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Oxidative Addition of Azide Anion to Triisopropylsilyl Enol Ethers: Synthesis of α-Azido Ketones.

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Abstract: Treatment of triisopropylsilyl enol ethers with ceric ammonium nitrate/sodium azide at -20°C in acetonitrile gives α-azido ketones in average to good yields (50-80%).

The introduction of nitrogen functionality adjacent to a carbonyl group using electrophilic aminating reagents is a topical area of research, particularly with respect to the synthesis of α-amino acids.[1] We have been examining the reaction of triisopropylsilyl (TIPS) enol ethers with the Sharpless reagent $(TsN)_2Se$,[2] and the reagent combination $PhIO/TMSN_3$.[3] The former reagent results in α-aminotosylation, while the latter leads to unprecendented β-azidonation. While this extraordinary reaction has revealed a new aspect of enol ether chemistry, we were still interested in electrophilic azidonation reagents that would introduce the azido-functionality in the α-position. A particularly interesting reaction, first reported in 1915, that has received little attention is the oxidation of sodium azide with ceric ammonium nitrate (CAN) to give dinitrogen.[4]

This quantitative determination of azide anion received no attention from organic chemists until 1971 when Trahanovsky and Robbins reported the treatment of olefins with NaN_3/CAN gave α-azido-β-nitrato alkanes.[5] In 1979 Lemieux and Radcliffe described an extension of this azidonitration procedure to enol ethers of carbohydrate substrates.[6] In 1990 Vogel described a single example of the formation of an α-azido ketone from oxidative azidation [CAN (3 eq)/NaN_3 (1.5 eq)/CH_3CN] of a *t*-butyl dimethylsilyl enol ether.[7] The yield of the α-azido ketone dropped dramatically, to less than 50%, on reaction scales larger than 100 mg, presumably due to hydrolysis of the silyl enol ether.

At the outset, we decided to employ the triisopropylsilyl enol ethers since they are less prone to hydrolysis. When **1** was treated with [CAN (3 eq)/NaN_3 (1.5 eq)/CH_3CN] only moderate yields (30-45%) of the α-azido ketone **2** were obtained.

The other products were cyclohexanone (11%), cyclohexenone (10%) and triisopropylsilanol (18%). It should be noted that cyclohexanone is inert to the above reaction conditions. Clearly, even **1** is being competitively hydrolyzed in the acidic (CAN) media. While attempts to buffer the reaction were unsuccessful, we found that increasing the amount of sodium azide (TABLE I, *entry 2*) greatly improved the yield of **2** (67%). Further increases in both NaN_3 and CAN (*entries 3* and *4*) gave **2** in 72 and 83% respectively. The best conditions are those in *entry 3*. since there are less by-products and the α-azido ketone **2** is more readily purified.

TABLE I

(Optimization of $CAN/NaN_3/CH_3CN/-20°C$ Reaction Conditions).

Entry	Conditions	Yield of 2 (%)
1	0.25 g (1.5 eq. NaN_3/3.0 eq. CAN)	44
2	0.25 g (3.0 eq. NaN_3/3.0 eq. CAN)	67
3	0.50 g (4.5 eq. NaN_3/3.0 eq. CAN)	72
4	0.25 g (5.0 eq. NaN_3/5.0 eq. CAN)	83[a]
5	0.25 g (2.0 eq. NaN_3/1.5 eq. CAN)	41[b]

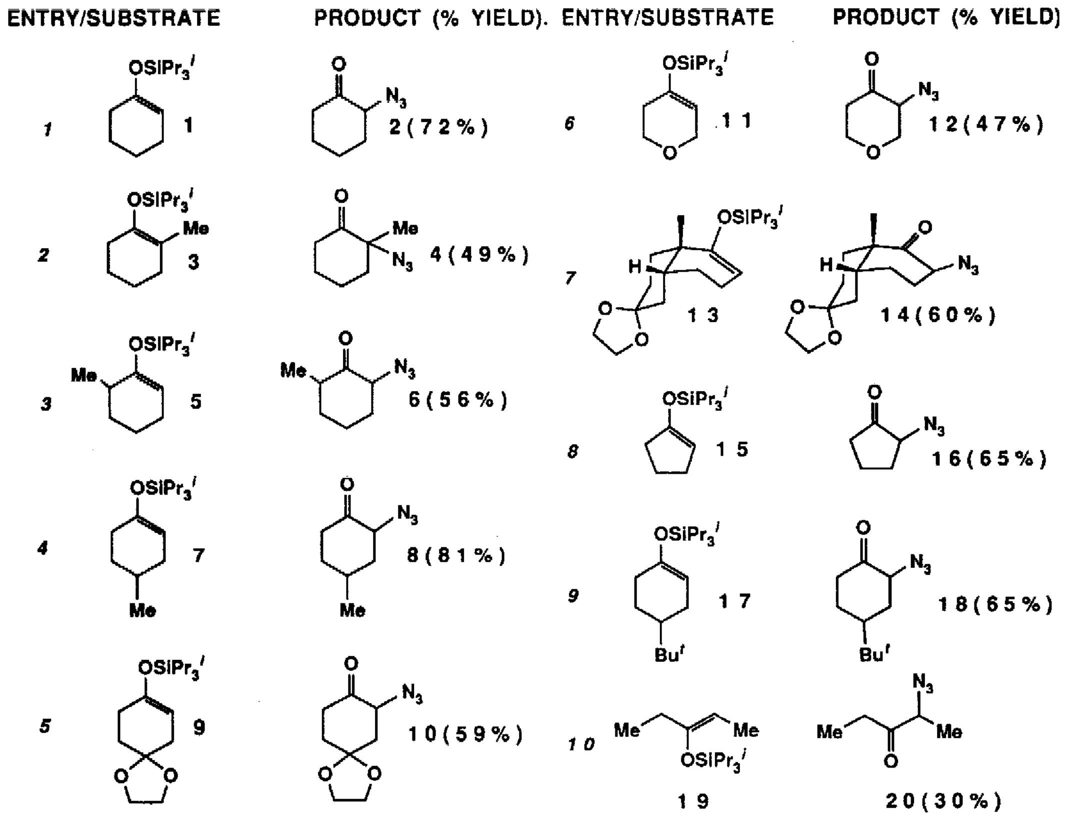
a) Impurities still present after purification. b) Recovered 37% of starting enol ether.

The separation of the azido ketone **2** from the triisopropylsilanol was troublesome, but when an of excess sodium azide was used the major reagent derived product is triisopropylsilyl azide, which can more easily be separated from the azido ketone. Trimethylsilyl enol ethers were not suitable substrates for the CAN/NaN_3 reaction due to the ease of hydrolysis to the ketone. The TMS enol ether derived from cyclohexanone gave **2** (38%) and hydrolysis to cyclohexanone.

The optimized ceric ammonium nitrate/sodium azide oxidation procedure was applied to the series of triisopropylsilyl enol ethers shown in **Table II**. The optimized reaction conditions led to more consistent reactions and were applicable to scale up (0.25-1.0 g), overcoming the limitations of the previously reported procedure.

The oxidative azidation was applied to a range of cyclohexanone derivatives, affording the α-azido ketones in average to good yields (*entries 1-5 and 9*). The reaction is not stereospecific as illustrated by the mixtures of diastereomers obtained in *entries 3, 4 and 9.* Introduction of azide at a tertiary center is illustrated by the formation of 2-azido-2-methylcyclohexanone (*entry 7*). This result is interesting as there are few methods available for the introduction of azide at a tertiary carbon adjacent to a carbonyl. 2-Azido-2-methylcyclohexanone **4** has reportedly been obtained *via* S_N2 displacement of the 2-bromo-2-methylcyclohexanone with lithium azide. The article fails to include any experimental data to support the identity of this compound.[8]

TABLE II



(The yields refer to isolated purified material).

In conclusion, the oxidative azidation of triisopropysilyl enol ethers provides a direct method for the synthesis of α-azido ketones rather than the normal halogenation followed by displacement with azide anion.[9]

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9. General Procedure for the Preparation of α-azido ketones:

To a cooled (-20°C) mixture of the triisopropylsilyl enol ether **1** (0.50g, 1.96 mmol) in anhydrous CH_3CN (5 mL) under an argon or nitrogen atmosphere was added NaN_3 (0.58g, 8.86 mmol, 4.5 eq), followed by dropwise addition of a solution of CAN (3.23g, 5.90 mmol, 3 eq.) in CH_3CN (14 mL). The progress of the reaction was monitored by tlc, when the reaction was complete (0.5 h), the mixture was quenched by the addition of ice-cold water. The aqueous mixture was extracted with ice-cold Et_2O, the layers were separated and the organic layer was washed once with ice-cold water. The aqueous layers were extracted once with Et_2O. The combined organic layers were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using silica gel, eluting with ether/pentanes (1:3) to give **2** (196mg, 72%) and triisopropylsilyl azide (126mg).

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