** in Scheme 1, for which two representative tautomers are shown) and pharmacophor-related quinolinocarbonyltetrazoles, as further candidates for HIV-1 integrase inhibitors,[1] we sought a rapid entry into the synthesis of tetrazole esters **2** and/or 5-acetyltetrazoles **3** (Scheme 1). Formation of tetrazole rings by cycloaddition between nitriles and organic azides is in principle the most direct method,[2] but it usually requires very harsh conditions. Moreover, since N-unsubstituted tetrazole rings are well-recognized bioisosters of the carboxyl groups,[2a] the development of any safe approach to tetrazoles of type **2** and **3**, as well as to derivatives of general formula **4** (Scheme 1), would be of great use in the pharmaceutical industry.



Scheme 1. Diketotetrazoles and putative precursors; PG = protecting group, EWG = electron-withdrawing group.

Most recent studies on the subject rely on a classical paper in which benzyl azide derivatives and alkyl cyanoformates (ROCO-CN) were heated without solvent at 130 °C in a sealed tube;[3] tetrazoles of type **2** can be achieved in roughly 60–70 % yields, at best. To reduce the hazards inherent to heating these polynitrogenated starting materials and products, Demko and Sharpless investigated a "click chemistry" approach[4,5] by using mainly acyl cyanides (RCO-CN) and organic azides, which allowed them to obtain compounds of type **3** (1,5-disubstituted) under solvent-free conditions, without catalysts, at 120 °C.[4a] From the more reactive *p*-toluenesulfonyl cyanide, excellent yields of 1,5-disubstituted tetrazoles were similarly obtained at 80–100 °C.[4b]

These outstanding results encouraged us to investigate a series of potential catalysts for these [3+2]-cycloaddition reactions, aimed at achieving even safer conditions. The copper(I) complexes $Cu_2(OTf)_2 \cdot tol$ and $Cu_2(OTf)_2 \cdot C_6H_6$ ($OTf = O_3SCF_3$, tol = toluene) allow one to carry out most of the above reactions at room temperature, with or without solvent. This catalytic activity was not observed for other Cu^I salts nor for a number of other transition-metal cations tested in these reactions.

As we planned to activate CN groups linked to EWGs, which lower the basicity of the CN nitrogen atoms, mainly cyanophilic cations were investigated.[6] Ethyl cyanoformate and *p*-methoxybenzyl azide ($PMB\text{-}N_3$) were mixed without solvent and, as summarized in Table 1, potential catalysts were added.

Besides the additives shown in Table 1, many others (that is, Cu powder, $AgSbF_6$, $AgBF_4$, AgF, AgOAc, $AuCl_3$, $Au(OTf)_3$, Ru/C, $RuCl_3$, $[RuCp^*(PPh_3)_2]Cl_2$ ($Cp^* = C_5Me_5$),[7] $[Pd_2(dba)_3] \cdot CHCl_3$ (dba = dibenzylideneacetone), $PdCl_2$, Pt/C, $PtCl_2$, $PtCl_4$, $Sc(OTf)_3$, and $LaCl_3$) were tested, but are not included in Table 1, as they turned out to be inactive.

Table 1 shows that cycloaddition was only catalyzed by some copper salts (entries 4, 7–11, 13, and 14). These salts appear to be those more soluble copper derivatives that, in blank experiments, do not cause a premature decomposition of the reactants. In fact, the results from the two commercially available or easily prepared[8] copper(I) triflates are remarkable, as no reduction or Lewis acid mediated decomposition of the azide was observed. The same reaction without catalyst requires heating at 130 °C to reach an acceptable yield,[3] as we have mentioned and confirmed. Trace amounts of trifluoromethanesulfonic acid (triflic acid, TfOH), which might be contained in these reagents or produced in the reaction medium, are not responsible for their activity, since TfOH does not catalyze the reaction (see entry 12 in Table 1).

For safety purposes, as mixing of pure liquids without a solvent to dissipate any exothermic decomposition of the

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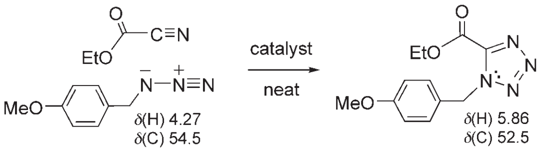
Table 1: Evaluation of the catalytic effect of different additives.[a]



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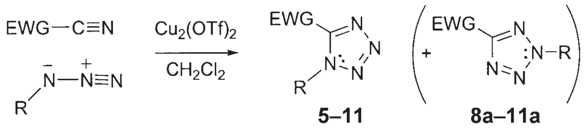
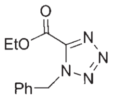
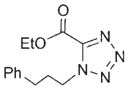
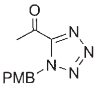
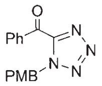
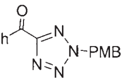
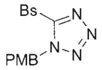
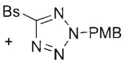
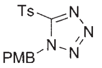
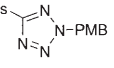
Entry	Catalyst (mol%)	*T* [°C]	*t* [h]	Yield [%]
1	none	60	24	5
2	CuCN (20)	20	24	0
3	Cu_2Cl_2 (10)	20	72	30
4	Cu_2Cl_2 (10)	60	12	50
5	CuBr·SMe_2 (20)	20	24	6
6	CuI (10)	60	6	10
7	$Cu_2(OTf)_2$·tol (5)	20	24	60
8	$Cu_2(OTf)_2$·tol (10)	20	24	75
9	$Cu_2(OTf)_2$·tol (10)	60	6	80
10	$Cu_2(OTf)_2$·C_6H_6 (10)	20	24	93
11	$Cu_2(OTf)_2$·C_6H_6 (10)	60	6	95
12	TfOH (10)	20	72	0[b]
13	$Cu(OTf)_2$ (10)	20	24	60[b]
14	$Cu(OTf)_2$ (20)[c]	20	72	50[c]
15	$CuCl_2$ (10)	20	24	0
16	$CuSO_4$ (10)[d]	60	24	0
17	$ZnCl_2$ (10)	20	24	0
18	$Zn(OTf)_2$ (10)	20	24	0
19	AgOTf (10)	20	24	0[b]
20	AuOTf (10)	20	48	0[b]
21	$[Au(PPh_3)]OTf$ (10)	20	48	0[b]

[a] Reactions were carried out under solvent-free conditions with PMB-N_3 (1.0 mmol) and EtOCO-CN (1.1 mmol). The potential catalyst was added, and stirring was maintained under Ar. Except for entries 10 and 11, conversion was incomplete. [b] Partial decomposition of the organic azide was observed (5–20% of 4-methoxybenzaldehyde was formed). [c] With larger amounts of catalyst, decomposition of the reactants increased. [d] Anhydrous and pentahydrate, with identical results. Addition of sodium ascorbate (aqueous solution or in *t*BuOH/H_2O)[4a, b, 5e] is not recommended, as partial hydrolysis of EtOCO-CN (EWG-CN) takes place.

Table 2: Reaction of aliphatic azides with EWG-linked nitriles in CH_2Cl_2, catalyzed by $Cu_2(OTf)_2$·C_6H_6.[a]



5–11 (**8a–11a**)

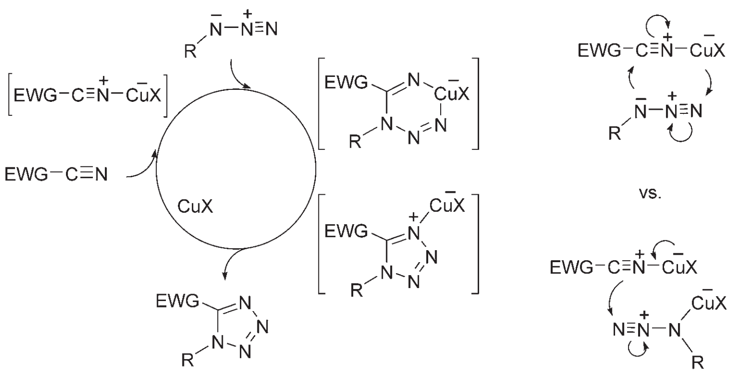
Entry	Reactants[a]	Conditions	Product(s)		Yield [%][b]
1	PMB-N_3 EtOCO-CN	20 °C, 48 h	**5**		90
2	PMB-N_3 EtOCO-CN	80 °C, 2 h, MW	**5**		94
3	$PhCH_2N_3$ EtOCO-CN	20 °C, 48 h			95
4	$PhCH_2N_3$ EtOCO-CN	80 °C, 2 h, MW	**6**		88
5	$Ph(CH_2)_3N_3$ EtOCO-CN	20 °C, 48 h			90
6	$Ph(CH_2)_3N_3$ EtOCO-CN	80 °C, 2 h, MW	**7**		97
7	PMB-N_3 MeCOCN[c]	20 °C, 48 h	 +  **8** **8a**	9:1	81
8	PMB-N_3 MeCOCN[c]	80 °C, 2 h, MW	**8/8a**	9:1	37[d]
9	PMB-N_3 PhCO-CN	20 °C, 48 h	 +  **9** **9a**	92:8	74
10	PMB-N_3 PhCO-CN	80 °C, 2 h, MW	**9/9a**	95:5	77
11	PMB-N_3 Bs-CN	20 °C, 4 h	 +  **10** **10a**	7:3	99
12	PMB-N_3 Ts-CN	20 °C, 4 h	 +  **11** **11a**	8:2	99

[a] Organic azide/nitrile/catalyst in a 1.0:1.1:0.1 molar ratio in CH_2Cl_2 (1 M solutions) unless otherwise indicated. [b] Overall yield of tetrazoles. [c] This nitrile decomposes under the reaction conditions, so that 1.5 equiv were added.[4a] [d] Heating is not recommended (compare with entry 7).

reagents or products may be dangerous on a large scale, we next investigated the most appropriate solvent for the above cycloaddition reaction. At 20 °C and approximately 1 M concentration, stirring for 24 h with 10 mol% of $Cu_2(OTf)_2$·C_6H_6, dichloromethane turned out to be the most appropriate among the solvents evaluated, according to the yields of the isolated tetrazole derivative. In fact, the order was as follows (yields in parenthesis): CH_2Cl_2 (85%), toluene (76%), THF (56%), CH_3CN (0%; the solvent itself does not react, see below), DMF (0%), and absolute EtOH (0%). Thus, the best coordinating solvents are not useful, probably due to the preferential solvation of the Cu^I ions; hydroxylic solvents partially react with EtOCO-CN (or, more generally, with EWG-CN), as was expected, and this process could be monitored by NMR spectroscopy.

Having optimized the catalyst and solvent, we applied the procedure to various organoazides and organocyanides. As shown in Table 2 (entries 1, 3, 5, 7, and 9), most reactions could be carried out at room temperature (or at 40 °C, data not shown) to afford mainly **5**–**9**, but to shorten the reaction times to 1–2 h, the samples were heated at approximately 80 °C in sealed vials. This procedure was carried out in a microwave (MW) synthesizer, with safe control of the temperature and pressure. With benzenesulfonyl cyanide ($PhSO_2$-CN, Bs-CN) and tosyl cyanide ($TolSO_2$-CN, Ts-CN), the conversion was complete within a few hours without heating (Table 2, entries 11 and 12), to give mainly **10** and **11**, respectively. It is remarkable that in this process Bs-CN and Ts-CN play the role of synthetic equivalents of HCN, the direct addition of which to organic azides is not feasible.

It is known that by thermal activation only 1,5-disubstituted tetrazoles are formed.[4] However, under our catalytic conditions (Table 2), minor amounts of several 1,4-regioisomers (**8a**–**11a**) were also obtained. These isomers were separated by chromatography (lower R_f value). The struc-



Scheme 2. A mechanism for the Cu^{I}-catalyzed cycloadditions. See text for details.

tures of both series of tetrazoles were confirmed by comparison of the ^{1}H and ^{13}C NMR spectra with the other compounds in the respective series and with known data.[2b,4] The chemical shifts of the methylene groups of *p*-methoxybenzyl (PMB) and PhCH$_2$ (Bn) groups of **5**–**6** and **8**–**11** are characteristic (δ(H) = 5.89–5.82, δ(C) = 52.7–52.2 ppm), whereas those of **8a**–**11a** lie at δ(H) = 5.80–5.68, δ(C) = 57.5–56.9 ppm). Both the decarboxylation of **5** (by hydrolysis)[3] and deacetylation of **8** (with NaOEt) gave 1-PMB-tetrazole.[9]

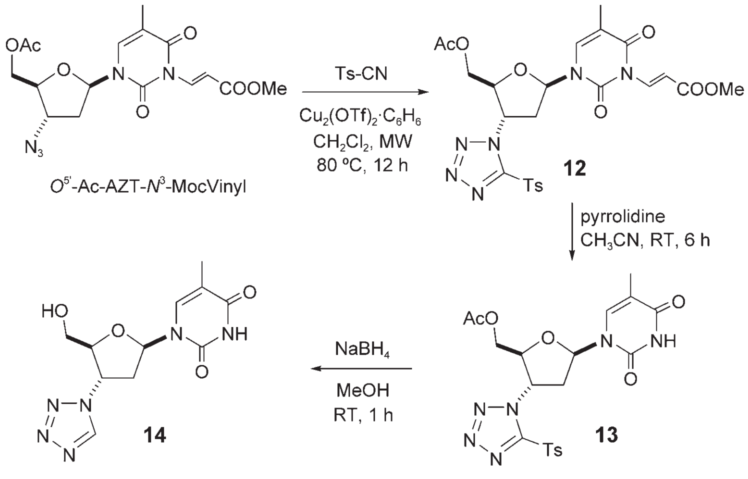
The **10**/**10a** and **11**/**11a** ratios were increased by carrying out the cycloaddition with only 1–2 mol% of Cu$_2$(OTf)$_2$·C$_6$H$_6$. The reactions were slower, but tetrazoles **10** and **11** were formed exclusively. On the other hand, with much larger amounts of Cu$_2$(OTf)$_2$·C$_6$H$_6$, the ratios were inverted. Thus, by mixing nitriles and organoazides in CH$_2$Cl$_2$ at −30 °C, adding 50–100 mol% of the catalyst, and stirring the resulting dark slurry (heterogeneous conditions) at 20 °C, the 1,4-isomers predominated. For example, **11a** was the major compound with 50 mol% of the copper salt (**11**/**11a** ratio of 1:10). With 100 mol% of the copper salt, only **11a** was obtained (together with 4-methoxybenzaldehyde and other decomposition products of PMB-N$_3$ because of such a large excess of the copper salt). In this way, even the previously unknown 1,4-disubstituted isomer **5a** (δ(H) = 5.77 and δ(C) = 57.2 ppm for the PMB methylene group) could be obtained (40:60 **5**/**5a**).

For the removal of the PMB protecting group of **5**, **5a**, **8**, **8a**, **9**, **9a**, **10**, **10a**, **11**, and **11a** to prepare tetrazole derivatives of formula **4**, we tried several known methods.[10] Using 2,3-dichloro-5,6-dicyano-1,4-quinone (DDQ) did not work, but oxidation with ammonium cerium(IV) nitrate (CAN) was very efficient (e.g. 1 mmol of **8**, 2.5 mmol of CAN, CH$_3$CN/H$_2$O, 3 h, 20 °C, 100%).[9a] Heating **5**, **11**, and **11a** as representative samples with 1:1 TFA/CH$_2$Cl$_2$ (TFA = trifluoroacetic acid) and an excess of methoxybenzene (to trap the released 4-methoxybenzyl cation) also gave clear final solutions and practically quantitative yields of the deprotected products.

Treatment of **11** with an excess of magnesium or NaBH$_4$ in MeOH led to complete removal of the Ts group to afford excellent yields of 1-PMB-tetrazole,[9a,b] the same product we obtained by decarboxylation of **5** and deacetylation of **8**. Removal of the Ts group of **11a** gave 2-PMB-tetrazole.[9c,d]

Standard aliphatic azides (e.g. PMB-N$_3$) do not react at all with CH$_3$CN or PhCN (i.e. with common nitriles) under any of the conditions mentioned here, which means that highly electrophilic nitrile carbon atoms are required for a successful addition. Organoazides polarized in the reverse sense (e.g. Ts-N$_3$, where an azido group is linked to an EWG), do not react at all with either CH$_3$CN or Ts-CN, even when forcing the conditions. We therefore suggest a mechanism (Scheme 2, where X = Cu(OTf)$_2$ or TfO, depending on the real ratio between the dimeric and monomeric copper species) for the catalyzed addition that gives **5**–**12**, in which the azido group adds to the Cu^{I}-complexed nitrile (as simplified in Scheme 2, top right). On the other hand, with an excess of Cu^{I} in the medium with regard to the organoazide, both the true reactants may be Cu^{I}-complexed species (as simplified in Scheme 2, bottom right), which might explain the reversal in regioselectivity, that is, the formation of larger amounts of **5a**–**11a**.

As an application of the procedures discussed above to more sterically hindered aliphatic azides, we studied the 3′-azido-3′-deoxythymidine (AZT/zidovudine) derivative shown in Scheme 3.[11] Conversion percentages of approximately 15% with EtOCO-CN and 25% with Ts-CN were achieved at 20 °C within 48 h, using 10 mol% of the catalyst. Thus, heating was necessary in this case. For safety purposes and to avoid the decomposition of the substrate at higher temperatures, we carried out the reaction at 80 °C in a MW synthesizer, as described above. This procedure afforded **12** in 80% yield within 12 h with 10 mol% of catalyst (i.e. under homogeneous conditions). With 50 mol% and even with 200 mol% of Cu$_2$(OTf)$_2$·C$_6$H$_6$, only **12** was also obtained, to our surprise. In light of the previous results with the **10**/**10a** and **11**/**11a** pairs, we had expected that the 1,4-disbutituted isomer **12a** would



Scheme 3. Preparation of tetrazole analogues of AZT. See text for details.

predominate. Deprotection of the methoxycarbonyl vinyl (MocVinyl) group of **12** with pyrrolidine (4–6 equiv, 20 °C, 6 h)[12] gave **13** in practically quantitative yield. Desulfonylation of **13** with $NaBH_4$/MeOH (4 mmol of $NaBH_4$ per mmol of **13**, added in portions, 20 °C, 1 h) took place with concomitant deacetylation to afford in excellent yield the desired tetrazole derivative **14**, the structure of which was confirmed by NMR spectroscopy.[13] We attribute the absence of the 1,4-disubstituted isomer in the present case to a steric effect, that is, to low percentages of [NNN(CuX)R] (see Scheme 2, bottom right, coordination to the internal N atom) in the medium when R is a branched chain.

In conclusion, we have discovered a click reaction, parallel to the well-known one between organoazides and terminal alkynes, which in many cases affords excellent yields of 1,5-disubstituted tetrazoles **5**–**11** in CH_2Cl_2 at ambient temperature with 1–10 mol % of soluble $Cu_2(OTf)_2{\cdot}C_6H_6$ as the catalyst. Under heterogeneous conditions with 50–100 mol % of the same catalyst, the reaction yields mainly 1,4-disubstituted tetrazoles **5a**–**11a**. Only with a reluctant secondary azide (an AZT derivative) did the reaction have to be carried out at 80 °C in a MW reactor; in the other examples, this activation was not strictly necessary, though the reaction times were then shortened to 2 h. For the tetrazoles prepared from PMB-N_3, the cleavage of the PMB−N bond is feasible in almost quantitative yields with standard reagents, as it is the cleavage of several EWG−C bonds (or, depending on the EWG, the elongation of this side chain, as will be reported elsewhere in connection with the development of new HIV integrase inhibitors). In other words, PMB-N_3, a synthetic equivalent of the toxic and explosive HN_3, can be made to react with EWG-CN, that is, with synthetic equivalents of the toxic HCN, under very mild, nonhazardous conditions. Overall, we have established the safest procedure reported to date for the installation of tetrazole rings directly from organic azides and nitriles.

Experimental Section

Caution: Polynitrogenated compounds may behave as explosives. We have not had any adverse reactions with the compounds reported here under the conditions of reference [3] (130 °C, solvent-free conditions, preparation of a sample of **5** as a blank) or, obviously, under our very mild conditions (20–80 °C), which were designed for working safely on a large scale.[14]

General procedure at room temperature: $Cu_2(OTf)_2{\cdot}C_6H_6$ (0.10 mmol) was added to a stirred mixture of the azide (1.0 mmol) and acyl cyanide (1.1 mmol) in anhydrous CH_2Cl_2 (1.0 mL), and the mixture was stirred in a water bath at 20 °C for 2 days or, for the most reactive samples, until no starting azide was observed by thin layer chromatography (TLC). The reaction mixture was then diluted with CH_2Cl_2/Et_2O (9:1, 20 mL) and aqueous NaHS (1.5 M, 5 mL) was added. The layers were separated and the aqueous one was extracted twice with CH_2Cl_2/Et_2O (9:1, 15 mL). The combined organic phases were washed with water (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated and the crude product was purified, when necessary, by flash chromatography with CH_2Cl_2 as the eluent.

General procedure under MW irradiation (Biotage Initiator Exp MW Synthesizer): A Biotage vial of 0.5–2.0 mL was filled with the azide (1.0 mmol), acyl cyanide (1.1 mmol), anhydrous CH_2Cl_2 (1.0 mL) and $Cu_2(OTf)_2{\cdot}C_6H_6$ (0.1 mmol). The vial was degassed with Ar, sealed, and irradiated at 80 °C for 2 h. Once cooled, the reaction mixture was diluted with CH_2Cl_2/Et_2O (9:1, 20 mL) and treated with aqueous NaHS (1.5 M, 5 mL). Isolation of the desired products was carried out as indicated above.

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Keywords: azides · copper · cycloaddition · homogeneous catalysis · tetrazoles

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[2] Reviews: a) R. J. Herr, *Bioorg. Med. Chem.* **2002**, *10*, 3379; b) R. N. Butler in *Comprehensive Heterocyclic Chemistry*, *Vol. 4* (Eds.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Oxford, **1996**, p. 621. c) The direct reaction of organic nitriles with the azide ion, when N-unsubstituted tetrazoles are aimed for, is much more common and easier to accomplish but poses other well-known safety requirements or handicaps (including the explosive nature of many transition-metal azides in catalytic reactions). For an additional review, see: V. Y. Zubarev, V. A. Ostrovskii, *Chem. Heterocycl. Compd.* **2000**, *36*, 759. d) For the reaction of nitriles with $NaN_3/ZnBr_2$ in water at only 80 °C, see: Z. P. Demko, K. B. Sharpless, *Org. Lett.* **2002**, *4*, 2525. e) For the reaction of nitriles with an in situ generated allylpalladium azide, see: S. Kamijo, T. Jin, Y. Yamamoto, *J. Org. Chem.* **2002**, *67*, 7413. f) For a very recent review on the chemistry of azides, see: S. Bräse, C. Gil, K. Knepper, V. Zimmermann, *Angew. Chem.* **2005**, *117*, 5320; *Angew. Chem. Int. Ed.* **2005**, *44*, 5188.
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[12] At concentrations of 0.1M. Either at higher concentrations, by concentrating the final mixture in the rotary evaporator, or when larger amounts of pyrrolidine are used, deacetylation also occurs during this step.

[13] In [$\mathrm{D_6}$]DMSO, H5″ (tetrazole ring) at $\delta = 9.56$ ppm and C5″ at $\delta = 143.6$ ppm. See the Supporting Information for the full spectra. This compound (**14**) and related derivatives (not substituted at C5″) had not been reported, to our knowledge. By opening anhydrothymidine with the tetrazolate anion, on heating at 120°C, only its 1,4-disubstituted isomer (the 2-tetrazolyl derivative) was obtained, as we have confirmed; See: A. A. Malin, V. A. Ostrovskii, *Russ. J. Org. Chem.* **2001**, *37*, 759.

[14] Throughout the more than thirty years in which organic azides have been used in our lab from time to time [see, e.g.: M. Rull, J. Vilarrasa, *Tetrahedron Lett.* **1976**, *17*, 4175; M. Bartra, V. Bou, J. Garcia, F. Urpí, J. Vilarrasa, *J. Chem. Soc. Chem. Commun.* **1988**, 270; M. Bartra, P. Romea, F. Urpí, J. Vilarrasa, *Tetrahedron* **1990**, *46*, 587; A. M. Costa, M. Faja, J. Farràs, J. Vilarrasa, *Tetrahedron Lett.* **1998**, *39*, 1835], only two explosions have ever taken place; in one case $\mathrm{NaN_3}$ and in the other one $\mathrm{Bu_4N^+N_3^-}$ had previously been in contact with $\mathrm{CH_2Cl_2}$. For information about $\mathrm{CH_2(N_3)_2}$, see: N. P. Peet, P. M. Weintraub, *Chem. Eng. News* **1994**, *72*(11), 4, and references therein; A. Hassner, M. Stern, H. E. Gottlieb, F. Frolow, *J. Org. Chem.* **1990**, *55*, 2304.