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A Stereoselective Thiocyanate Conjugate Addition to Electron Deficient Alkynes and Concomitant Cyclization to *N, S*-Heterocycles

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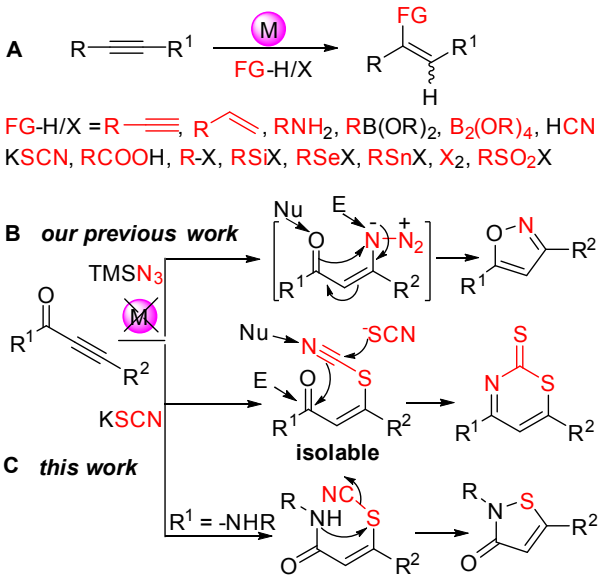
A regio- and stereoselective thiocyanate addition to ynones is achieved using KSCN in AcOH at 70 °C. The reaction is extendable to ynal, ynesulfone, ynoic acid and ynoate. The adduct from ynones were readily transformed to thiazine-2-thione derivatives under slightly modified reaction conditions. In contrast, thiocyanated adducts from ynamides underwent an in situ decyanative amido cyclization towards isothiazolones. None of these events needed any transition metal or catalyst attaining a high synthetic value.

Hydrofunctionalization of alkynes[1-2] is a remarkable strategy to access a variety of highly substituted/functionalized olefins with very high regio and stereo selection (Scheme 1A)[1]. This has uncovered the ways to solve several long lasting problems in selective synthesis of olefins through conventional methods. The strategy is highly reliable because the starting materials required are readily accessible alkynes and the criteria necessary is usually a simple electronic or steric bias. Few recent breakthroughs reveal that a coordinating group in a nearby region also can help the event occur in a highly selective manner. Using the high intrinsic electronic bias, electron withdrawing group (EWG) tethered alkynes can be selectively functionalized through conjugate addition[2]. Although ubiquitous on conjugated olefins, this addition is hardly explored on EWG-tethered alkynes. We recently reported a catalyst-free azide addition to ynones[2b] where the resultant vinyl azide underwent an in situ denitrogenative cyclization to yield isooxazoles (Scheme 1B). As another similar example, and as part of our ongoing program of uncovering the novel activities of functionalized alkynes,[1g,1k-l,2b,3] we report herein a thiocyanate conjugate addition of ynones under catalyst/metal free conditions (Scheme 1C). Showing a hitherto uncovered derivatization of thiocyanate group, the resultant 3-thiocyanato-α,β-unsaturated carbonyl could be cyclised in situ via a second thiocyanation with a slight increase of temperature and time. Pleasingly, this double C-S bond formation event also does not require support of any catalyst/transition metal. Ynamides in contrast underwent a decyanative amido cyclization subsequent to the thiocyanate addition to deliver isothiazolones under similar conditions.



Scheme 1. Hydrofunctionalization/addition of alkynes.

Insertion of sulfur can result in a dramatic change in both the physical characteristics and the biological properties of molecules. As a result, apart from being prevalent in nature, organosulfur compounds are commonly found in pharmaceuticals, agrochemicals and material science.[4] The sources of sulfur being used to achieve such targets usually elemental sulfur (S_8), thiols, thioacetates, thiocyanates or thioureas.[5] Out of these, thiocyanates prove to be more promising as they can be further modified[6] due to presence of active CN group on sulfur. Jiang et al. have recently reported an elegant silver catalyzed hydrothiocyanation of

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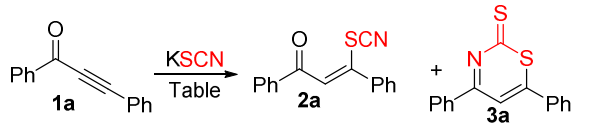
bromoalkynes using KSCN as thio source.[7] We herein show this thiocyanation on electron-deficient alkynes and various concomitant cyclizations all under the metal/catalyst free conditions.

We commenced our optimization studies with the addition of KSCN to ynone **1a** in the presence of AgOAc (Table-1). No reaction was observed at room temperature in AcOH (entry 1). When the same reaction contents were heated to 70 °C, the substrate was totally consumed in 1h. Pleasingly, the desired product **2a** was obtained in 60% yield but with a surprising formation of thiazine-2-thione **3a** in 20% as a byproduct (entry 2). We reasoned that **3a** was formed from **2a** through the reaction with another molecule of KSCN (*Vide Infra*, mechanism). This was proved through a separate conversion of **2a** to **3a** in similar conditions (conditions mentioned in entry 9). This unprecedented derivatization of thiocyanate and the medicinally unexplored new dithio heterocycle **3a** prompted us to explore separate conditions for the exclusive formation of both the products. Other catalysts like AgOTf, Ag_2O and $Cu(OTf)_2$ were neither selective nor as productive (entries 3-5). Surprisingly, the exclusion of the catalyst and reduction of the reaction time to 30 min cleanly converted the substrate to thiocyanate addition adduct **2a** in 89% yield (entry 6). No double thiocyanation/cyclization adduct **3a** was observed. Very pleasingly, increase of quantity of KSCN and elevation of temperature slowly converted **2a** to **3a** (entries 7-9). Thus, use of 3 equiv of KSCN at 100 °C for 4 h cleanly afforded **3a** as a single product in 85% yield. Change of solvent from AcOH to DMSO, dioxane, DCE, EtOH or H_2O was found to be either inappropriate or totally unproductive (entries 10-14). AcOH was thus identified as the only appropriate solvent.

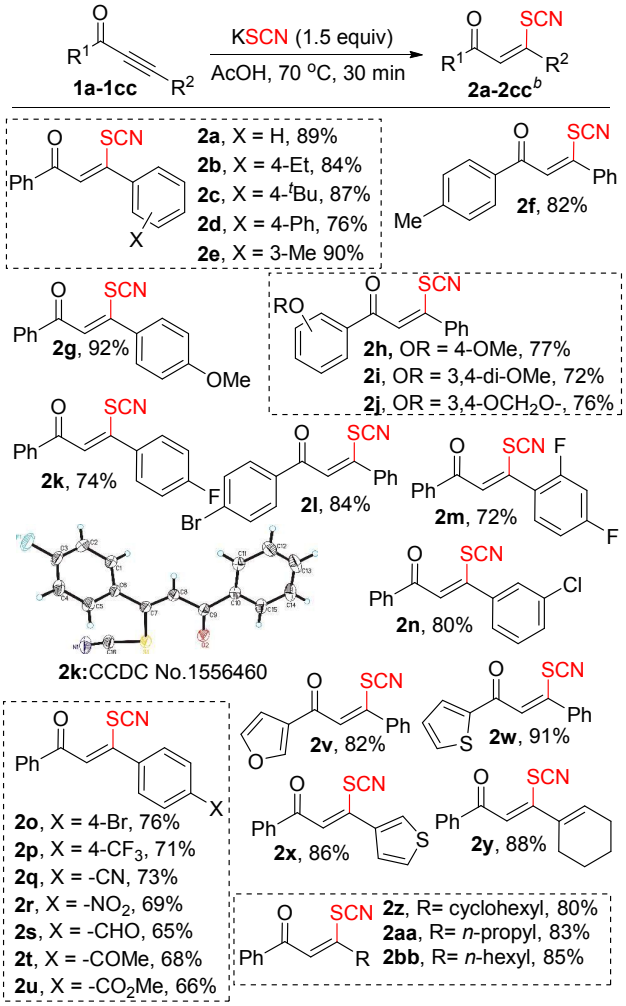


entry	catalyst	solvent	temp (°C)	time	yield(%)[b] (**2a**:**3a**)
1	AgOAc	AcOH	RT	12 h	N.R
2	AgOAc	AcOH	70	1 h	60 : 20
3	AgOTf	AcOH	70	1 h	40 : 10
4	Ag_2O	AcOH	70	1 h	25 : trace
5	$Cu(OTf)_2$	AcOH	70	1 h	30 : trace
6	**--**	**AcOH**	**70**	**30 min**	**89 : 00**
7[c]	--	AcOH	80	4 h	20 : 60
8[d]	--	AcOH	90	4 h	10 : 75
9[d]	**--**	**AcOH**	**100**	**4 h**	**00 : 85**
10[d]	--	DMSO	100	4 h	10 : 00
11[d]	--	Dioxane	100	4 h	N.R
12[d]	--	DCE	80	10 h	N.R
13[d]	--	EtOH	80	10 h	N.R
14[d]	--	H_2O	100	10 h	N.R

[a]Reaction conditions: **1a** (0.5 mmol), KSCN (0.75 mmol), catalyst (0.15 mmol) in solvent (4 mL) under air. [b]Isolated yield. [c]1 mmol of KSCN. [d]1.5 mmol of KSCN in 6 mL of solvent.

Table 1: Optimization studies.

With separate optimized conditions in hand for both addition and cyclized adducts, we investigated the scope of the selective thiocyanate addition to ynone as shown in Scheme-2. Alkyl/phenyl substitution on the phenyl ring on either end of the ynone (**1b-f**) did not affect the reaction and thus afforded the corresponding hydrothiocyanated products **2b-f** in 76-90% yields. Electron-rich substitution on the alkyne terminus (**1g**) promoted the reaction (92% of **2g**) whereas the same on keto terminal (**1h-j**) led to slight erosion of the yields (72-77%).



[a]**1a** (0.5 mmol), KSCN (0.75 mmol) in 4 mL AcOH under air. [b]Isolated yield.

Scheme 2. Thiocyanate conjugate addition to ynones.

All halo groups survived in the reaction irrespective of their position, and the substrates possessing them reacted as good as electronically neutral substrates. Thus, **1k-p** afforded **2k-p** in 71-84% yields. Pleasingly, highly reactive functional groups like formyl, acetyl, ester and cyano comfortably survived in the reaction (**2q-u**). Electron-poor substrates were found to be relatively less productive. In contrast, the heteroaryl substitution on either end of ynone (**1v-x**) showed excellent reactivity to afford the products (**2v-x**) in 82-91% yields. Further, enynone **1y** selectively reacted to give **2y** with olefin group intact. Expanding the scope, Thus, the alkyl-substituted ynones (**1z**, **1aa-bb**) were also proved to be equally effective substrates for this metal-free thiocyanate addition and

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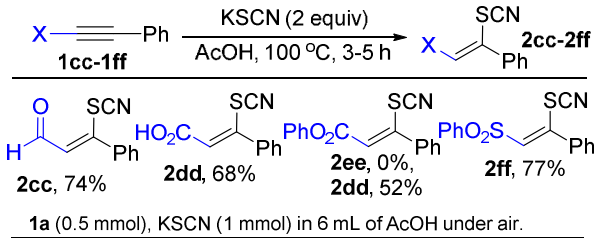
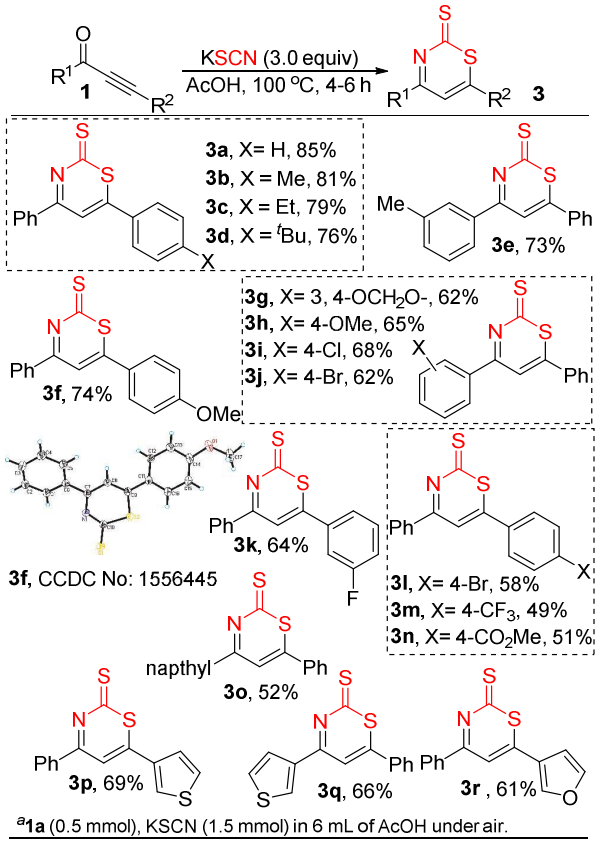
transformed to the corresponding thiocyano enones **2z**, **2aa**-**bb** were obtained in 80-85% yields.



Scheme 3. Thiocyanation of EWG tethered alkynes.

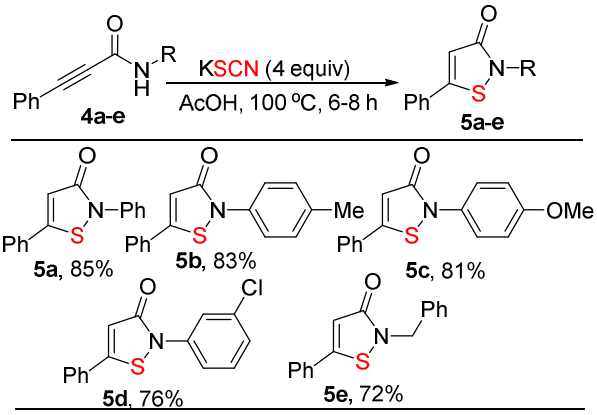
Our focus next turned to investigating other potential activating groups on the alkyne that could allow this metal-free thiocyanation (Scheme-3). Pleasingly, ynal **1cc** underwent the addition smoothly to afford thiocyano enal **2cc** in 74% yield. Ynoic acid **1dd** was found to react equally well where as the ynoate **1ee** underwent hydrolysis after intended addition (**2dd**). Delightedly, extending the reaction scope further, sulfonyl acetylene **1ff** also smoothly participated in this selective hydrothiocyanation to give **2ff** in 77% yield.



Scheme 4. Thiazine-2-thione from ynones.

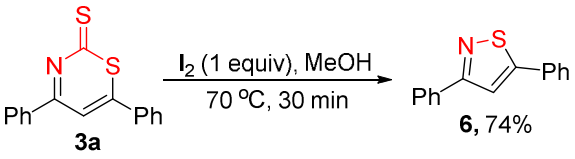
With these exciting results, we next moved on to evaluate the generality of the tandem thiocyanate addition and concomitant thiocyanative cyclization (**1** to **3**, Scheme 4). Almost all the substrates used for hydrothiocyanation cleanly underwent this tandem transformation to afford the desired thiazine-2-thione using 3 equiv of KSCN at 100 °C for 4-6 h. Thus alkyl-phenyl ynones were initially transformed to the corresponding thiazine-2-thione **3a-e** in excellent yields of 73-85%. Alkoxy- and halophenyl ynones also smoothly passed through the reaction to afford **3f-l** in practical yields (58-74%). Further, ynones with tifluoromethyl, ester, naphthyl and heteroaryl groups were also proved to be suitable substrates for the reaction showing its generality (**3m-r** in 49-69% yields).

In contrast to all the above alkynes with various EWG, ynamides under similar conditions afforded isothiazolones, an underexplored N,S-heterocycle,[8] (Scheme 5) via thiocyanation followed by decyanative intramolecular amido cyclization. Amide being ready and appropriate intramolecular nucleophile might have quickly interfered the double thiocyanate addition and led to this new adduct formation. The reaction was consistent with all the substrates **4a-e** that we used and afforded the new N, S-heterocycles **5a-e** in excellent yields (72-85%).



Scheme 5. Isothiazolones from ynamides.

Finally, as part of derivatization, a dethiocarbonylative ring contraction of **3** (**3a**) using iodine in MeOH was achieved (Scheme 6) to get the another N,S-heterocycle isothiazole **6**[9] in 74% yield.



Scheme 6. Isothiazole from thiazene-2-thione.

A proposed mechanism for the tandem thiocyanate conjugate addition and thiocyanative/decyanative cyclization is depicted in Scheme 7. Accordingly, the nucleophilic addition of thiocyanate occurs with the help of AcOH catalysis (to give **2** from **1** and **C** from **4**) and the stereoselection is a result of orienting large groups trans to one another (thermodynamic control). In the case of **2**, the second thiocyanate attacks on electrophilic CN group of vinyl thiocyanate and the incipient imide anion adds on the nearby carbonyl group. Finally, expulsion of KOCN revealed the desired thiazine-2-thione **3**. In case of **C**, the ready amide nucleophile in close premises cyclizes on to thiocyanate to afford **5** by expelling the cyanide group.

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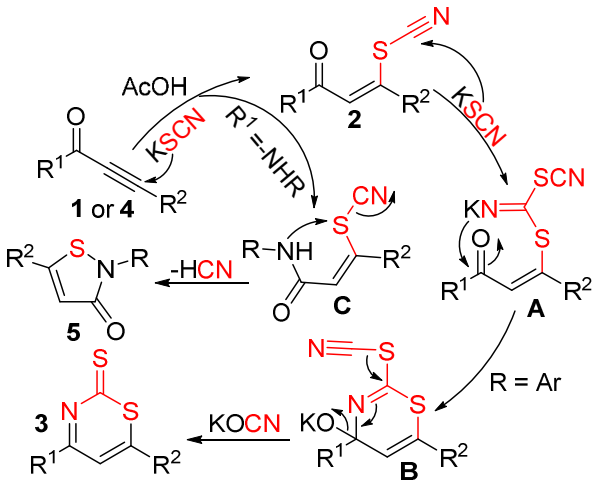

Scheme 7. Proposed mechanism.

In summary, we have shown a catalyst-free thiocyanate conjugate addition to ynones, ynal, ynoic acid, ynoate and ynesulfone. Derivatising the thus synthesized thiocyanoenone, a concomitant second thiocyanation followed by cyclization was achieved to access thiazine-2-thiones with a mere increase of time and temperature. Ynamides in contrast underwent a quick decyanative cyclization after hydrothiocyanation to afford isothiazolones. The excellent regio- and stereoselectivity, broad scope, and high synthetic yields are some of the noteworthy features of the present method.

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