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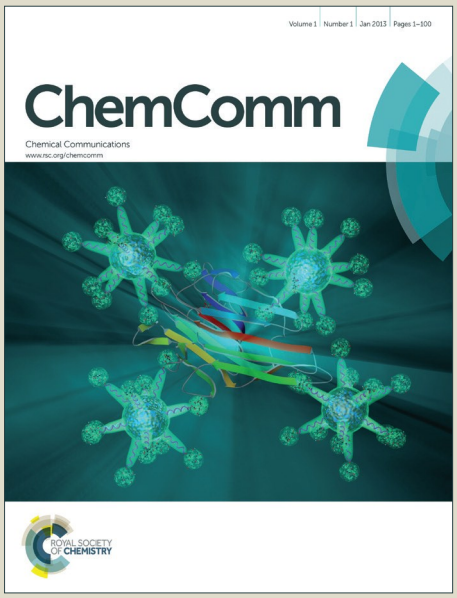

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A Direct Access to Isoxazoles from Ynones using Trimethylsilyl Az-ide as Amino Surrogate under Metal/Catalyst free Conditions

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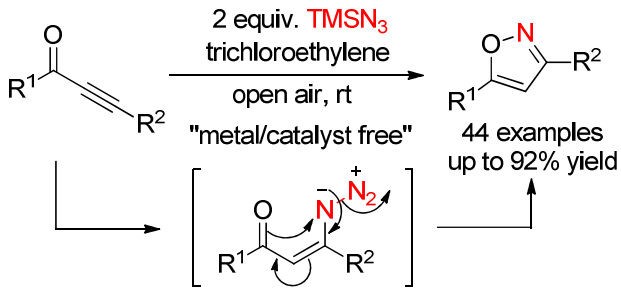

A general access to isoxazoles from readily available ynones is described with outstanding functional group compatibility using trimethylsilyl azide as amino surrogate under exceptionally simple conditions.

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COMMUNICATION

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Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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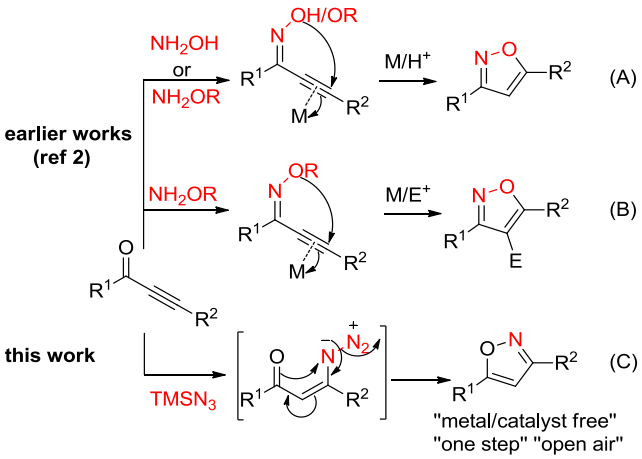
A general method for isoxazoles from readily available ynones using trimethylsilyl azide as amino surrogate, likely via an unprecedented hydroazidation of alkyne and denitrogenative cyclization, is demonstrated. The method neither required any catalyst nor demanded the unusual conditions to afford the products with outstanding functional group compatibility.

Cyclization via inter- and/or intramolecular functionalization of alkynes has become extensively sought after approach in modern chemistry for the synthesis of wide range of hetero- and carbocycles with vast new patterns of substitutions.[1] Soft modes of activation together with the ready accessibility of alkyne intermediates led to their frequent use as the precursors. Possibility of tandem couplings, rearrangements, isomerizations, etc. renders it a highly amenable pathway for otherwise difficult outcomes. On the same line, Larock et al. reported an elegant approach for the synthesis of isoxazoles,[2a-b] highly privileged scaffolds in drug discovery (valdecoxib: COX-2 inhibitor; sulfamethoxazole: anti-bacterial; sulfafurazole: PABA antagonist; cloxacillin: β-lactam antibiotic; isoxaflutole: 4-hydroxyphenylpyruvate dioxygenase inhibitor; danazol: for treating endometriosis; leflunomide: antirheumatic drug),[3] from oxime ethers of ynones *via* electrophilic halocyclization (Scheme 1B). Subsequently, several groups disclosed various metal mediated cyclizations of the same substrates (oximes or oxime ethers of ynones) for variety of substituted isoxazoles (Scheme 1A & 1B).[2c-k] The latter included the highly useful tendem cyclization/coupling pathways for highly substituted isoxazoles.

In continuation of interest in uncovering new activities of functionalized alkynes,[4] we herein present a direct access to isoxazoles from ynones using $TMSN_3$ as amino surrogate (Scheme 1C). This new method is step economical and it does not require (1) assistance of any metal/catalyst, (2) harsh reaction conditions, and (3) exclusion of air or moisture.



Scheme 1. Synthesis of isoxazoles from ynones.

We began our studies with the optimization of reaction conditions for the conversion of **1aa** to **2aa** (Table 1). Initially, when we treated **1aa** with 2 equivalents of $TMSN_3$ in presence of 10 mol% of $AgCO_3$ in DMSO (entry 1), the desired product **2aa** was obtained only in 10% yield along with the simple triazole as the major product.[5] Elevation of reaction temperature (entry 2) or change of silver catalyst (entries 3-5) brought in no improvement in the outcome. Change of solvent to DMF slightly improved the yield, but still the triazole was found to be the major adduct (entry 6). No reaction occurred when other solvents like 1,2-dichloroethane (DCE), MeCN, THF or toluene were employed (entries 7-10). Dramatically, when we switched the solvent to trichloroethylene (TCE), the only desired product **2aa** was cleanly formed in 80% (entry 11). Surprisingly, a control experiment revealed that the reaction indeed did not require the assistance of the silver catalyst (entry 12). Thus, stirring of a mixture of **1aa** and $TMSN_3$ in TCE at room temperature cleanly furnished the product in 82% yield. Noteworthy is that the reaction was performed under open atmosphere. In fact, the reaction was almost halted under anhydrous conditions (entry 13), indicating that the presence of water is necessary. Thinking that the presence of nitrogen along with pressure (balloon) might have affected the

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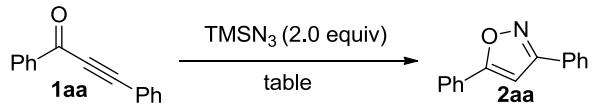
Electronic Supplementary Information (ESI) available: See
DOI: 10.1039/x0xx00000x

progress of the reaction by reducing the rate of denitrogenation step (*vide infra*, see mechanism), we conducted a reaction with a $CaCl_2$

Table 1. Optimization of reaction conditions.[a]



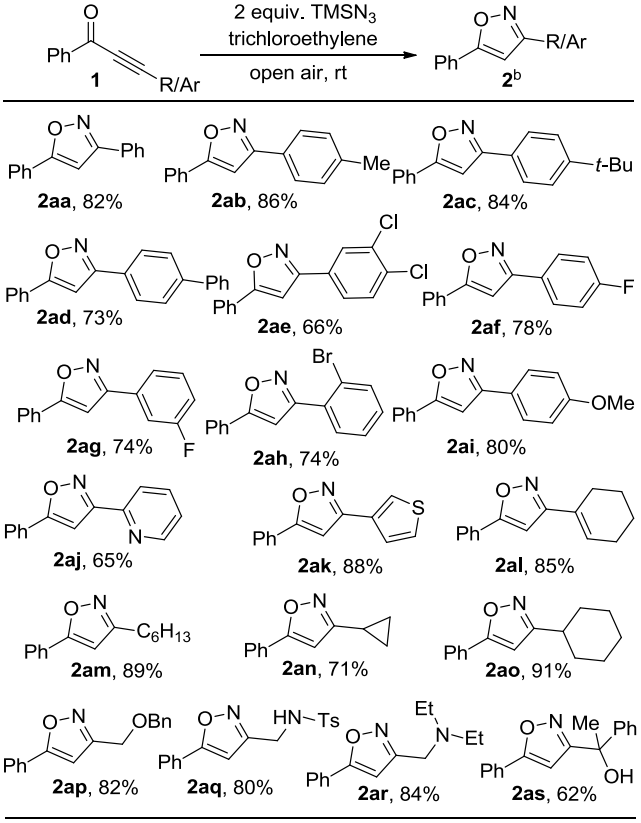
entry	catalyst (10 mol%)	additive (2 equiv)	solvent	temperature	yield[b]
1	Ag_2CO_3	-	DMSO	rt	10%
2	Ag_2CO_3	-	DMSO	80 °C	trace[c]
3	Ag_2OAc	-	DMSO	rt	11%
4	$AgNO_3$	-	DMSO	rt	–[c]
5	AgOTf	-	DMSO	rt	–[c]
6	Ag_2CO_3	-	DMF	rt	18%
7	Ag_2CO_3	-	DCE	rt	–[d]
8	Ag_2CO_3	-	MeCN	rt	–[d]
9	Ag_2CO_3	-	THF	rt	–[d]
10	Ag_2CO_3	-	Toluene	rt	–[d]
11	Ag_2CO_3	-	trichloroethylene	rt	80%
12	-	-	trichloroethylene	rt	82%
13[e]	-	-	trichloroethylene	rt	17%
14[f]	-	-	trichloroethylene	rt	19%
15	-	H_2O	trichloroethylene	rt	70%
16	-	TEA	trichloroethylene	rt	80%

[a]Reaction conditions: 1 mmol of **1** and 2 mmol of $TMSN_3$ in 5 mL of solvent in open air at rt for 12 h. [b]Isolated yields. [c]Simple triazole was major product. [d]Starting material recovered as such. [e]Reaction conducted in inert atmosphere (N_2 balloon). [f]$CaCl_2$ guard tube instead of a N_2 balloon.

guard tube (entry 14) which maintains the anhydrous atmosphere without any external pressure. The result was same as in presence of nitrogen suggesting that the hydroazidation (with the help of water), and not azidosilylation, of alkyne was only the feasible reaction. However, addition of 2 equivalents of water (entry 15) to the reaction did not increase the rate of the reaction but slightly affected the yield demonstrating that the addition of water must be very slow (atmosphere) along with the reaction over 12 h. Further, we did an experiment in presence of 2 equiv. of TEA to see if any trace of HCl in the solvent was responsible for the reaction (entry 16). But it could not affect the reaction, producing the product as good as in a base free reaction.

With these observations, we next headed to evaluate the generality of this new and direct access to isoxazoles from ynones. We first studied the reaction scope against the change of substitution at the alkyne terminal. As is evident from table 2, the reaction showed no bias in accommodating substrates with disparate electron properties. Thus, the substrates with phenyl ring on alkyne terminal with substitution ranging from simple alkyl (**1ab-ac**) or phenyl (**1ad**) to halo (**1ae-ah**) or methoxy (**1ai**) all produced the corresponding products (**2ab-ai**) in excellent yields (66-86%). The smooth formation of bromo adduct **2ah** shows that the ortho substituents on the benzene moiety display no apparent effect on the outcome. Heteroaryl (pyridyl and thiophenyl) substituted ynones (**1aj-ak**) were found to be equally viable substrates for the reaction to furnish the products (**2aj-ak**) in 65-88% yields. Enynone **1al** with two terminals (β and δ) for initial azide addition showed no interference from olefin portion to deliver the desired adduct **2al** in 85% yield. Next we tested the scope of the reaction toward aliphatic substitution. Pleasingly, the substrates with both acyclic (**1am**) and cyclic (**1an-ao**) alkyl substitution passed through the reaction smoothly to afford the products in excellent yields (71-91%). Furthermore, the reaction proceeded well with the substrates derived from protected propargyl-alcohol (**1ap**) and –amine (**1aq-ar**). Remarkably, substrate **1as** with free propargyl hydroxyl showed hassle-free participation in the reaction to deliver the corresponding adduct **2as** in 62% yield. Subsequently, we verified the scope of the reaction with respect to substitution on carbonyl terminal of ynone. The results are summarized in Table 3. Initially we screened various aryl ynones through the standard conditions. Thus, similar to the basic substrate **1aa**, methyl- and isopropyl- substituted phenyl ynones **1ba-bb** afforded the corresponding adducts **2ba-bb** in

Table 2. Synthesis of isoxazoles from ynones.[a]

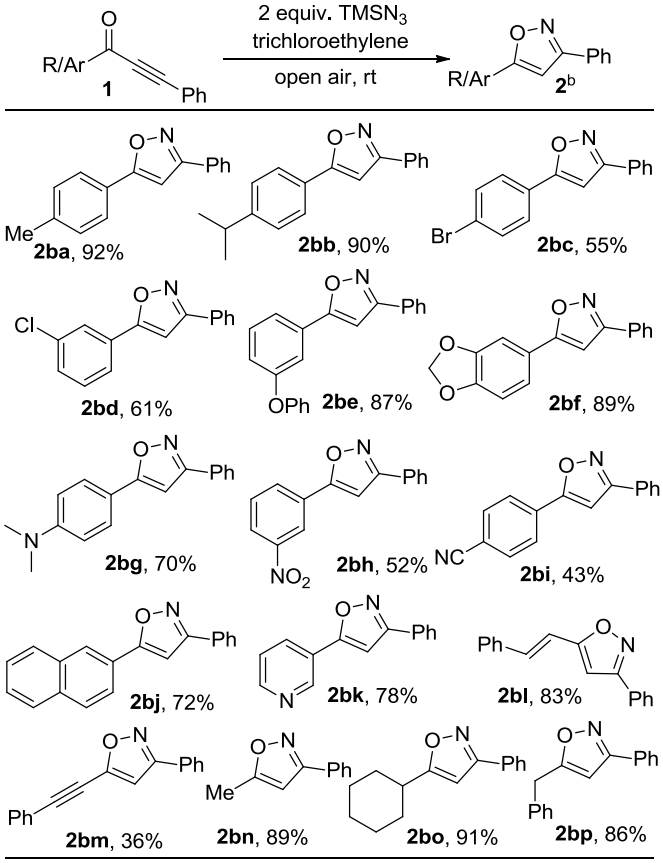


[a]Reaction conditions: 1 mmol of **1** and 2 mmol of $TMSN_3$ in 5 mL of trichloroethylene in open air at rt for 12 h. [b]Isolated yields.

90-92% yields. Bromo- and chloro-phenyl substituents in **1bc-bd** were comfortably accommodated to yield the adducts with ready handles for further functionalization. Electron rich alkoxy and amino substituted substrates **1be-bg** were found to be highly productive (70-89% of **2be-bg**; **2bg** unstable in open air) whereas its electron deficient nitro and cyano substituted counterparts **1bh-bi** were slightly reluctant to reaction (43-52% of **2bh-bi**; partial decomposition) likely due to reduced nucleophilicity of carbonyl group (*vide infra*, reaction mechanism in Scheme 3). Next, naphthyl and pyridyl adducts (**2bj-bk**) were obtained smoothly (72-78%).

Very interestingly, enynone **1bl** with two Michael acceptor terminals selectively underwent the desired transformation to deliver the corresponding product **2bl** in 83% yield. Similarly, diynone **1bm** yielded the acetylynic isoxazole **2bm** but in a low yield of 36%. Having successfully tested the method for conjugated substitution at C5, we next aimed to synthesize 5-alkyl oxazoles. Thus methyl adduct **2bn** was obtained from corresponding alkyl ynone **1bn** in 89% yield. Note that **2bn** is the precursor of non-steroidal anti-inflammatory drug veldicoxib.[6] Finally, cyclohexyl and benzyl ynones **1bo-bp** were cleanly converted to **2bo-bp** using the standard protocol.

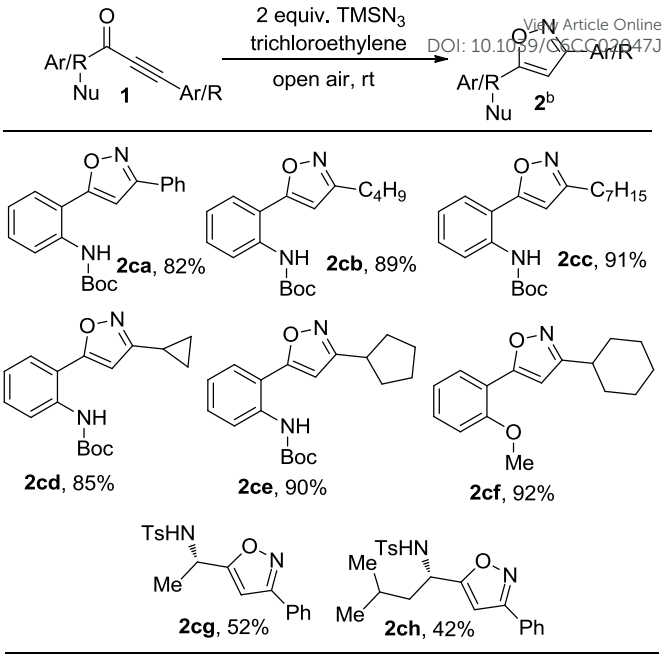
Table 3. Synthesis of isoxazoles with varying substitution at C5.[a]



[a]Reaction conditions: 1 mmol of **1** and 2 mmol of $TMSN_3$ in 5 mL of trichloroethylene in open air at rt for 12 h. [b]Isolated yields.

To explore any further generality of the method, we next chose the substrates like **1ca-ch** with a nucleophile flanking nearby. They in general readily undergo intramolecular electrophilic cyclization, especially in the typical metal (or any acid) mediated conditions.[7] Delightedly, when we subjected **1ca** to the standard conditions, the expected product **2ca** was obtained in excellent yield of 82% without any interference of NHBoc group. The reaction went equally well with *n*-alkyl (**1cb-cc**) and cycloalkyl (**1cd-ce**) substitution at the alkyne terminal of ynone. Similarly, o-methoxy variant **1cf** too showed high productivity (2cf in 92%). Very pleasingly, amino acid (alanine) derived ynone **1cg** also underwent the desired transformation to yield the isoxazole (**2cg**) with a chiral substitution.

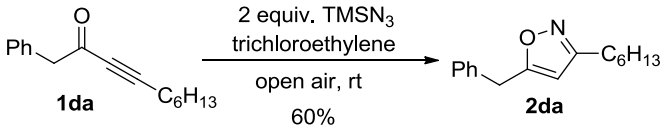
Table 4. Synthesis of isoxazoles from ynones bearing nearby nucleophile.[a]



[a]Reaction conditions: 1 mmol of **1** and 2 mmol of $TMSN_3$ in 5 mL of trichloroethylene in open air at rt for 12 h. [b]Isolated yields.

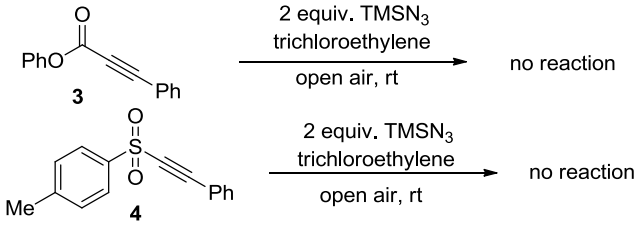
Likewise, leucine derived ynone **1ch** was converted to **2ch** in 42% yield.

Next, we headed to verify the scope of the method towards the substrate with aliphatic substitution on both terminals of the ynone, i.e. ynone without any external activation. Pleasingly, **1da** delivered the expected **2da** but in moderate yield of 60% (Scheme 2).



Scheme 2. Synthesis of isoxazoles from ynones.

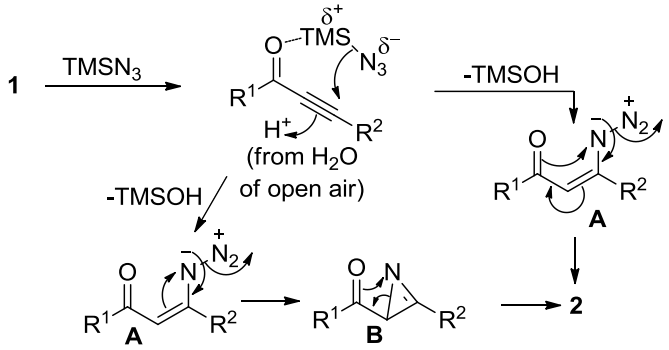
Finally, we became curious to check the fate of ynoate 3 and alkynyl sulfone **4** under the standard conditions (Scheme 3). Setting a limitation, no reaction occurred perhaps the initiation step i.e. Michael addition did not take place due to weak acceptor nature unlike ynones.



Scheme 3. Attempts for reaction of ynoate **3** and sulfonyl acetylene **4** with $TMSN_3$.

A probable mechanism for the above direct access to isoxazole from ynone is described in Scheme 4. The coordination of TMS group of $TMSN_3$ with ynone oxygen, which is electron rich due to conjugation, reduced the barrier of Michael addition reaction and hence enabled it (**A**) without the assistance of the activating catalyst.

Further, this coordination was responsible for the addition of azide syn to the carbonyl group which is necessary for the subsequent cyclization. The thus added azide group increased the nucleophilicity of already nucleophilic (due to conjugation) enone carbonyl group which hence readily underwent cyclization to form O-N bond relieving the nitrogen molecule. Perhaps this nucleophilic nature is reduced by the powerful withdrawing groups on the adjacent aryl rings in case of **2bh** and **2bi** that hence showed low yielding. As the literature supports the formation of azirine from vinyl azides,[8] we also propose an alternate route for **2** from **A** through azirine **B** (azirine ring formation followed by ring opening to release the strain).



Scheme 4. Proposed mechanism.

In summary, we have illustrated a highly general and straightforward method for the synthesis of isoxazoles from readily available ynones using $TMSN_3$ as amino surrogate. The reaction likely proceeds via tandem azidation and denitrogenative cyclization (providing a new set of disconnections), offering a single pot C-N and O-N bond formation. The reaction mainly features: (1) step economy, (2) no necessity of metal/catalyst, and (3) highly ambient conditions (under open air and at room temperature). Further, a high reaction scope with respect to both terminals of ynone together with excellent product yields makes it a practical approach for the highly privileged scaffold.

GRK and YKK thank CSIR for the fellowships. We thank SAIF division CSIR-CDRI for the analytical support. We gratefully acknowledge the financial support by CSIR-SPLENDID (BSC 0104). CDRI Communication No: (will be inserted if accepted).

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