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Authors: Akhila Kumar Sahoo, Shubham Dutta, Rajendra K. Mallick, Rangu Prasad, and Vincent Gandon

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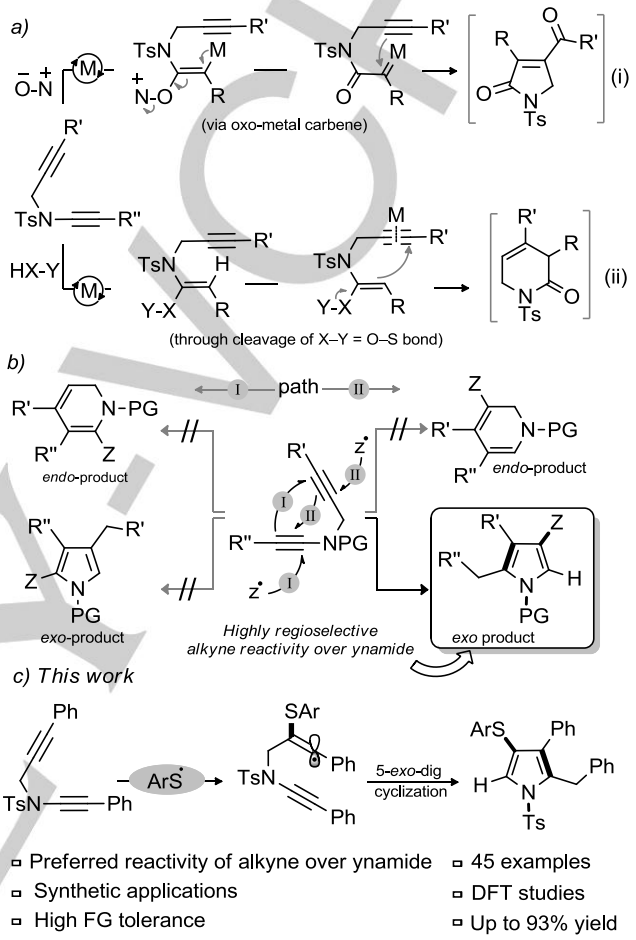
Alkyne Reactivity Preferred over Ynamide: Regioselective Radical Cyclization of Yne-Ynamides

Shubham Dutta,[†] Rajendra K. Mallick,[†] Rangu Prasad,[†] Vincent Gandon[‡¥]* and Akhila K. Sahoo[†]*

Abstract: Ynamides are typically more reactive than simple alkynes and olefins. However, a serendipitous observation revealed a rare case where the reactivity of simple alkynes exceeds that of ynamides. This led to the development of a unique sulfur radical-triggered cyclization of yne-tethered-ynamides, which involves the attack of a thiyl radical to the alkyne and then that of the ynamide. A wide range of novel 4-thioaryl pyrroles that could tolerate common functional moieties and *N*-protecting groups were expediently constructed by this strategy. The current method opposes to the typical cyclization of yne-ynamides, which involves the attack of the ynamide core to the alkyne moiety. Control experiments and DFT calculations supported the participation of the sulfur radical in the reaction and the regioselective cyclization. The synthetic potential of the substituted pyrroles is also discussed.

Ynamides, a distinct class of *N*-substituted alkynes, have been used for various cyclization/cycloisomerization processes towards the construction of structurally diverse complex *N*-heterocyclic building blocks.[1] In this context, the transition-metal-catalyzed, *N*-oxide and Brønsted/Lewis acid-triggered cyclizations of yne-tethered-ynamides have shown great potential. Importantly, all these transformations involve nucleophilic attack of the ynamide motif (via oxo-metal carbene[2]/ketene *N*,*O*-acetal) to the alkyne scaffold (Scheme 1a).[3,4] In contrast, synthetic techniques that are based on reversing the usual reactivity of ynamides over alkynes have been only rarely reported.[5] A worthwhile endeavor is to unravel a radical-mediated cyclization[6] of yne-tethered-ynamides, with the prediction of a preferred radical attack to the alkyne rather than to the inherently polarized ynamide (path II over path I; Scheme 1b), which, to the best of our knowledge, is unprecedented. The radical-triggered 6-*endo*-/5-exo-cyclization of the alkyne to the ynamide would result in the formation of 6- or 5-membered *N*-heterocycles, respectively (path II, Scheme 1b). To overcome this challenge, we have developed a highly regioselective thiyl-radical attack to an alkyne motif, followed by regioselective 5-*exo*-dig intramolecular attack to the ynamide moiety of yne-tethered-ynamides. This reaction yields novel highly substituted 4-thioaryl-pyrroles (Scheme 1c). The reaction has a broad scope and allows for the synthesis of unnatural pyrrole derivatives (Scheme 1c).

The study started by examining the reaction of yne-tethered



Scheme 1. a) Known cyclization protocols of ynamides, b) Radical-triggered cyclization and hypothesis, c) Current work. [Ts = SO_2*p*-Tolyl]

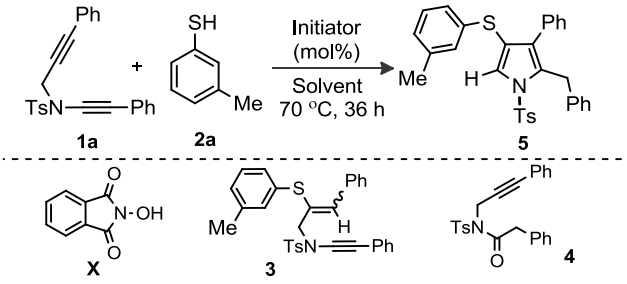
ynamide **1a** with 3-methylbenzenethiol (**2a**) and a radical initiator. The results are detailed in Table 1. When the reaction was performed in the presence of AIBN (1.5 equiv) in CH_3CN for 24 h at 70 °C, the desired product **5** was isolated in 40% yield along with the alkyne hydrothiolation compound **3** (15%), and the ynamide hydration product **4** (30%) (entry 1). This result encouraged us to screen other radical initiators. The oxidant $K_2S_2O_8$ (1.0 equiv) or *N*-hydroxyphthalimide (20 mol %) proved more efficient, affording **5** in 48% and 61% yield respectively, yet along with substantial amount of **3** (entries 2 and 3). In air and in the absence of initiator, **5** (30%) was also produced (entry 4). However, the reaction in DMF selectively provided **3** (entry 5), justifying the attack of the thiyl-radical to the propargyl alkyne moiety over the ynamide motif (DFT studies corroborate this observation, vide infra). The yield of **5** (78%) was enhanced when the reaction was conducted in dichloromethane (DCM) (entry 6). On the other hand, the reaction at 50 °C was less efficient (entry 7). The use of 1,2-dichloroethane (DCE), acetone, or toluene as solvent, or even neat conditions, also resulted in

[†] Shubham Dutta, Rajendra. K. Mallick, Rangu. Prasad and Prof. Dr. Akhila K. Sahoo, School of Chemistry, University of Hyderabad Hyderabad (India)
E-mail: akhilchemistry12@gmail.com
Homepage: http://chemistry.uohyd.ac.in/~aks/index.htm
[‡] Vincent Gandon, Institut de Chimie Moléculaire et des Matériaux d'Orsay, CNRS UMR 8182, Université Paris-Sud, Université Paris-Saclay, Bâtiment 420, 91405 Orsay cedex (France)
[¥] Vincent Gandon, Laboratoire de Chimie Moléculaire (LCM), CNRS UMR 9168, Ecole Polytechnique, Université Paris-Saclay, route de Saclay, 91128 Palaiseau cedex (France)

10.1002/anie.201811947

lower yields of **5** (entries 8–11). Only a trace of **5** was detected when the reaction was performed under inert atmosphere (entry 12). Use of phenyl disulfide radical source also did not provide the desired product (entry 13).

Table 1. Optimization of thiyl-radical triggered cyclization of yne-ynamides[a]



Entry	Initiator	(mol%)	Solvent	Yield (3/4/5) %
1	AIBN	150	CH_3CN	(15/30/40)
2	$K_2S_2O_8$	100	CH_3CN	(41/—/48)
3	X	20	CH_3CN	(31/—/61)
4	Air	--	CH_3CN	(—/40/30)
5	X	20	DMF	(75/—/10)
6	**X**	**20**	**CH_2Cl_2**	**(—/10/78)**
7	X	20	CH_2Cl_2, 50 °C	(—/10/40)
8	X	20	$ClCH_2CH_2Cl$	(—/25/63)
9	X	20	acetone	(40/—/50)
10	X	20	toluene	(—/25/40)
11	X	20	neat	(—/25/64)
12[b]	--	--	CH_2Cl_2	(—/—/trace)
13[c]	X	20	CH_2Cl_2	(05/—/00)

[a]Reaction condition: yne-ynamide **1** (0.3 mmol), thiophenol **2a** (0.75 mmol), initiator (0.06–0.45 mmol), solvent (0.5 mL) at 70 °C for 36 h. [b]Under inert atmosphere without **X**. [c]Phenyl disulfide (Ph_2S_2) (0.75 mmol) instead of **2a**. (Ts = SO_2*p*-Tol).

To probe the synthetic generality, reactions between various yne-ynamides (displaying substituents at the alkyne/ynamide terminus and *N*-PG) and thiol derivatives were carried out under the established conditions corresponding to Table 1, entry 6. The results are outlined in Figure 1. To start with, the aryl thiol derivatives **2a**–**h** [having *m*-Me (**2a**), *m*-OMe (**2b**), *p*-Me (**2c**), *p*-^{i}Pr (**2d**), *p*-^{t}Bu (**2e**), *p*-OMe (**2f**), *o*-Me (**2g**) and *o*-OMe (**2h**) substituents] were reacted with **1a**. The respective 2-benzyl-4-(thioaryl)-3-phenyl-1-tosyl-1*H*-pyrrole **5**–**12** were successfully produced in 72–84% yield (Figure 1a). Thiophenol (**2i**) reacted well with **1a** to afford **13** (88%). The halogenated aryl thiols [**2j** (*p*-Cl), **2k** (*p*-Br), **2l** (*o*-Br), **2m** (*m*-F)] did not affect the radical-triggered cyclization, as shown by the efficient formation of **14** (68%), **15** (80%), **16** (58%), and **17** (56%), respectively. Pyrroles **18** (66%) and **19** (80%) were obtained from the reaction of **1a** with sterically hindered β-naphthylthiol (**2n**) and 2,6-dimethyl thiophenol (**2o**). The unprotected OH group containing thiophenol (**2p**) reacted well to provide the desired product **20** (65%). On the other hand, the aliphatic ethanethiol did not react, presumably due to the poor stability of the alkyl thiyl radical.

The thiyl radical-triggered cyclization of yne-ynamides having substitution at the alkyne terminus was next probed (Figure 1b). Thus, the cyclization of **1b** [having *p*-Me-aryl motif at the propargyl terminus] with **2a** under the optimized conditions led to **21** in excellent yield (92%). Likewise, reaction of yne-ynamides possessing electron-rich aryl motifs at the propargyl terminus [*p*-OMe (**1c**), *o*-OMe (**1d**), *o*-Ph (**1e**), and *o*,*m*-*di*Me (**1f**)] with 2-methyl thiophenol (**2g**) delivered **22** (79%), **23** (72%), **24** (71%), and **25** (87%), respectively. The desired pyrrole derivatives **26**–**29** (62–91%) were readily isolated from the cyclization of **2g** with yne-ynamides having electron-withdrawing aryl groups at the propargyl terminus [*p*-COMe (**1g**), *m*-NO_2 (**1h**), *p*-F (**1i**), and *m*-F (**1j**)]. Besides, yne-ynamides having 2-Br/unprotected 2-NH_2 bearing aryls (**1k**/**1l**) reacted well with **2g**, providing **30** (90%) and **31** (51%), respectively. Thus, electronic and steric effects of the aryl moiety at the propargyl terminus of the yne-ynamides did not affect the reaction outcome. Moreover, electron-withdrawing (possibly radical inhibitors) halo/ester/nitro, and (possibly catalyst inhibitors) amino/hydroxyl groups never obstructed the reaction progress and productivity. Ynamides having alkyl moieties at the alkyne terminus resulted in complex mixtures; presumably due to the less stability of the vinyl radical generated in situ upon attack of thiyl radical to the alkyne.

Owing to the inherent *N*-lone pair polarization of the ynamide, the electron distribution could possibly affect the reaction outcome. To examine this, we used yne-ynamides having substituents with various steric and electronic properties at the ynamide terminus in the radical-triggered cyclization (Figure 1c). Thus, electron-rich [*p*-Me (**1m**), *o*-Ph (**1n**), and *m*,*p*-*di*Me (**1o**)], electron-poor [*p*-COMe (**1p**), *m*-CN (**1q**)], and halo-containing [*p*-F (**1r**), *o*-I (**1s**)] aryl moieties at the ynamide termini of **1** underwent cyclizations with **2g** to yield the corresponding 4-thioaryl substituted pyrroles [**32**–**38** (74–92%)]. Once again, the reaction proved successful irrespective of the electronic/steric effects of the functional groups at the periphery of the ynamide scaffold. Despite repeated attempts, the reaction of yne-ynamides having alkyl substituents at the ynamide terminus with **2g** failed to deliver the desired product **49a**. Only the hydrothiolation product was observed in such case. We hypothesized that the alkyl moiety inhibited the cyclization of the putative vinyl radical generated in situ upon the addition of the thiyl radical to the alkyne.

Next, the reaction of yne-ynamides (**1t**–**y**) with diverse substitutions (arenes bearing electron-withdrawing/electron-donating groups) at both the propargyl and ynamide terminus with **2a**/**2g** in the presence of *N*-hydroxyphthalimide successfully dispensed **39** (86%), **40** (82%), **41** (77%), and **42** (85%) (Figure 1d). Similarly, thienyl substituted pyrrole derivatives **43** (78%) and **44** (73%) were synthesized. Yne-ynamides **1z** and **1aa** with different *N*-protecting groups [*N*-SO_2Ph / *N*-Ms (mesyl)] took part in this thiyl radical-mediated cyclization and delivered the corresponding *N*-SO_2Ph (**45**), *N*-Ms (**46**) derived pyrroles in appreciable yields.

Finally, the utility of this thiyl radical-triggered cyclization of yne-ynamides was demonstrated in the synthesis of tetra-substituted pyrrole derivatives (Figure 1d). This can be realized from yne-ynamides having alkyl substituents at the propargyl sp^3-carbon. Gratifyingly, the desired 2-Me substituted pyrrole scaffolds **47**/**48** were constructed from the cyclization of **1ab/1ac** with **2g** under the established conditions. Moreover, the reaction of **2g** with **1ad** (having an alkyl moiety at the ynamide terminus and 2-Me substitution in the propargyl side) produced **49**, albeit in a moderate 47% yield.

To gain some insights into the reaction mechanism, the reaction between **1a** and *p*-chlorobenzenethiol (**2j**) in the presence of N-

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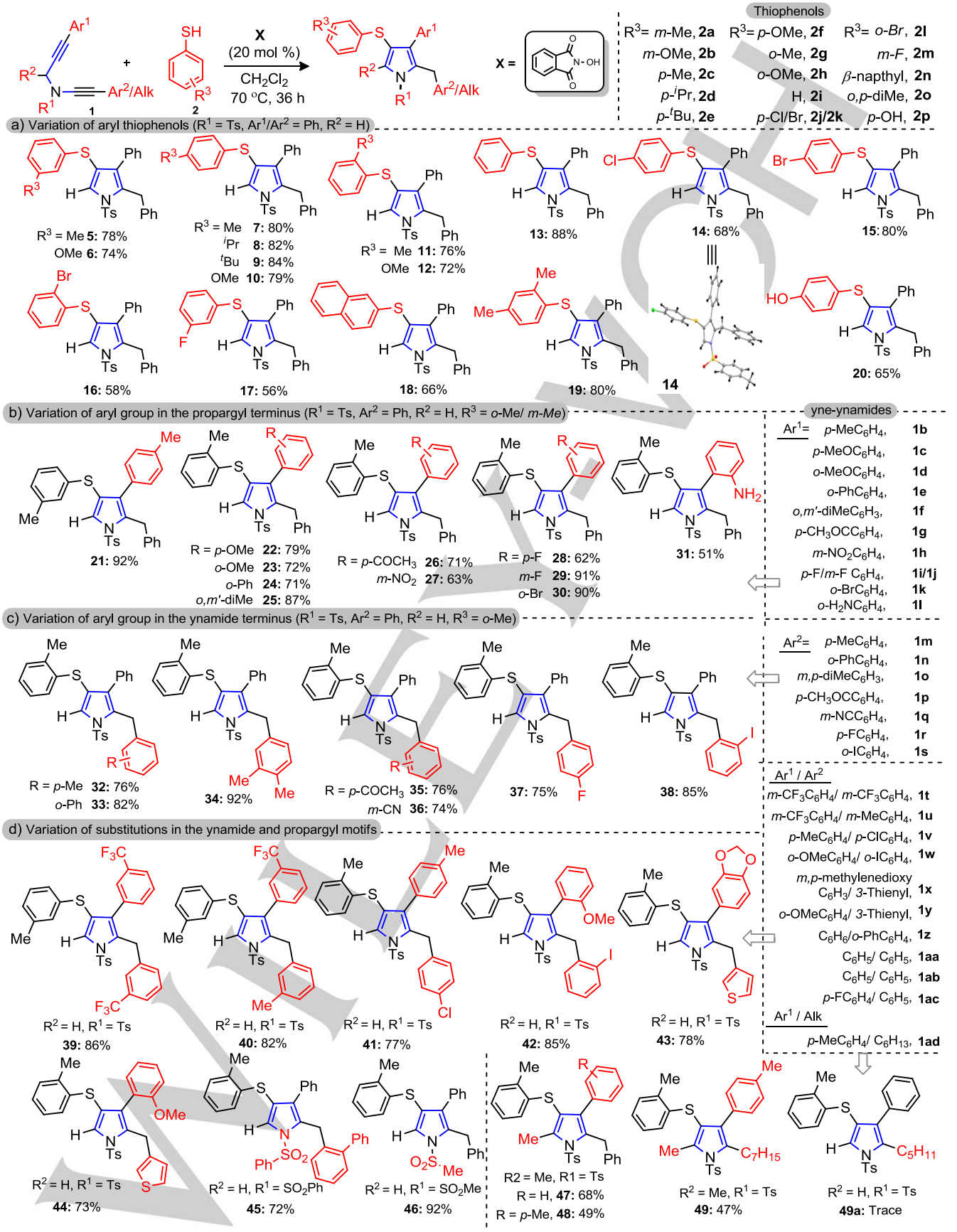

Figure 1. Scope of thiyl radical triggered cyclization of yne-ynamides (synthesis of 4-thioaryl-pyrroles). [Ts = SO_2*p*-Tolyl]

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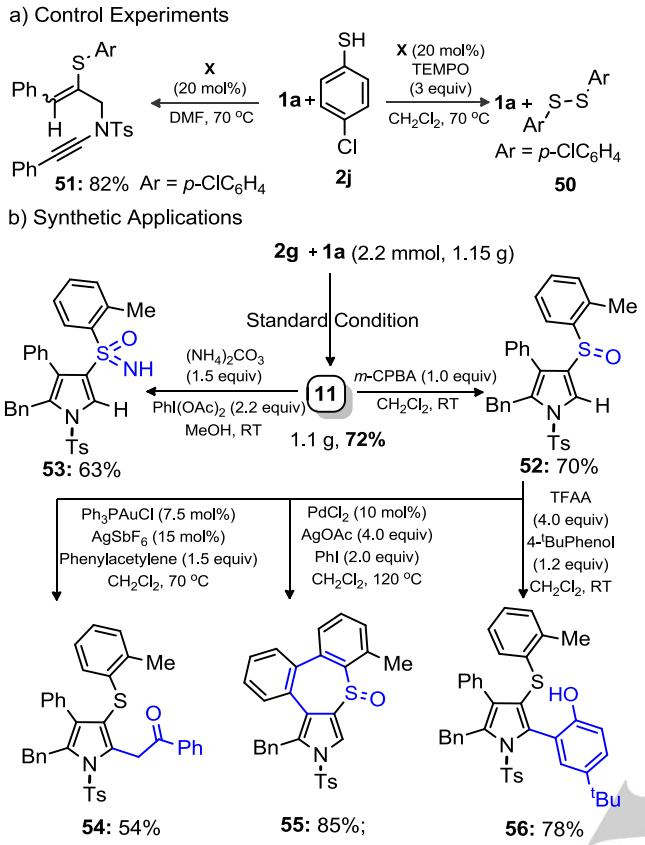

Scheme 2. Control Experiments and Synthetic Applications. [DMF = *N*,*N*-dimethylformamide, *m*-CPBA = *meta*-chloroperbenzoic acid, TFAA = trifluoroacetic anhydride]

hydroxyphthalimide and the radical scavenger TEMPO under the standard reaction conditions was performed. The respective bis(4-chlorophenyl)disulfane **50** was exclusively produced, leaving **1a** untouched (Scheme 2a). On the other hand, the same reaction in DMF at 70 ºC produced the hydroathiolation product **51** (82%). Thus, the attack of the thiyl radical across the alkyne initiates the reaction (DFT studies support this observation, see the SI; Scheme S2 and Table S2). The robustness of the catalytic system has been tested in the gram scale synthesis of **11** (1.1 g, 72%) from **1a** (1.15 g, 2.2 mmol) and **2g** (6.6 mmol) (Scheme 2b).

The reactivity of **11** was further explored through the *m*-CPBA assisted oxidation of the S-atom to the corresponding sulfoxide **52** (70%), and the direct synthesis of sulfoximine **53** (63%) (Scheme 2b).[7] The reaction of sulfoxide **52** with phenyl acetylene in presence of Ph_3PAuCl (7.5 mol%) and $AgSbF_6$ (15 mol%) provided the alkylation product **54**.[8] The cross-dehydrogenative-coupling of **52** led to the unusual [6,7]-fused thiepino-pyrrole **55** in 85% yield.[9] Exposing **52** to *p*-^{t}Bu-phenol in presence of TFAA delivered the arylation product **56** via Pummerer-type transformation.[10]

To validate a radical cyclization pathway and rationalize the selective formation of 4-thioaryl-pyrroles, DFT computations were carried out using the Gaussian 09 software package (see the SI for details).[11,12] In principle, four sites of the two yne units

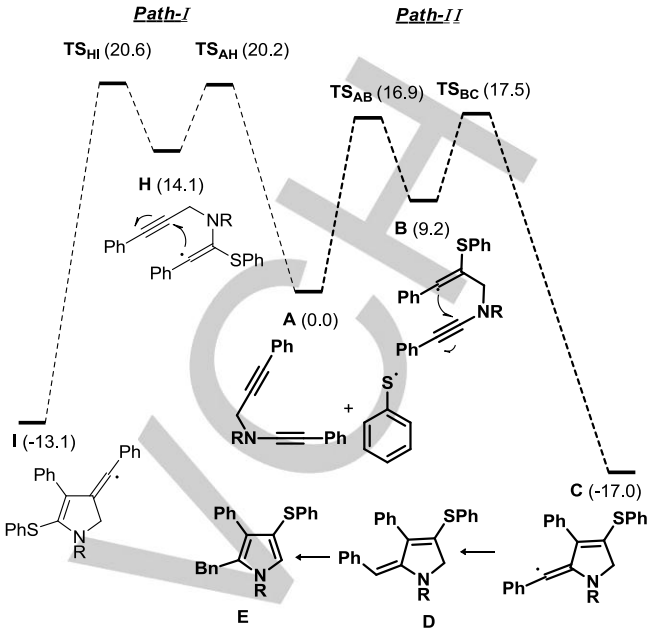

Figure 2. Computed Free Energy Profile [ΔG_{343}, kcal/mol; R = SO_2Ph]

of the yne-ynamide scaffold are available for the attack of the thiyl radical,[13] which would eventually result in eight different products on the basis of specific *exo*/*endo*-mode of cyclization. All these possibilities have been investigated and are presented in the Supporting Information (Schemes S2, S4, Table S3). Only radical additions via 5-*exo*-dig cyclizations, which turn out to be the best computational options, are discussed here. The values are ΔG_{343} in kcal/mol obtained at the UB3LYP[14]/6-311++G(d,p)[15] level including solvent correction for CH_2Cl_2 (PCM method[16]) (Figure 2). The B3LYP functional remains widely used in the computational study of radicals.[17] Starting from system **A** comprising a model yne-ynamide and the benzothiyl radical, two pathways can provide pyrroles. The radical can attack the internal propargyl alkyne carbon to give **B**,[18] which then undergoes a 5-*exo*-dig cyclization to yield **C**.[19] The first step is endergonic by 9.2 kcal/mol, and the second one is exergonic by 17.0 kcal/mol. The corresponding transition states have free energies of 16.9 and 17.5 kcal/mol.[20] Radical **C** is then likely to abstract a hydrogen atom from thiophenol to give **D**. The latter should then easily tautomerize to the aromatic 4-thioaryl-pyrrole **E**, which displays the experimentally observed regiochemistry. If the benzothiyl radical attacks the internal ynamide carbon, vinyl radical **H** would be formed. Its transformation into the 5-membered ring radical **I**, which displays an unobserved 2-thio regioselectivity, was then modeled through a 5-*exo*-dig cyclization. Both inter- and intramolecular radical additions leading to **I** are more difficult to achieve than those providing **C**. Indeed, the corresponding transition states have free energies of 20.2 and 20.6 kcal/mol. The preference for $\mathbf{TS_{AB}}$ over $\mathbf{TS_{AH}}$ can be rationalized on the basis of electronic and steric effects (see the SI). Despite our effort, we could not find an energetically reasonable pathway for the selective formation of **3** over **5** in DMF (see the SI).[21] In spite of a good match between our method and the known calculated BDE of

thiophenol (see the SI),[22, 23] the computed mechanism remains to be validated.

In summary, a metal-free regioselective radical cyclization of arylthiols with yne-tethered ynamides to fully substituted 4-thioaryl-pyrroles has been developed. The transformation involves an attack of a thiyl radical to the alkyne motif, followed by the cyclization with the ynamide core. The preferred reactivity of an alkyne over an ynamide, although previously observed, remains a rare case. The transformation is general, exhibiting a broad substrate scope and high functional group tolerance (the free NH_2, OH groups and the common radical trap electron-withdrawing groups did not affect the reaction outcome). Control experiments suggest the involvement of radical intermediates. Preliminary DFT calculations support the reaction pathway involving the alkyne moiety as the most reactive part of the yne-ynamide. Implementation of this method for the synthesis of complex molecules of biological significance and detailed mechanistic studies are currently underway. We believe these findings would open new avenues for discovering novel methods in yne/allene/olefin tethered ynamides.

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Keywords: • Radical cyclisation • alkyne reactivity preferred over ynamide • 5-*exo*-dig cyclization • 4-thioaryl-pyrrole

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[20] For computations on the intermolecular addition of a sulfonyl radical to the alkyne moiety of a cyano-yne substrate, followed by 5-*exo*-dig cyclization of vinyl radical to the C≡N fragment, see: K. Sun, X.-L. Chen, S.-J. Li, D.-H. Wie, X.-C. Liu, Y-.L. Zhang, Y. Liu, L.-L. Fan, L.-B. Qu, B. Yu, K. Li, Y.-Q. Sun, Y.-F. Zhao, *J. Org. Chem*. **2018**, *83*, 14419. In this case as in ours, the first step is endergonic.

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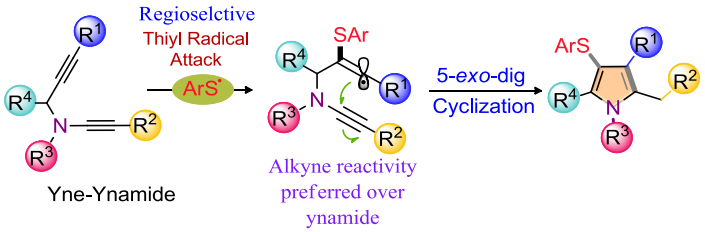

Shubham Dutta, Rajendra K. Mallick, Rangu Prasad, Vincent Gandon, and Akhila K. Sahoo

Alkyne Reactivity Preferred over Ynamide: Regioselective Radical Cyclization of Yne-Ynamides

Discussed herein is an unprecedented radical cyclization of arylthiols with alkyne-tethered ynamides to highly-substituted 4-arylthio-pyrroles. The transformation involves an unusual attack of a thiyl radical to the alkyne motif followed by the cyclization with the ynamide core, showcasing the reactivity of an alkyne preferred over an ynamide. Density functional theory (DFT) studies support the proposed mechanism.