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New Preparation of *N*(1)- and *N*(2)- Alkylated Tetrazoles via Displacement of Activated Alcohols.

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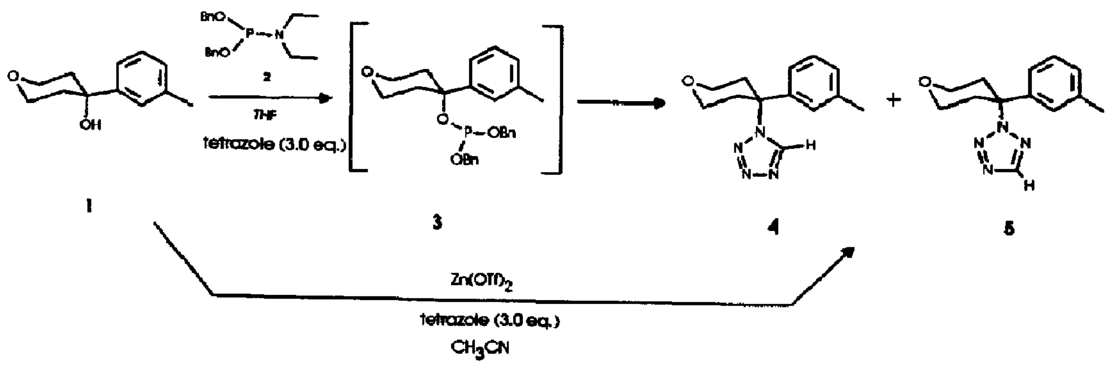
Abstract: A facile and convenient synthesis of *N*(1)- and *N*(2)-alkyltetrazoles is described. Tetrazole in the presence of zinc triflate reacts smoothly with activated alcohols to give the corresponding alkyltetrazole in high yield.

During the course of our investigation relating to the preparation of 5-lipoxygenase inhibitors,[1] we wished to prepare phosphite triesters such as **3** from the corresponding tertiary alcohol **1**. It is reported[2] that di-benzyl *N,N*-diethylphosphoramidite **2** is a highly reactive phosphitylating agent, which upon activation with 1H-tetrazole, reacts rapidly with simple alkyl or aryl alcohols to give the dibenzylphosphite triester analogs. To our surprise, the reaction of activated alcohols such as **1** under the described conditions did not give the corresponding phosphite triester **3**[3] but rather *N*(1)- and *N*(2)-alkyltetrazoles **4** and **5**[4] in moderate yield (50-60%). Typically, the formation of alkyltetrazoles proceeds via the reaction of ambident tetrazolate anions with an alkyl halide or sulphate.[5] To our knowledge, there is no precedence for the direct substitution of an activated alcohol by a tetrazole as illustrated in Scheme 1. Therefore, we have investigated this reaction process in an attempt to make it a general procedure for the preparation of alkyltetrazoles.

SCHEME 1



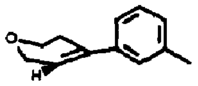
One of our initial observations in the course of studying the reaction conditions was that the substitution reaction could also be achieved by replacing **2** with a catalyst. Herein, we describe our optimized reaction[6] conditions which involve the use of zinc triflate, and an activated alcohol in acetonitrile in the presence of tetrazole. This reaction is very attractive for its simplicity, effectiveness, mildness of the conditions employed, and represents a new way to rapidly access *N*(1)- and *N*(2)-alkylated tetrazoles.

Since formation of *N*(1)- and *N*(2)-alkyltetrazoles derives from the phosphine triester **3**,[4] we first investigated the replacement of the di-*tert*-butyl N,N-diethylphosphoramidite reagent by a catalyst which could activate the alcohol. We have found that di-*tert*-butyl N,N-diethylphosphoramidite could be easily replaced by catalysts such as $Zn(OTf)_2$, BF_3-OEt_2, ZnI_2 and $SnCl_4$. Optimal conditions (Table 1) for the reaction are obtained using 0.1 eq. of $Zn(OTf)_2$, giving an 85:15 ratio of (4+5)/6. We found that when the amount of $Zn(OTf)_2$ increases to 0.5 eq. the reaction time diminishes considerably (1 hour), but gives 45% of the undesired eliminated product **6**. The other catalysts that we tried are either not reactive enough (PPTS, TFA, Ag_2O, CH_3CO_2H), produce extensive elimination (BBr_3, $AgBF_4$, TfOH) or simply give moderate yields of the desired compound (p-TsOH, $AlCl_3$).

TABLE 1. HPLC determination of the products obtained[6] with different amount of $Zn(OTf)_2$.

SOLVENT	EQUIVALENT of tetrazole	EQUIVALENT of $Zn(OTf)_2$	TIME [a]	RATIO $(4+5)^b$ / 6
CH_2Cl_2	2.0 eq	0.1 eq	18 h.	85 : 15
		0.3 eq	3 h.	70 : 30
		0.5 eq	1 h.	55 : 45

a) time for complete conversion.
b) ratio for (4/5) was (1:3).



6

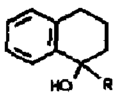
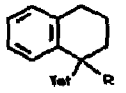
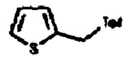
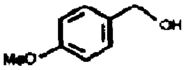
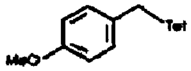
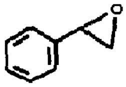
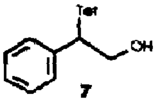
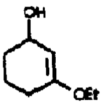
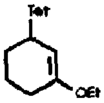
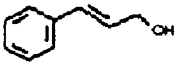
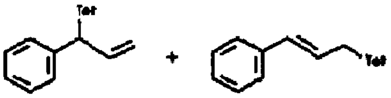
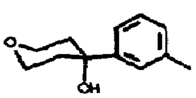
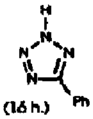
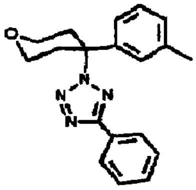
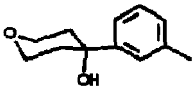
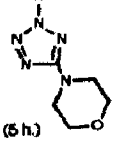
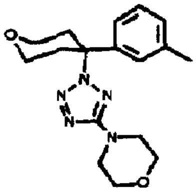
Acetonitrile, nitromethane and dichloromethane are the preferred solvents for optimum yield and reproducibility. Coordinating solvents such MeOH, DMF, DME, dioxane, ether, and THF are unsatisfactory. A strong coordination of the solvent with the catalyst might explain the lack of reactivity. Other solvents such as toluene, hexane and CS_2 give very low yields of the expected products. Interestingly, an increase in the amount of tetrazole (from 1.0 to 3.0 eq) results in less elimination product **6** (Table 2) in both CH_2Cl_2 and CH_3CN. The fact that the concentration of tetrazole is not important in the reaction rate (Table 2), suggests that a Sn1 type process is involved. We are currently investigating the mechanism of this reaction. When tetrazole (pKa = 4.9) is substituted by triazole (pKa = 9.5) or imidazole (pKa = 14.5), no reaction is observed, demonstrating that this reaction is specific to tetrazole. Also, benzoic acid (pKa = 4.8) which has a pKa similar to tetrazole, gives after 4 days of reaction only 50% yield of elimination product **6**.

TABLE 2. HPLC determination of the products obtained[6] with different amounts of tetrazole.

SOLVENT	EQUIVALENT of tetrazole	EQUIVALENT of $Zn(OTf)_2$	TIME [a]	RATIO (4+5) / 6
CH_2Cl_2	1.0 eq	0.1 eq	18 h.	75^b : 25
	3.0 eq		18 h.	90^b : 10
CH_3CN	1.0 eq	0.1 eq	3 h.	95^c :5
	3.0 eq		3 h.	99^c :1

a) time for complete conversion.
b) ratio of (4/5) was (1:3).
c) yield of isolated products, ratio of (4/5) was (1:1).

TABLE 3 Tetrazole displacement of activated alcohols.

ENTRY	SUBSTRATES	CONDITIONS[a] (time)	PRODUCTS	YIELD[b]
1	 R = Et	(4.5 h.)	 R = Et	92%
2	R = H	(4 h.)	R = H	86%
3		(16 h.)		80%
4		(16 h.)		60%
5	Dodecanol	(72 h.)	No Reaction	-
6		(16 h.)	No Reaction	-
7		(16 h.)	 **7**	63%
8		no catalyst quenched with NH_4OAc (2 h.)	 **8**	78%
9		(16 h.)		60%
10		 (16 h.)		93%[c]
11		 (5 h.) reflux		85%[c]

a) Reaction conditions are described in ref. 6.
b) Isolated yield (ratio of *N*(1)- and *N*(2)-alkyltetrazole is 1:1).
c) Only one isomer is isolated.

An interesting solvent effect is observed (Table 2) when the reaction is conducted in CH_3CN rather than CH_2Cl_2. We found that the reaction proceeds **faster** in CH_3CN and almost **no elimination product** is formed. A ratio of 1:1 of *N*(1)-alkyltetrazole **4** and *N*(2)-alkyltetrazole **5** is obtained[7] in CH_3CN while a slightly higher ratio of *N*(2)-alkyltetrazole (1:3) is produced in CH_2Cl_2. Many attempts were made to increase the predominance of one regioisomer, without success. Even when the tetrazole was *N*(1)-protected by a trimethylsilyl derivative, we still obtained a ratio of 1:1, but in this case the reaction rate increased dramatically (1 h.). The *N*(1)-tributyltin derivative gave no reaction. Very low interconversion of *N*(1)-alkyltetrazole **4** to *N*(2)-alkyltetrazole **5** is obtained when *N*(1)-alkyltetrazole **4** is subjected to the reaction conditions for 3 days. It is possible to increase interconversion of the isomers to 1:1 by heating the reaction mixture at reflux for 1 hour, but formation of the elimination product diminished the yield considerably.

As can be seen in Table 3, primary, secondary and tertiary activated alcohols could be easily displaced by a tetrazole.[6] No reaction is observed when the alcohol is not activated (entry 5) or when the alcohol is not sufficiently activated (entry 6). The formation of *N*(1)- and *N*(2)-alkyltetrazoles is not restricted to the use of alcohols, since an epoxide (entry 7) also gives the expected products **7**. With a highly activated alcohol (entry 8) under normal reaction conditions,[6] the corresponding enol ether **8** is isolated with or even without catalyst. In the case of cinnamyl alcohol (entry 9), α and γ addition are observed. Finally, 5-substituted tetrazoles (entries 10,11) give only one regioisomer in very good yield.

In conclusion, the reaction of tetrazoles with activated alcohols in the presence of zinc triflate represents a general, simple, and efficient method for the preparation of *N*(1)- and *N*(2)-alkyltetrazoles, particularly when sensitive substrates preclude the use of base or basic anions.

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REFERENCES.

1) Girard, Y.; Fortin,R.; Delorme, D.; Dubé,D.; Hamel,P.; Ducharme,Y.; Gillard,J.W. US 5,252,599 Oct.12,1993.
2) Perich, J.W.; John,R.B.; *Tetrahedron Lett.*, **1987**, *28*, 101.
3) The formation of phosphite triester **3** was seen by tlc but reacted further with the excess of tetrazole. We were able to isolate the phosphite triester **3** in excellent yield (85%) by addition of only two equivalents of tetrazole (instead of three equivalents as suggested by R.B. John)[2] using a syringe pump over 60 min.
4) The phosphite triester **3** is the intermediate leading to *N*(1)- and *N*(2)-alkyltetrazoles **4** and **5** since addition of excess of tetrazole (3 eq.) to the isolated phosphite triester **3** gave *N*(1)- and *N*(2)- alkyltetrazoles **4** and **5**.
5) Katritzky,A.R.; Rees,C.W.; *Comprehensive Heterocyclic Chemistry Pergamon Press.* **1984**; *5*, 817.
6) *In a typical procedure, tetrazole (1.2 mmol) was added to a solution of 4-(m-tolyl)tetrahydropyran-4-ol (1.0 mmol) in dry CH_3CN (5 mL). To the solution was added dried zinc triflate (0.1 mmol) and the clear resulting solution was stirred at room temperature for 3 hours. The reaction mixture was quenched with brine (5 mL) and the products extracted with CH_3CO_2Et (3x5ml). The combined organic extracts were washed with brine and dried over $MgSO_4$, filtered and evaporated. The resulting syrup was chromatographed in a column of silica gel, eluting with hexane-CH_3CO_2Et (70:30) to afford a 99% yield of the two regioisomers in a ratio of 1:1 .*
7) The elucidation of the structure of each regioisomer was done by nOe experiments. Only 1-alkyltetrazole **4** exhibits significant nOe's between the hydrogens of the pyrane's ring (2 eq. and 3 ax.) and the hydrogen of the tetrazole.

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