New Trialkylsilyl Enol Ether Chemistry: Direct 1,2-Bis-azidonation of Triisopropylsilyl Enol Ethers: an Azido-radical Addition Process Promoted by TEMPO

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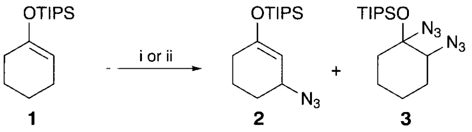
Treatment of triisopropylsilyl enol ethers with PhIO/TMSN$_3$/TEMPO (cat.) −45 °C results in 1,2-bis-azidonation, which appears to occur through a radical addition process; the 1-azido group can be replaced by carbon nucleophiles such as allyl, methyl, cyano, acetylene and acetonyl.

While examining the scope of the β-azidonation of triisopropylsilyl (TIPS) enol ethers we found a dramatic effect of temperature on the product ratios of **2** and **3**. For example, treatment of **1** with PhIO–TMSN$_3$ at −78 °C gave **2** and **3** (1 : 9), whereas the same reaction at −20 °C gave **2** and **3** (20 : 1). This unexpected change from α-bis-azidonation to β-azidonation with increasing temperature suggests that two competing mechanisms are operating, and we speculate that the former is a radical addition process, and the latter an ionic dehydrogenation. We have explored the effect of certain additives on the reagent combination PhIO–TMSN$_3$.[1] It was found that the stable radical TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl) can be used to modify the outcome of this reaction.[2] Catalytic quantities of TEMPO significantly reduced the β-azidonation and increased the α-bis-azidonation reaction (Scheme 1, Table 1).

The use of TEMPO and choice of temperature allows either the β-azide **2** or the 1,2-bis-azide **3** to be obtained predominantly, and in good yield. Table 2 lists the results for the conversion of a number of substituted cyclic TIPS enol ethers to their 1,2-bis-azido derivatives.[3,4]

The yields varied from 91% for the unsubstituted compound **3** (entry 1) to 41% for product **8** (entry 6). The reaction is stereoselective and in three cases (entries 1, 2 and 4) none of the minor diastereoisomer could be detected (^{1}H NMR). The relative stereochemistry of the 1,2-bis-azides **3**, **4** and **6**, are assigned as *trans*-diaxial on the basis of the CH–N$_3$ coupling. In the case of **9**, (entry 7) the *trans*-diaxial relationship of the 1,2-bis-azide was shown by X-ray crystallography. For the subsequent transformations described below, the stereochemical integrity of the quaternary centre (C-1) is lost, so assignment, although desirable, was not critical. In a blank reaction a TIPS enol ether was treated with TMSN$_3$ and a stoichiometric amount of TEMPO in the absence of iodosobenzene. No reaction occurred.



Scheme 1 (TIPS = triisopropylsilyl) *Reagents and conditions*: i, PhIO (1.2 equiv.)/TMSN$_3$ (2.4 equiv.)/CH$_2$Cl$_2$; ii, PhIO (1.5 equiv.)/TMSN$_3$ (3.0 equiv.)/CH$_2$Cl$_2$/TEMPO (10 mol%)

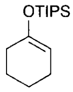
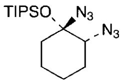
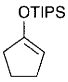
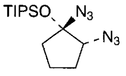
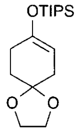
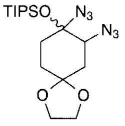
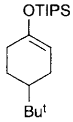
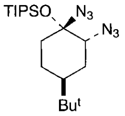
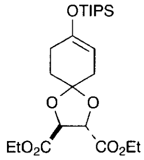
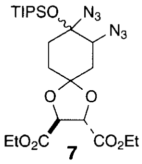
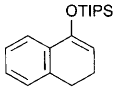
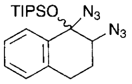
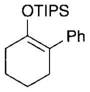
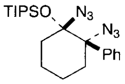
Table 1 Temperature variation of the azidonations shown in Scheme 1

Temperature/°C	Ratio of **2** : **3** without TEMPO	Ratio of **2** : **3** with TEMPO (10 mol%)
−78	1 : 9	
−60	1 : 3	
−45	1 : 1	1 : >10
−20	20 : 1	1 : 4
0	>99 : 1	1 : 1.5

In the above reactions (Table 2) the TEMPO additive was consumed. For entry 1 we could isolate the adduct **10** (5%). Also, conducting the reaction in the presence of 2,6-di-*tert*-butyl-4-methylphenol (10%, no TEMPO) caused formation of **2**/**3** (1 : 1 at −45 °C) and the adduct **11** (6%). The formation of **10** strongly implicates the radical intermediate **1a**, whereas **11** could arise from **1a** or the onium ion **1b**, Scheme 2.

The β-azido TIPS enol ether **2** can be ionized with Lewis acids to an enonium ion and trapped with a variety of nucleophiles resulting in 'conjugate addition without the enone'.[1] In a complementary fashion we have found that the bis-azido TIPS enol ether **3** may be ionized by aluminium based Lewis acids to the onium ion **1b** and trapped with a range of nucleophiles in a similar way (Table 3).

Table 2 Reactions of TIPS enol ethers with PhIO/TMSN$_3$/10 mol% TEMPO[a]

Entry	TIPS enol ether	1,2-bis-azido product	Yield[b]
1		 **3**	91%[c] Single diastereoisomer
2		 **4**	60% Single diastereoisomer
3		 **5**	82% (3 : 1)[d]
4		 **6**	71% Single diastereoisomer
5		 **7**	67% (4 : 2 : 1)[d]
6		 **8**	41% (4 : 1)[d]
7		 **9**[e]	59%[c] (5 : 1)[d]

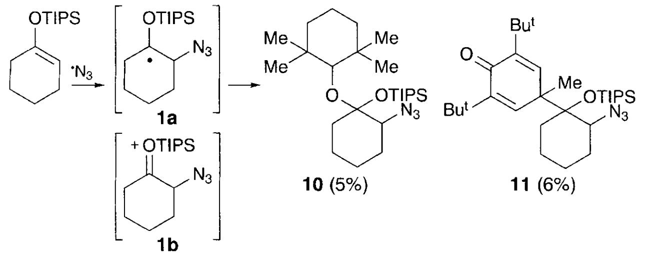
[a] PhIO (1.5 equiv.)/TMSN$_3$ (3.0 equiv.)/TMPO (0.1 equiv.)/CH$_2$Cl$_2$, −45 °C, 16 h. [b] Isolated yield of diastereoisomeric mixture after chromatography. [c] Reaction carried out in toluene. [d] Diastereoisomeric ratio determined by ^{1}H NMR. [e] Structure confirmed by X-ray crystallography.

Yields ranged from 96% for the methyl addition product **12** (entry 1) to 38% for the nitrile addition product **13** (entry 2). The stereochemistry of **12** was determined by X-ray analysis of the triazole (**i**) derivative.† In most cases studied there was high selectivity for one stereoisomer, presumably in the same direction as **12**. ^{1}H NMR data is in agreement with this assumption since for entries 1, 3 and 5 the alkyl substituent would lie in an equatorial conformation.[5] ^{1}H NMR coupling constants show that the 2-azido group also to be equatorially disposed and therefore *cis* to the silyloxy group. For entry 2 the nitrile group would be axially disposed and ^{1}H NMR analysis shows the 2-azido group to be axial, and it remains *cis* to the silyloxy group.

The *cis* relationship between the silyloxy and azido groups is the opposite stereochemistry to that obtained by ring opening of epoxides by trimethylsilyl azide.[6] As such this new transformation is a complementary addition to existing procedures for the preparation of 1,2-aminoalcohols.[6]

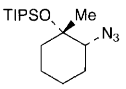
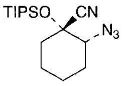
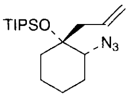
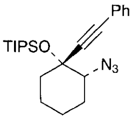
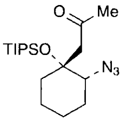
For example, treatment of **12** with TBAF/THF at 20 °C followed by reduction of the azide functionality ($LiAlH_4$) gave *cis*-1-hydroxy-1-methyl-2-aminocyclohexane (60%).

The generation of azide radicals from similar reagent systems such as $PhI(OAc)_2$ and NaN_3 is precedented.[7] Evidence for a radical addition process is shown in Scheme 3. Treatment of **18** with the PhIO/$TMSN_3$/TEMPO reagent system gave the ring opened product **19** (90%). Presumably, the azido-radical adds to **18** to give **18a** which undergoes ring cleavage to the tertiary radical **18b**. The substrate **17** gave a complex mixture of products from which we could isolate the adduct **21** (7%). Again, this can be rationalized by formation of a primary radical **17b** (from **17a**), combination with TEMPO to give **20**, and β-azidonation (TEMPO has been consumed) to give **21**.



Scheme 2

Table 3 Reactions of **3** with Lewis acids/nucleophiles

Entry	Conditions	Product[a]	Yield[b]
1	Me_3Al (2 equiv.), CH_2Cl_2, − 70 to 0 °C		**12** 96% (92:8)
2	Et_2AlCN (2 equiv.), $ClCH_2CH_2Cl$, 83 °C, 4 h		**13** 38% (4:1)
3	Me_2AlCl (2 equiv.), Hexane −70 to 0 °C $Bu_3SnCH_2C(H)CH_2$ (2 equiv.)		**14** 71% (>95%)
4	Me_2AlCl (2 equiv.), Hexane, −70 to 0 °C PhC≡CLi (2 equiv.)		**15** 59% (2:1)
5	Me_2AlCl (2 equiv.), $ClCH_2CH_2Cl$, −15 °C, 15 min, TMSOC(Me)CH_2 (3 equiv.)		**16** 57% (>95%)

[a] Major diastereoisomer shown. [b] Isolated yield of diastereoisomeric mixture after chromatography.

A similar azide radical trapping occurs when cyclohexene is treated with the PhIO/$TMSN_3$/TEMPO reagent system to yield **22** (5%) and the known bis-azide **23** (80%) Scheme 3.[3] For comparison, this reaction was carried out in the absence of TEMPO, and the yield of **23** dropped to 49% (lit. 40%)[3] and the diastereoisomeric ratio changed to *ca.* 1:1.

The observed coupling of TEMPO with a reactive intermediate is evidence that this intermediate is radical in nature. It has been shown that the reactivity of the PhIO/$TMSN_3$ reagent system can be fine-tuned by adjustment of reaction temperature and addition of the stable radical TEMPO. The use of TEMPO in this sense is unprecedented. A plausible mechanism for the generation of azide radicals is shown in Scheme 4. The intermediate **24** can add TEMPO to give the I^{IV} species **24a** which can reversibly dissociate to give **25** and azide radical. The adduct **25** can further dissociate to regenerate TEMPO and **25a**. The radical **25a** can recombine with azide radical to give **24**. Once the reaction is complete (TEMPO and the TIPS enol ether consumed) the intermediate **24** will decompose to iodobenzene, dinitrogen and hexamethyl disiloxane.

Bis-azidonations using hypervalent iodine chemistry have been reported on cyclohexene and aromatic alkenes *via* a proposed ionic pathway involving initial electrophilic attack of the hypervalent iodine species upon the double bond.[3] A cycloaddition pathway has been suggested as a pathway towards the bis-azidonation of allylsilanes.[4] We have obtained evidence that the PhIO/$TMSN_3$/TEMPO reagent system reacts with alkenes in a radical addition process.[8]

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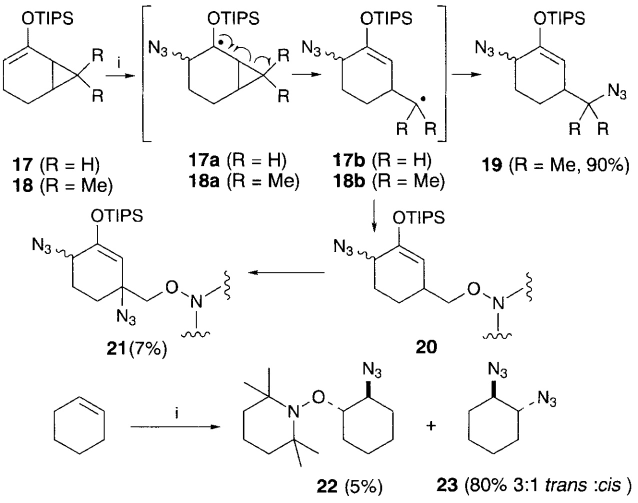
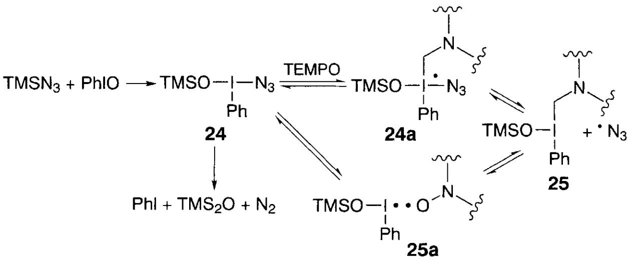


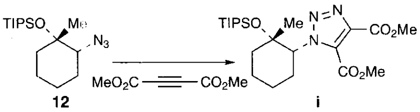
Scheme 3 *Reagents and conditions*: i, PhIO (1.5 equiv.)/$TMSN_3$ (3.0 equiv.)/TEMPO (0.1 equiv.)/CH_2Cl_2, −45 °C, 16 h



Scheme 4

Footnote

† The stereochemistry of **12** was obtained by making the crystalline adduct **i** and obtaining an X-ray structure.



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8 Trimethylsilyl enol ethers also react with the PhIO/TMSN$_3$/TEMPO reagent to give unstable 1,2-bis-azides, which upon mild acid hydrolysis give α-azidoketones. The TIPS 1,2-bis-azides do not desilylate without extensive decomposition. For the α-azidonation of ketones see: P. Magnus and L. Barth, *Tetrahedron Lett.*, 1992, 2777. For the preparation of α-azidoketones from simple alkenes see: J. Ehrenfreund and E. Zbiral, *Liebigs Ann. Chem.*, 1973, 290; *Tetrahedron*, 1972, **28**, 1697.