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Proximity-Assisted Cycloaddition Reactions—Facile Lewis Acid-Mediated Synthesis of Diversely Functionalized Bicyclic Tetrazoles

Stephen Hanessian,* Daniel Simard, Benoît Deschênes-Simard, Caroline Chenel, and Edgar Haak

Department of Chemistry, Université de Montréal, C.P. 6128, Succursale Centre-Ville, Montréal, Québec H3C 3J7, Canada

stephen.hanessian@umontreal.ca

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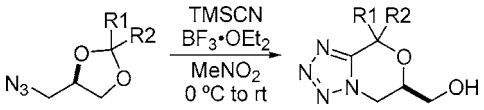
ABSTRACT



Aliphatic azidonitriles separated by three or four carbon atoms undergo facile Lewis acid-induced cycloadditions to give bicyclic tetrazoles, even at 0 °C. Extension to 3-azido-2-aryl-1,3-dioxolanes and the corresponding 1,3-dioxanes in the presence of TMSCN and BF_3·OEt_2 leads to a series of diversely functionalized novel oxabicyclic tetrazoles. The reactions represent new aspects of proximity-assisted dipolar cycloadditions that afford thermodynamically controlled enantiopure products proceeding through discrete oxocarbenium ion intermediates.

Dipolar cycloaddition reactions have been the cornerstone of heterocyclic chemistry for over 50 years.[1] In this regard, tetrazoles have gained prominence in medicinal chemistry in recent years owing to their unique electronic and spacial characteristics.[2,3]

The first reported synthesis of a tetrazole is attributed to Bladin in 1885.[4] Since then, a plethora of examples has been published for the synthesis of tetrazoles by intermolecular cycloadditions of an activated nitrile and an azide.[5] Normally, high temperatures and polar aprotic solvents are used. Other methods are also known using oximes[6] or amides.[7] Von Kereszty,[8] Carpenter,[9] and Smith[10] provided early examples of intramolecular cycloadditions to produce 5,5- or 5,6-bicyclic 1,5-disubstituted tetrazoles. With a few exceptions,[11] such reactions are conducted in solvents such as DMF or DMSO at temperatures above 100 °C.[12]

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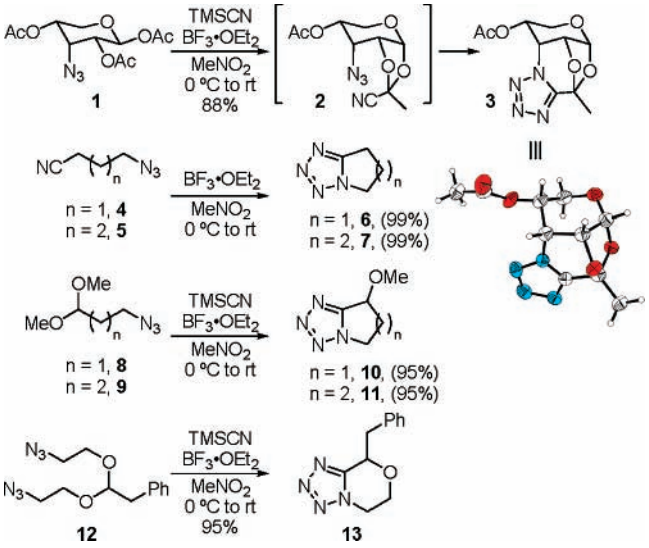
Herein, we report on an exceptionally facile formation of bicyclic tetrazoles containing functionally useful groups at room temperature or lower. Our work was instigated by an unexpectedly mild formation of a tetracyclic tetrazole in conjunction with a synthetic approach to malayamycin[13] and *N*-malayamycin.[14] Thus, treatment of the triacetate **1** with TMSCN in nitromethane in the presence of $BF_3{\cdot}OEt_2$ (2 equiv) led to the crystalline tetrazole **3** via the intermediate acetal **2** (Scheme 1). Model cyclization of ω-azido-

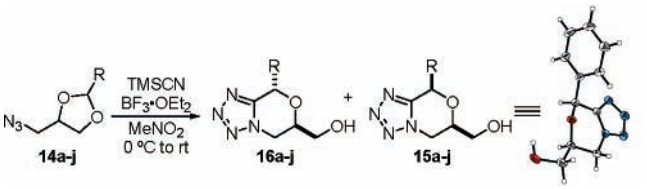
Scheme 1. Formation of Tetrazoles from Different Acetals and Azido-nitriles



nitriles **4** and **5** at 0 °C gave the corresponding bicyclic tetrazoles **6** and **7**, respectively, in over 90% yield. Related compounds had been previously obtained in the presence of concentrated H_2SO_4 in chloroform.[8,9] ω-Azido dimethyl acetals **8** and **9** gave the bicyclic methoxy tetrazoles **10** and **11** respectively (Scheme 1).

Extension to 5,7-systems could not be achieved in agreement with previous observations.[8−10] Finally, a bis-ω-azido acetal **12** gave the *C*-benzyl oxabicyclic tetrazole **13** in 95% yield. These preliminary results paved the way to a study of ω-azido cyclic acetals as versatile precursors to hitherto unknown functionalized oxabicyclic tetrazoles. Thus, treatment of the readily available 1-azido-2,3-*O*-arylidene-2,3-propane diols **14a−j** prepared from the corresponding racemic diols with TMSCN in $MeNO_2$ in the presence of $BF_3{\cdot}OEt_2$ (0 °C to rt), afforded the corresponding *cis*-oriented bicyclic tetrazoles **15a−j** as major isomers in good to excellent yields depending on the aromatic substituent (Table 1). The reaction was equally successful on an enantiopure diol.[15]

Table 1. Formation of Oxabicyclic Tetrazoles from Azido 2-aryl-1,3-dioxolanes[a]

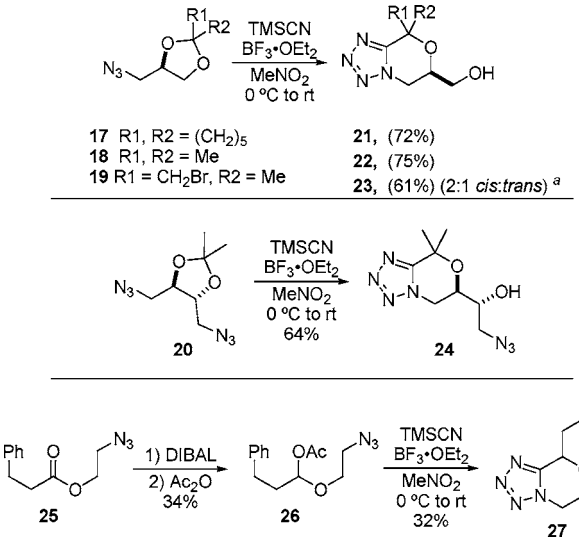


entry	R[a]	yield (%)[b]	*cis*(**15**)/*trans*(**16**)[c]
a	Ph[d]	94	>19:1
b	*o*-Cl−Ph	74	10:1
c	*m*-Cl−Ph	74	>19:1
d	*p*-Cl−Ph	78	>19:1
e	*m*-NO_2−Ph	48	10:1
f	*p*-NO_2−Ph	29	10:1
g	*m*-MeO−Ph	97	>19:1
h	*m*-Br−Ph	73	10:1
i	*m*-CF_3-Ph	43	>19:1
j	*m*-CN−Ph	46	>19:1

[a] Racemic series. [b] Isolated yield. [c] NMR ratio. [d] From enantiopure **14a**, 81%, >19:1.

Extension to ketals **17**−**20** was equally successful leading to spiro oxabicyclic and related disubstituted oxabicyclic tetrazoles **21**−**24** (Scheme 2). The scope of the reaction was

Scheme 2. Formation of Diverse Oxabicyclic Tetrazoles from 2,2′-Substituted 1,3-Dioxolanes and from β-Azido Ethyl Esters



[a] NMR ratio.

expanded by starting with a β-azido ester **25**. Reduction with Dibal-H, acetylation of the intermediate hemiacetal[16] to **26**, and treatment with TMSCN led to a monosubstituted oxabicyclic tetrazole **27**. In principle, this nonoptimized

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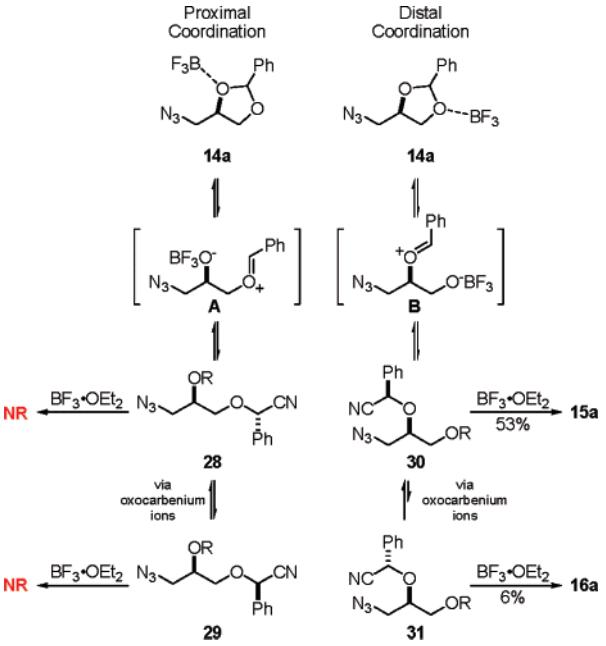
(16) Rychnovsky, S. D.; Vitale, J.; Jasti, R. *J. Am. Chem. Soc.* **2004**, *126*, 9904.

approach can be extended to other 2-azido ethyl esters of other carboxylic acids.

The Lewis acid-catalyzed ring opening of cyclic acetals has been the subject of numerous studies.[17] In the case of the 2- and 2,2′-substituted 1,3-dioxolanes exemplified by **14a**, proximal and distal coordination of BF_3·OEt_2 could lead to two oxocarbenium ions **A** and **B**, respectively (Scheme 3).

Scheme 3. Formation and Reaction of Isolated Cyanohydrins[a]

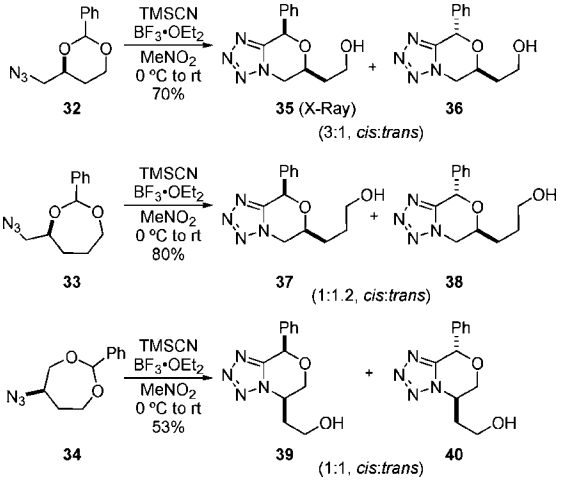


[a] R = BF_2 or BF_3.

These can each lead to two pairs of diastereoisomeric cyanohydrins **28**, **29** and **30**, **31**, respectively.[18] Only the latter pair can engage in cycloaddition to give **15a** and **16a**, respectively.

The formation of **15a** (and related analogues) as the major product, denotes a preference for transition states that lead to the *cis*-diequatorially disposed isomer over the *trans* (minor), arising from **30** and **31**, respectively. The alternative oxepan analogues coming from the other cyanohydrin pair (**28**, **29**) were not observed. Thus equilibration of the cyanohydrins **28**−**31** during the course of the reaction favors the thermodynamically more stable *cis*-isomer **15a**. In fact, treatment of isolated cyanohydrins **28** and **29** with BF_3·OEt_2 led to no reaction and eventual hydrolysis. On the other hand, both cyanohydrins **30** and **31** cyclized to give the *cis*-isomer **15a** in preponderance although much slower in the case of **31**.[19] The dioxane analogue **32** gave a 3:1 mixture of the *cis*- and *trans*-oxabicyclic tetrazoles **35** and **36**, while the dioxepane **33** gave **37** and **38** as a 1:1.2 separable mixture. The isomeric dioxepan **34** also gave a separable 1:1 mixture of **39** and **40** (Scheme 4).

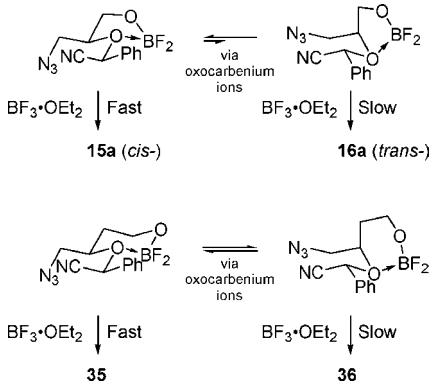
Scheme 4. Reaction of 2-Phenyl-1,3-dioxane and 1,3-Dioxepane Analogues[a]



[a] NMR ratios.

Although the exact nature of coordinated species is still under investigation, it is possible that pseudocyclic alkoxyborinate intermediates[20,21] are present (Scheme 5). Activation of the nitrile by a second equivalent of BF_3·OEt_2 results in the observed facile cycloaddition.

Scheme 5. Possible Alkoxydifluoroborinate Intermediates[15]



A slower rate of cycloaddition of **31** to the *trans*-isomer **16a** allows for equilibration to the pro-*cis*-precursor **30** which

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(19) It should be noted that re-enactment of the cycloaddition reaction starting with the individually isolated cyanohydrins does not accurately represent the same oxygen-coordinated intermediates found in the acetal-opening reaction. The O-TMS ether of **30** cyclized with an 83% yield to **15a** exclusively.

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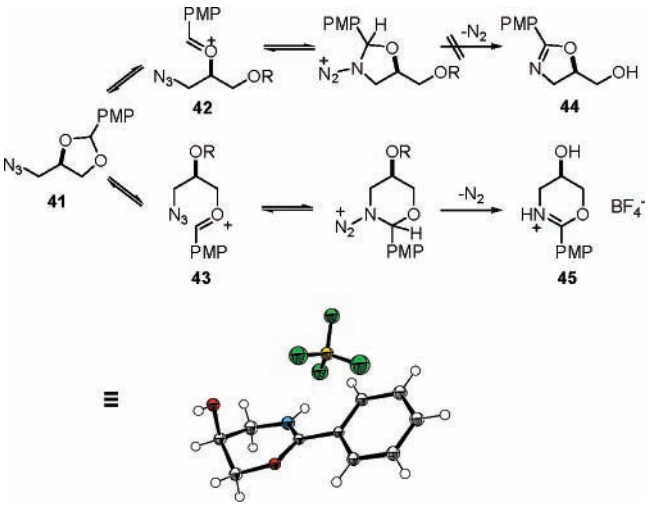
(21) A negative ion mass spectrum of the reaction mixture containing uncyclized cyanohydrins showed ion masses corresponding to [M + BF_3] and [M + BF_2OH]. See Supporting Information.

undergoes faster ring closure to the thermodynamically more stable *cis*-adduct **15a**. Presumably, in the case of the dioxane and dioxepane analogues (Schemes 4, 5), the respective boron-coordinated dioxacyanohydrins are each relatively stable and do not equilibrate as readily as in the dioxolane analogues.

We next studied the nature of the Lewis acid, the solvent polarity, and the source of cyanide. Nitromethane and BF_3•OEt_2 were found to be the most effective combination leading to the highest yields. Me_2AlCl, Me_3Al or BF_3·OEt_2 in hexanes (2-phase system) was surprisingly good although the diastereoselectivity was slightly diminished.[15] Other Lewis acids were either ineffective or did not lead to product.[15] Two equivalents of BF_3·OEt_2 were required to achieve maximum conversion. As observed by Sharpless and co-workers,[22] zinc bromide (but not chloride) gave acceptable results (77% yield, 81:19 *cis:trans*). Using TBSCN, KCN, Bu_4NCN, etc. resulted in recovery of starting acetal or eventual hydrolysis. The least effective solvents were THF, ether, CH_2Cl_2, toluene, $CHCl_3$, and CH_3CN.[15]

Finally we comment on the influence of substituent effects on the aromatic ring. Selectivities ranging from *cis:trans* 10:1 to over 20:1 were observed for selected *o*-, *m*-, and *p*-substituents which were not highly stabilizing to the incipient oxocarbenium ions **42** and **43** that could arise from the *p*-methoxyphenyl acetal **41** (Scheme 6). Surprinsingly, the *p*-methoxyphenyl acetal led instead to the dihydrooxazine **45** in 91% yield. A plausible explanation is illustrated in Scheme 6. The highly stabilized proximal oxocarbenium ion **42** can undergo reversible attack by cyanide to give the tetrazole. However, another pathway is via the distal oxocarbenium ion **43** which undergoes an Aubé-type[23] reaction by internal azide attack leading to the observed product **45**. Interestingly, the corresponding dihydro-oxazoline **44** is not formed most probably because of an unfavorable endo-trig closure.[24] Dihydrooxazines such as **45** were also the major products when traces of water (e.g., undistilled nitromethane) were present.[15]

Scheme 6. Aubé-type Reaction Leading to the Formation of Dihydro-oxazine[a]



[a] R = BF_2 or BF_3.

The facile synthesis of diversely functionalized bicyclic tetrazole scaffolds should find ample utility in a variety of applications related to medicinal chemistry, agrochemistry, and material science.

Acknowledgment. We thank the National Science and Engineering Council of Canada (NSERC), and Le Fonds Québecois de la Recherche sur la Nature et les Technologies (FQRNT) for financial assistance. We thank Dr. Michel Simard (Université de Montréal) for X-ray structures. We also thank Alexandra Furtos and Karine Venne (Université de Montréal) for high-resolution mass spectrometric analysis.

Supporting Information Available: General experimental procedures, characterization of main compounds, and X-ray ORTEP structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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