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Letter

Azido-Enolonium Species in C−C and C−N Bond-Forming Coupling Reactions

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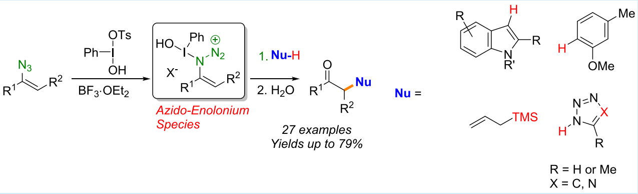
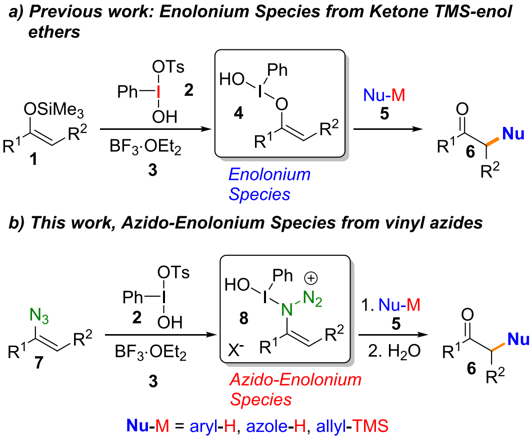
ABSTRACT: Vinyl azides react with boron trifluoride activated Koser's hypervalent iodine reagent to afford azido-enolonium species. These previously unknown azido-enolonium species react efficiently with aromatic compounds, allyltrimethylsilane, and azoles under mild conditions, with no need for a transition-metal catalyst, forming C−C and C−N bonds to give a variety of *α*-functionalized ketones. The intermediacy of the proposed azido-enolonium species is supported by spectroscopic studies.



Discrete enolonium species[1] (**4**) are umpoled[2] ketone enolate equivalents, i.e., electrophiles, and are typically formed by the reaction of TMS-enol ethers (**1**) with Lewis acid activated hypervalent iodine reagents (Scheme 1a).[3] Numerous reactions including fluorination,[4] chlorination,[5] acetoxylation,[6] tosylation,[7] amination,[8] arylations,[9] and alkylations[10] have been proposed to involve formation of similar, but transient, enolonium species. Recently, we have shown that discrete enolonium species (**4**) are able to undergo *α*-arylation,[11] and allylation,[1] as well as cross coupling with TMS-enol ethers to form unsymmetrical 1,4-dicarbonyl compounds (Scheme 1a).[12] Maulide has shown that the *α*-arylation is also possible intramolecularly using similar conditions.[13] In addition, we have shown that discrete enolonium species (**4**) may react with nitrogen nucleophiles such as azides and azoles in C−N bond-forming reactions.[14]

Scheme 1. This Work in Context



While the scope of nucleophiles available for reaction with enolonium species (**4**) keeps expanding, the source of enolonium species (**4**), whether discrete or transient, remains largely limited to TMS-enol ethers[8,15] and dicarbonyl compounds.[10,13] Thus, it would be attractive to develop alternative readily accessible enolonium species. We were particularly interested in studying the effect of an azido-nitrogen in place of the enol oxygen (i.e., as in **8**, Scheme 1b) hoping to find increased reactivity.[16] Importantly, vinyl azides (**7**) are readily available from alkenes[17] or alkynes[18] in a single step. In comparison to TMS-enol ethers, vinyl azides are available in one less step than most aromatic ketones that are produced from alkenes by the Wacker reaction,[19] from oxygenation of alkanes, or oxidation of alcohols. An additional goal was to compare the reactivity of these novel species with that of other enamines. Enamines,[20] enamine-ones,[21] and enamides[22] have mainly been reported to undergo attack at the *α*-position by carboxylates rather than C−C bond-forming reactions. However, Du and Zhao have reported a cyclization of enamines of anilines to give indoles using PIDA[23] as well as arylation of the enamine nitrogen with concomitant iodination.[24] Waser has reported stable *N*-tosyl-*N*-*p*-methoxyphenylenamide hypervalent iodine reagents and has shown their value in transition-metal-catalyzed Stille and Sonogashira cross-coupling reactions.[25]

Vinyl azides (**7**) are chameleonic species with a rich chemistry[26] that enables them to react as enamine equivalents with electrophiles as well as with strong nucleophiles like organolithium reagents depending on conditions and reaction

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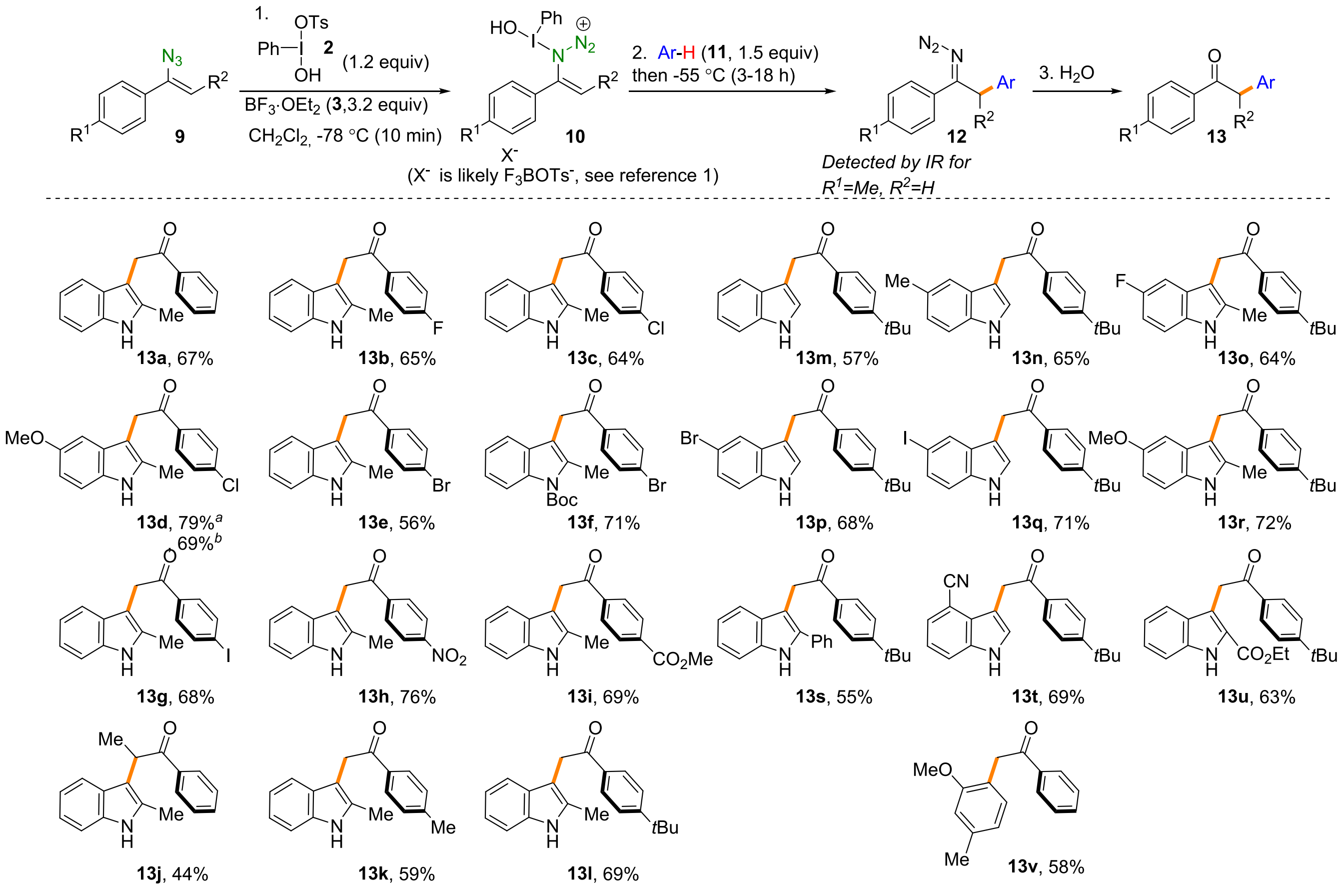
Scheme 2. Scope of the Reaction of Azido-Enolonium Species 10 Generated from Vinyl Azides 9



^{a}At 0.5 mmol scale. ^{b}At 1 mmol scale using 1.5 equiv of Koser's reagent (**2**).

partners.[27] Notably, vinyl azides do not themselves undergo reaction with simple aromatic compounds.

Rapidly, it was found that vinyl azides (**9**) react with Koser's reagent (**2**)[7a] preactivated by boron trifluoride etherate (**3**) and aromatic compounds to give arylated ketones after hydrolysis during water workup (Scheme 1b and Scheme 2). Only 1.5 equiv of the aromatic compounds is necessary to achieve the yields shown in Scheme 2.

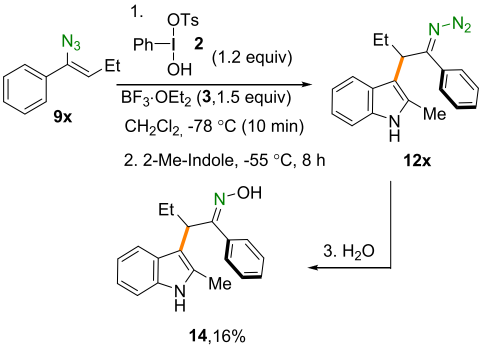
The scope with respect to vinyl azide and aromatic coupling partner is quite wide. Simple 1-phenyl-vinyl azide (**9**, R^1 = H, R^2 = H) reacts with 2-methylindole to give **13a** in 67% yield. The vinyl azide coupling partner may contain a number of different functionalities (Scheme 2). For example, 1-(4-fluorophenyl)-vinyl azide, 1-(4-chloro-phenyl)-vinyl azide, 1-(4-bromo-phenyl)-vinyl azide, and 1-(4-iodophenyl)-vinyl azide react with 2-methylindole to give products **13b**, **13c**, **13e**, and **13g** in comparable yields in the 56–68% range (Scheme 2). In particular, the formation of **13e** and **13g** is notable, as these halogens could in principle be oxidized by the hypervalent iodine reagents. Electron-withdrawing functionalities such as nitro and methylester are also compatible with the reaction conditions. Thus, 1-(4-nitrophenyl)-vinyl azide provides product **13h** in 76% yield. The corresponding methyl 4-(1-azidovinyl)benzoate (**9i**, R^1 = CO$_2$Me, R^2 = H, Scheme 2) provides product **13i** in 69% yield. This is quite comparable to yields achieved via the analogous enolonium species **4** (Scheme 1a).[11] Simple alkyl groups are compatible with the reaction conditions as well. Methyl-substituted 1-(4-methylphenyl)-vinyl azide reacts with 2-methylindole under the standard conditions to give **13k** in 59% yield. With a *tert*-butyl substituent, the analogous product **13l** is formed in 69% yield. Importantly, azido-enolonium species **10**, like those of its analogue **4**, is not limited to terminal enolonium species although the yield is reduced. Thus, (**9**, R^1 = H, R^2 = Me, Scheme 2) affords product **13j** in 44% yield.

The scope of the aromatic coupling partner was also investigated mainly using 1-(4-*tert*-butyl-phenyl)vinyl azide (**9**, R^1 = *t*-Bu, R^2 = H, Scheme 2) as the starting material. This vinyl azide reacts with simple indole to afford **13m** in 57% yield compared to 2-methylindole product **13l**, which was formed in 60% yield. The lower yield of **13m** may have to do with substituted indole products being less prone to react twice under the reaction conditions. 5-Methyl-1*H*-indole reacts with 1-(4-*tert*-butyl-phenyl)-vinyl azide to give **13n** in 65% yield. However, 2-phenylindole reacts with 1-(4-*tert*-butyl-phenyl)-vinyl azide to give **13s** in 55% yield. In contrast, the reaction with 3-methylindole leads to formation of a complicated reaction mixture. 5-Fluoro-1*H*-indole reacts with 1-(4-*tert*-butyl-phenyl)-vinyl azide to give **13o** in 64% yield, while the corresponding 5-bromo-1*H*-indole and 5-iodo-1*H*-indole react with 1-(4-*tert*-butyl-phenyl)-vinyl azide to give **13p** and **13q** in 68% and 71% yield, respectively. This again shows the compatibility of bromo and iodo functionalities with the reaction conditions. An important result in view of these functions may be used subsequently as handles for, e.g., palladium-catalyzed cross-coupling reactions. Another notable compatibility is that the electron-rich group of 5-methoxy-2-methyl-1*H*-indole is left unscathed under the reaction conditions when coupled with 1-(4-*tert*-butyl-phenyl)-vinyl azide to give **13r** in72% yield. 1-(4-Chloro-phenyl)-vinyl azide also reacts with 5-methoxy-2methyl-1*H*-indole to give **13d** in 79% yield.

A cyano group is tolerated as well, as shown in the production of **13t** in 69% yield. Even an ethyl ester in the aromatic coupling partner is tolerated as shown by the preparation of **13u** in 63% yield. An acid-sensitive Boc protecting group is also compatible with the reaction conditions. Thus, (**9**, R^1 = Br, R^2 = H) reacts with *tert*-butyl 2-methyl-1*H*-indole-1-carboxylate to give **13f** in 71% yield. Finally, 1-methoxy-3-methylbenzene was used to test a benzene derivative. This compound reacted with (**9**, R^1 = H, R^2 = H) to give **13v** in 58% yield. This is an important advantage of azido-enolonium species **10** in comparison to their analogues **4** that do not react at all with 1-methoxy-3-methylbenzene.[11] Indeed, two or three methoxy group are necessary to activate a benzene derivative to couple with **4** (R_1 = Ph, R^2 = H, see the structure in Scheme 1a).[11] The reactivity with other benzene derivatives will be explored further in a later full report.

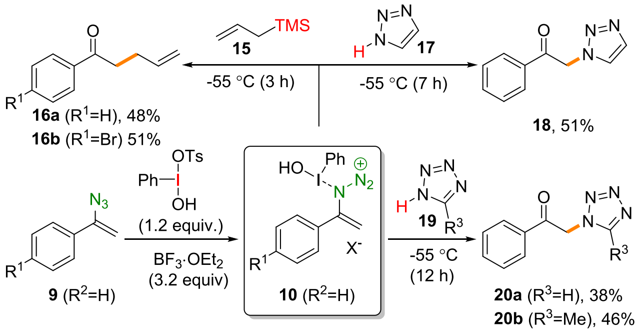
The intermediacy of azido-enolonium species **10** is supported by IR studies of the reaction mixture (see the Supporting Information). Thus, when 1-(4-methyl)phenylvinyl azide **9** (R^1 = Me, R^2 = H) is made to react with 2-methylindole, compound **12** (R^1 = Me, R^2 = H) is observed as indicated by a strong signals at 1623 and 2111 cm^{-1} (Figure S1). The latter signal is diagnostic for N_3 species. Further, when water is added the product **13k** is formed. The formation is accompanied by disappearance of the signal at 1623 cm^{-1} and formation of a new signal at approximately 1683 cm^{-1} (Figure S2). Importantly an azide signal remains at 2103 cm^{-1} (Figure S2) indicating release of inorganic azide anion. The isolated product of the reaction has a characteristic carbonyl stretch at 1676 cm^{-1} in solution (Figure S3). Importantly, the purified product **13k** has no signals in the 2110 cm^{-1} region (Figure S3). Further evidence for **10** and **12** was found in the reaction of (*Z*)-(1-azidobut-1-en-1-yl)benzene (**9x**) with 2-methylindole (Scheme 3). When water is added a complex reaction mixture results. From this product oxime **14** was isolated in 16% yield. Compound **14** is not a hydrolysis intermediate as neither it nor trace oxime products found in other reactions undergo further hydrolysis to the ketone even in the presence of aqueous acid. Apparently, the relatively sterically hindered **12x** does not undergo attack by water at the imine carbon allowing other reactions to take place including the displacement of nitrogen (N_2) by water on the imine nitrogen leading to**14**. This result opens up for future work aimed at favoring formation of the oxime.

Scheme 3. Oxime Formation for a Hindered Product



We have shown that enolonium species **4** are capable of undergoing other C−C forming reactions, such as allylation,[1] cross coupling with TMS-enol ethers,[12] and C−N bond forming reaction with azoles.[14] Thus, in order to demarcate the capabilities of azido-enolonium species **10** we also tested their reaction with allyltrimethylsilane (**15**) as well as triazole (**17**) and two tetrazoles (**18**, Scheme 4).

Scheme 4. Preliminary Experiments on Coupling of Azido-Enolonium Species 10 with Allyltrimethylsilane (15), Triazole (17), and Tetrazoles (19)



When azido-enolonium species **10** (R^2 = H) is prepared in situ as before and allyltrimethylsilane (**15**, 1.5 equiv) is added to the reaction mixture, the products **16a** and **16b** form within 3 h and are isolated in 48% and 51% yield, respectively. The same azido-enolonium species also reacts with triazole (**17**) within 18 h to afford the α-triazolium acetophenone **18** in 51% yield. Finally, **10** reacts with tetrazole and 5-methyl-1*H*-tetrazole to give the coupling products **20a** in 38% yield and **20b** in 46% yield.

In summary, we have presented the first example of azido-enolonium species and outlined their reactivity in arylation, allylation, and N-heteroarylation reactions. These studies show that azido-enolonium species **8** (Scheme 1b) are as reactive as ketone-derived enolonium species **4** (Scheme 1a), show increased reactivity toward a benzene derivative, and compatibility with a wide range of common functional groups. The mechanism is supported by IR studies. Further studies on the structure and reactivity of this new species will follow.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b03824.

> Experimental description, characterization data (NMR, IR, HRMS), and reproduction of NMR spectra; IR spectra of the reaction mixture before and after water was added (PDF)

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Notes

The authors declare no competing financial interest.

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