JOC Notes

Base-Promoted Reactions of Bridged Ketones and 1,3- and 1,4-Haloalkyl Azides: Competitive Alkylation vs Azidation Reactions of Ketone Enolates

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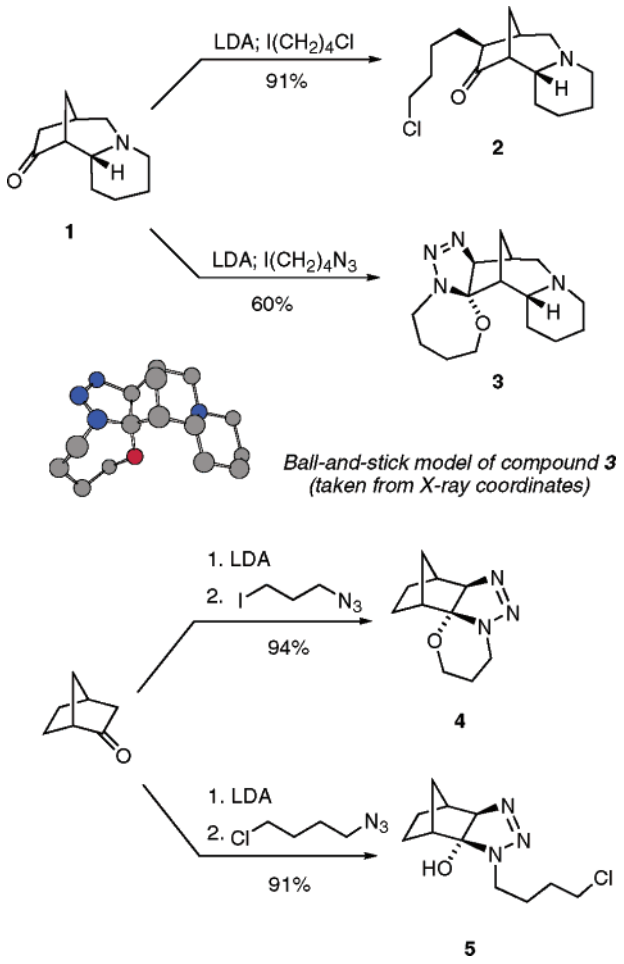
Received November 1, 2003

Abstract: The reactions of 1,3- and 1,4-haloalkyl azides with enolates of 2-norbornanone (and a ring-expanded analog) afford polycyclic 1,2,3-triazolines in good yields. The reaction occurs by the initial azidation of the ketone enolate, followed in order by triazoline formation and *O*-alkylation. An interesting element of this process is the preferential reaction of the alkyl azide with an enolate anion as opposed to the more familiar reaction of the alkyl halide (including Cl and I derivatives). Reactions of acyclic or monocyclic enolates generally lead to 1,2,3-triazoles but none of the alternative *C*-alkylation product.

Along with carbonyl compounds, alkyl halides (Cl, Br, I) are arguably *the* classic electrophiles in organic synthesis. In contrast, reactions of alkyl azides with enolates are known but much less common. In the late 1960s and early 1970s, Krieger and Olsen studied the base-promoted reactions of alkyl azides and ketones or aldehydes, which result variously in 4-hydroxy-1,2,3-triazolines or their fully unsaturated analogues, depending on substrate and conditions.[1] The base-promoted Smalley cyclization of ω-azidoketones affords a synthetically useful route to α-aminoketones.[2] Probably most heavily used in this category currently is the reaction of enolates with arenesulfonyl azides, which is a valuable method for the α-amination of enolates and is particularly useful for the asymmetric synthesis of amino acid equivalents.[3]

In this note, we report the reactions of 1,3- and 1,4-haloalkyl azides with enolates derived from a variety of ketones. In reactions with certain bridged ketones, an unprecedented bicyclization reaction occurred, followed by *O*-alkylation. Other ketones afforded more familiar 1,2,3-triazole derivatives as products but, contrary to expectations, in both cases the initial event was preferential enolate *azidation* in lieu of enolate *C-alkylation*.

SCHEME 1



In work associated with a recent total synthesis project,[4] the lithium enolate of ketone **1** was alkylated with 1,4-chloroiodobutane to give the expected *exo* alkylation product **2** in high yield (Scheme 1). Since the ultimate intent was to convert the chloride of **2** into its

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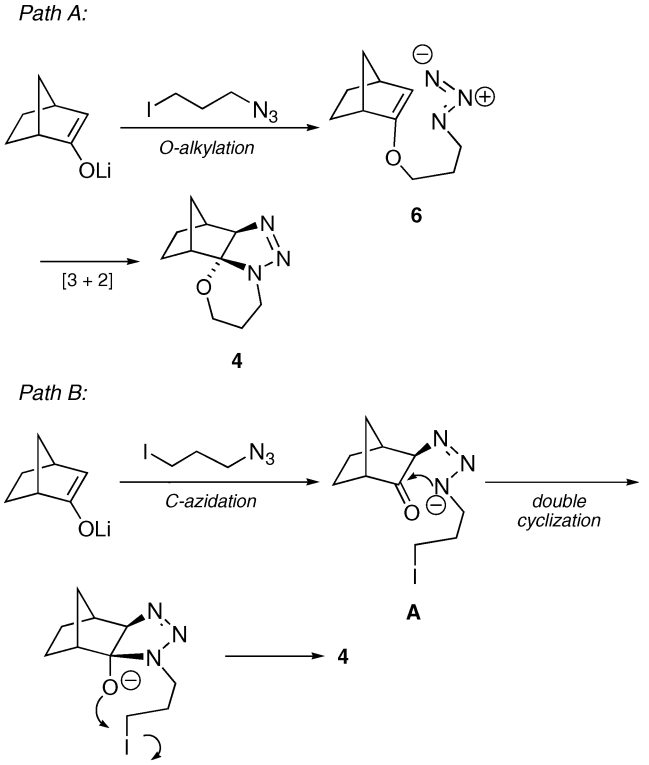
10.1021/jo0356098 CCC: $27.50
Published on Web 02/06/2004

SCHEME 2



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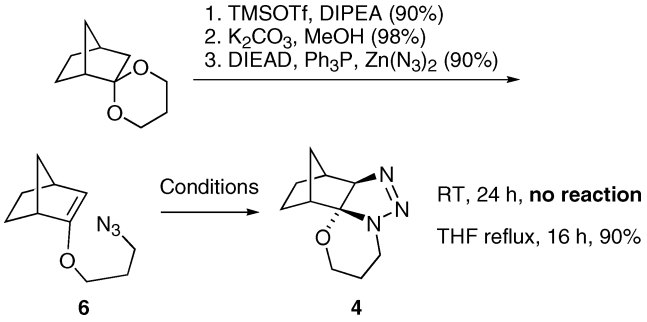
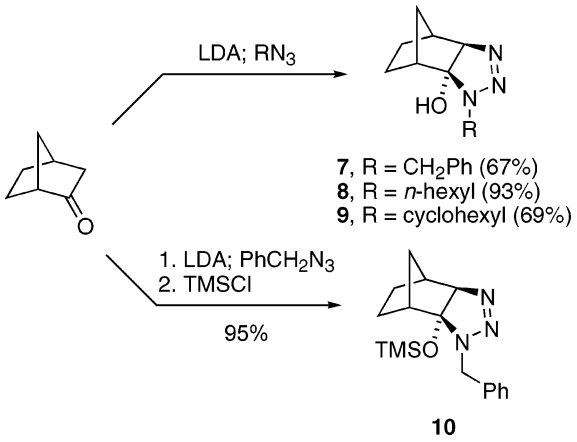


SCHEME 4



corresponding azide, we reacted the enolate from **1** with 1-azido-4-iodobutane to increase the convergency of our synthesis. However, no simple alkylation product was formed in this experiment at all. Instead, the pentacyclic triazoline **3** was formed in good yield; the structure of this compound was assigned on the basis of X-ray crystallography. A similar product was obtained when 2-norbornanone was treated with 1,3-azidopropyl iodide. Interestingly, when the homologue 1,4-azidobutyl chloride was reacted with the same substrate, compound **5** resulting from simple azidation was obtained.

Initially, two mechanisms were considered to account for the formation of the multicyclic heterocyclic compounds (Scheme 2). The exo orientation of the 1,2,3-triazoline relative to the norbornanone platform would be consistent with an initial *O*-alkylation followed by 1,3-dipolar cycloaddition (path A). This possibility was disfavored at the outset, in part due to the awkward necessity of explaining why the replacement of an ω-chloride with an azide would divert the enolate from *C*- to *O*-alkylation. Further evidence against this pathway was marshaled when the potential enol ether intermediate **6** was synthesized by the unambiguous route shown in Scheme 3.[5] Although **6** did afford compound **4** under conditions of THF reflux, extended exposure to room temperature (mimicking the 0 °C → RT conditions used to make **3** in Scheme 1) did not result in triazoline formation.[6] The alternative path B is left as the most likely alternative. In this case, the azide is directly attacked by the enolate to afford intermediate **A**, which can then cyclize to generate an alkoxide. Up to this point, the mechanism follows the accepted pathway leading to the Olsen 4-hydroxy-1,2,3-triazoline synthesis,[1] but in this case the alkoxide is neither protonated nor ultimately eliminated but rather undergoes an intramolecular alkylation. To our knowledge, this represents the first trapping of such an intermediate.[7]

As expected, the facility of the enolate/azide reaction was readily confirmed in a series of intermolecular reactions (Scheme 4). In addition, the potential of trapping the intermediate alkoxide was briefly examined in this intermolecular context. Exo azidation followed by addition of trimethylsilyl chloride gave **10** but the addition of even reactive carbon-based alkylating agents (allyl bromide, benzyl bromide) afforded only the 4-hydroxylated **7**.

The analogous 1,3- and 1,4-chloroalkyl azides were also reacted with a variety of ketones (Table 1). The ketone enolates were generated by treatment with LDA at 0 °C, the azide added, and the reactions allowed to rise to room temperate and stirred for a period of 2−20 h. In most cases, simple 1,2,3-triazoles were formed in good yields as the exclusive products of these reactions, resulting from azidation, triazoline ring closure, and finally dehydration.

The failure of the initially formed 4-hydroxy-1,2,3-triazoline salts to undergo intramolecular alkylation is

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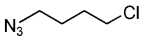
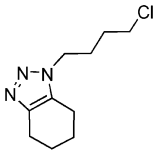
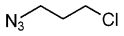
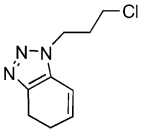
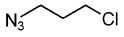
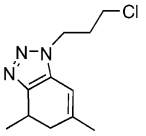
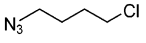
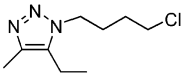
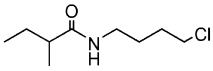
(6) Similarly, reaction of the TMS enol ether of 2-norbornanone with benzyl azide did not result in any 1,2,3-triazoline when reacted at room temperature for the 2 h required for the conversion of the enolate of 2-norbornanone to compound **10** (see Scheme 4). However, heating of these reactants at 60 °C for 2 days afforded the same product in high yield: Auberson, Y.; Vogel, P. *Tetrahedron* **1990**, *46*, 7019−7032.

(7) Another possibility, not shown, is that the conversion of the enolate to the alkoxide intermediate involves a direct [3+2] cycloaddition of the alkyl azide onto the enolate. We have no evidence to either support or exclude such a possibility at the present time.

TABLE 1. Reactions of 1,3- and 1,4-Chloroalkyl Azides with Ketones[a]

entry	ketone	azide	product(s)	yield (%)
1				95
2				52
3				69
4				32
			and	
				30

[a] Enolates were generated by treatment of the ketone with LDA, then the azide was added and the reaction allowed to come to room temperature. See the Supporting Information for further details.

possibly due to the relative instability of the resultant ring system in these substrates. The reaction of an acyclic ketone afforded a rearrangement product in addition to the 1,2,3-triazoline, which was in this case obtained in only modest yield (entry 4). In every case, however, *C*-azidation was observed to the complete exclusion of *C*-alkylation.

In summary, these 1,*n*-haloalkyl azides react with enolates to exclusively afford products resulting from an initial *C*-azidation reaction, despite the presence of an otherwise-reactive alkyl halide moiety. As a class, structurally divergent triazolines are interesting substructures for possible drug discovery and diversity-oriented synthesis efforts.[8] With respect to the latter, we note that the ability to incorporate a halogen into these heterocycles provides a handle for further modification of the product compounds.

Acknowledgment. We thank the National Institutes of Health (GM-49093) for support of this work.

Supporting Information Available: Experimental procedures and characterization of compounds, including X-ray crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0356098

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