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A 1,3-amino group migration route to form acrylamidines†

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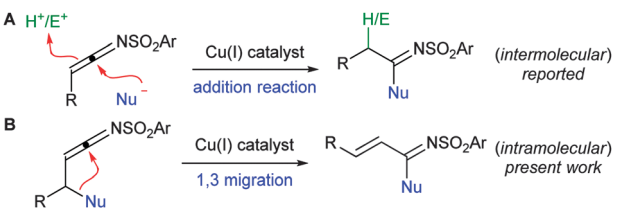
Dinesh Pratapsinh Chauhan, Sreejith Jayasree Varma, Arjun Vijeta, Pallavi Banerjee and Pinaki Talukdar*

A novel 1,3-amino group migration strategy for the synthesis of acrylamidines is presented. Cu(I) catalyzed reaction of *N,N*-disubstituted propargylamine with tosylazide generates a highly reactive ketenimine intermediate which is trapped by a tethered amino group leading to the rearrangement reaction.

Click chemistry,[1] primarily known for the synthesis of triazoles *via* the copper-catalyzed cycloaddition reaction between alkyl or aryl azides and terminal alkynes,[1a,2,3] has provided colossal applications in the fields of bioconjugation,[4] materials science,[5] and drug discovery.[2a,6] Soon after its discovery, a novel feature of triazole as a N_2 releasing source was disclosed.[7] In particular, either sulfonyl azides[7b] or phosphoryl azides[8] were demonstrated to react with terminal alkynes under mild Cu(I)-catalytic conditions to form a highly reactive ketenimine intermediate which instantaneously participates in nucleophilic addition reactions[9] with amines,[7b] water,[10] alcohols,[11] pyrroles,[12] indoles,[12,13] ammonium salts,[14] *etc.* (Scheme 1A). This three-component approach was further extended to the four-component version by the introduction of either strong electrophiles *e.g.* aldehyde[15] or Michael acceptors *e.g.* nitro olefins.[16]



Scheme 1 Participation of ketenimine in addition reaction with an external nucleophile (A) and 1,3-migration of a tethered nucleophile (B).

Department of Chemistry, Mendeleev Block, Indian Institute of Science Education and Research, Pune, India. E-mail: ptalukdar@iiserpune.ac.in; Fax: +91 20 2589 9790; Tel: +91 20 2590 8001

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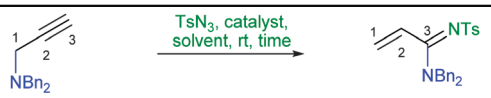
Herein, we report the reaction of the *in situ* generated ketenimine with a tethered amino nucleophile to form acrylamidine *via* the 1,3-migration of the amino group (Scheme 1B). Acrylamidine[17] is an important skeleton for atropisomerism studies.[18] It is also a synthetic precursor of amidine which is present in various bioactive compounds,[19] *e.g.* selective muscarinic agonists,[20] NR2B subtype-selective antagonists,[21] *etc.* Considering the wide synthetic applicability of amidine,[19,22] the α,β-unsaturation can be viewed as a handle for various chemical transformations *e.g.* epoxidation, hydroxylation, C=C cleavage, Michael addition, *etc.* In 2005, Chang and coworkers reported nucleophilic addition of water to ketenimine bearing a tethered –NHBoc group to form the corresponding β-amino sulfonamide.[10] We envisaged the potential of the tethered amino group to undergo 1,3-shift if it is made sufficiently nucleophilic because Wentrup *et al.* have reported a ketenimine–ketene rearrangement mediated by a flanking amino group under flash vacuum thermolysis conditions.[23] However, Cu(I)-catalytic formation of ketenimine is advantageous to investigate the 1,3-shift under milder reaction conditions.

The results are shown in Table 1. When *N,N*-dibenzylpropargylamine **1** was treated with 1.1 equivalents of tosylazide in $CHCl_3$ under open air conditions in the presence of a CuI catalyst (10 mol%) and Et_3N base at room temperature, the reaction proceeded up to 30 minutes, forming acrylamidine **2** in 84% yield (entry 1). The structure of **2** was confirmed by NMR (Fig. S50 and S51, ESI†) and single crystal X-ray diffraction studies (Fig. S1, ESI†).

Table 1 Cu(I)-catalyzed formation of acrylamidine **2**



Entry	Catalyst	Solvent	Base	Time (min)	Yield (%)
1	CuI	$CHCl_3$	Et_3N	30	84
2	CuBr	$CHCl_3$	Et_3N	3	95
3	CuCl	$CHCl_3$	Et_3N	3	96
4	—	$CHCl_3$	—	30	0
5	CuCl	$CHCl_3$	—	30	60
6	—	$CHCl_3$	Et_3N	30	0

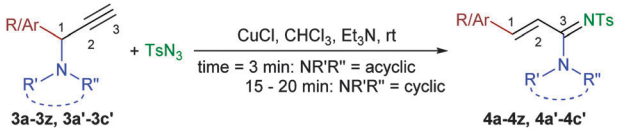
Introduction of a CuBr catalyst (10 mol%) facilitated the reaction within 3 minutes and improving the yield to 95% (entry 2). A further alteration of the catalyst to CuCl (10 mol%) resulted in 96% yield of **2** (entry 3). Formation of **2** was not favored in the absence of CuCl confirming the importance of the catalyst (entries 4 and 6). The catalytic reaction when carried out in the absence of Et_3N proceeded for 30 minutes and furnished **2** with only 60% yield (entry 5).

To establish the scope of methodology, the optimized conditions were applied to a wide range of propargylamines **3a–3j** having alkyl substitution (R = alkyl) at the C_1-position and acyclic amino groups (–NR′R″) to deliver corresponding acrylamidines **4a–4j** (Table 2, entries 1–10). The effect of different R groups was studied by keeping fixed –NR′R″ = $–NBn_2$ and no significant difference was observed upon variation of the group through ethyl (entry 1, yield = 96%), butyl (entry 2, yield = 91%), cyclohexyl (entry 3, yield = 91%) and (*S*)-2,2-dimethyl-1,3-dioxolane (entry 4, yield = 95%). A subsequent modification of the amino group (–NR′R″ = $–NEt_2$) did not affect the time and yields of reactions. Excellent yields of 95%, 96%, 96% and 89% for R = Et (entry 5), Bu (entry 6), cyclohexyl (entry 7) and (*S*)-2,2-dimethyl-1,3-dioxolane (entry 8), respectively, were observed. Introduction of an unsymmetrical amino group (–NR′R″ = –NMeBn) also did not affect the yield of the acrylamidine **4i** (entry 9, yield = 93%). When the effect of neighboring nucleophilic groups was evaluated by introducing a di-hydroxy containing R-group, the desired product **4j** was obtained in moderate 60% yield (entry 10). However, no byproduct that corresponds to the attack of an alcohol nucleophile on a ketenimine intermediate was isolated.

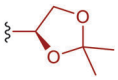
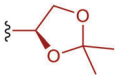
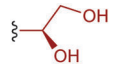
On the basis of these findings, we explored the effect of cyclic amino groups such as pyrrolidine, piperidine and morpholine in the formation of acrylamidines. It was found that reactions of propargylamines **3k–3r** with tosylazide were relatively slow (reaction time = 15–20 min) under the optimized conditions using CuCl (Table 2, entries 11–18). When pyrrolidine containing propargylamines, **3k** and **3l** were used, moderate yields of **4k** (58%) and **4l** (70%), respectively, were observed (entries 11 and 12). For piperidine ring containing propargylamines **3m**, **3n** and **3o** isolated yields were significantly low, *i.e.* 48%, 51% and 63%, respectively, (entries 13–15). When propargylamines **3p**, **3q** and **3r** having a morpholine ring were treated with tosylazide a significant improvement in yields, *i.e.* 83% for **4p**, 85% for **4q** and 83% for **4r** was observed (entries 16–18).

To expand the scope of the methodology, we evaluated the effect of aromatic groups at the C_1-position by introducing propargylamines **3s–3z** and **3a′–3c′** (Table 2, entries 19–29). In these cases, reactions were completed within 3 minutes. For substrates **3s** (Ar = Ph) and **3t** (Ar = C_6H_4-*p*-Me), reactions provided 96% and 93% yields of **4s** and **4t**, respectively, (entries 19 and 20). For aryl groups consisting of an electron donating –OMe substituent at *ortho*-, *meta*- and *para*-positions, reactions proceeded smoothly with excellent yields of **4u** (89%), **4v** (96%), and **4w** (95%), respectively (entries 21–23). On the other hand, introduction of strong electron withdrawing substituents *e.g. ortho*-NO_2, *meta*-NO_2 and *para*-CN resulted in slightly lower yields of **4x** (80%), **4y** (75%) and **4z** (71%), respectively, (entries 24–26). However, a weak electron withdrawing *meta*-Br substituent did not affect the yield of **4a′** (entry 27, yield = 96%). When extended aromatic groups (Ar = α-naphthyl and 1-pyrenyl) were introduced reactions provided excellent yields of **4b′** (96%) and **4c′** (98%), respectively.

Table 2 Scope of the 1,3-amino group migration strategy



3a-3z, 3a'-3c' 4a-4z, 4a'-4c'

Entry	3	§—R/Ar	§—NR′R″	4	Yield (%)
1	**3a**	§—Et	§—NBn_2	**4a**	96
2	**3b**	§—Bu	§—NBn_2	**4b**	91
3	**3c**	§—Cy	§—NBn_2	**4c**	91
4	**3d**		§—NBn_2	**4d**	95
5	**3e**	§—Et	§—NEt_2	**4e**	95
6	**3f**	§—Bu	§—NEt_2	**4f**	96
7	**3g**	§—Cy	§—NEt_2	**4g**	96
8	**3h**		§—NEt_2	**4h**	89
9	**3i**	§—H	§—NMeBn	**4i**	93
10	**3j**		§—NBn_2	**4j**	60
11	**3k**	§—Bu	§—*N*-pyrrolidine	**4k**	58
12	**3l**	§—Cy	§—*N*-pyrrolidine	**4l**	70
13	**3m**	§—H	§—*N*-piperidine	**4m**	48
14	**3n**	§—Bu	§—*N*-piperidine	**4n**	51
15	**3o**	§—Cy	§—*N*-piperidine	**4o**	63
16	**3p**	§—H	§—*N*-morpholine	**4p**	83
17	**3q**	§—Bu	§—*N*-morpholine	**4q**	85
18	**3r**	§—Cy	§—*N*-morpholine	**4r**	83
19	**3s**	§—Ph	§—NEt_2	**4s**	96
20	**3t**	§—(C_6H_4-*p*-Me)	§—NEt_2	**4t**	93
21	**3u**	§—(C_6H_4-*o*-OMe)	§—NBn_2	**4u**	89
22	**3v**	§—(C_6H_4-*m*-OMe)	§—NBn_2	**4v**	96
23	**3w**	§—(C_6H_4-*p*-OMe)	§—NEt_2	**4w**	95
24	**3x**	§—(C_6H_4-*o*-NO_2)	§—NBn_2	**4x**	80
25	**3y**	§—(C_6H_4-*m*-NO_2)	§—NBn_2	**4y**	75
26	**3z**	§—(C_6H_4-*p*-CN)	§—NBn_2	**4z**	71
27	**3a′**	§—(C_6H_4-*m*-Br)	§—NBn_2	**4a′**	96
28	**3b′**	§—(α-naphthyl)	§—NEt_2	**4b′**	96
29	**3c′**	§—(1-pyrenyl)	§—NEt_2	**4c′**	98

Variable temperature ^{1}H- (Fig. 1, Fig. S110, ESI†) and ^{13}C-NMR (Fig. S111, ESI†) experiments were carried out for **4t** to resolve the slow rotamer interconversion and thus broadening of peaks was observed at room temperature.

A plausible mechanism for the formation of acrylamidine from *N*,*N*-disubstituted propargylamine is depicted in Scheme 2. *N*-Sulfonyl triazolyl copper intermediate **I**, formed upon reaction of propargylamine with tosylazide, releases one molecule of N_2 and undergoes protonation to generate ketenimine **II**.[7a,c] Subsequent transformation of **II** to **IV** occurs in two steps. At first a 4-*exo*-*dig* cyclization of **II** generates the intermediate **III**. The tethered nitrogen (N_1) due to its available lone pair facilitates the attack on the highly

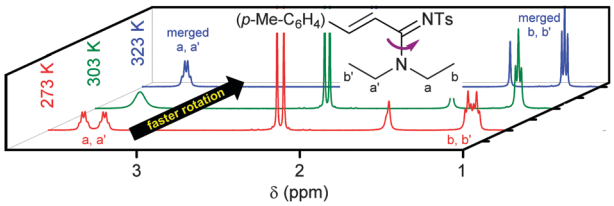
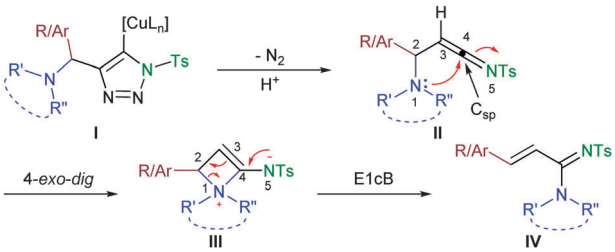


Fig. 1 Variable temperature ^{1}H-NMR (400 MHz) of **4t** in $CDCl_3$.



Scheme 2 Plausible mechanism for the formation of acrylamidine.

electrophilic C_4-center. The formation of **III** is also favored due to delocalization of the negative charge on the N_5-center by a sulfonyl group. A subsequent E1cB elimination type ring opening process results in the formation of **IV**. Generation of **III** from **II** is considered as the rate determining step due to formation of a strained 4-membered ring from an acyclic system. This prediction was supported by longer reaction times of cyclic amino group containing propargylamines **3k–3r** and poorer yields of the corresponding products **4k–4r**. In these cases, formation of spiro-transition states contributes to the slower reaction rates. The preferential *E*-stereochemistry around the C=C bond as predicted by the mechanism was confirmed by NMR and single crystal X-ray diffraction studies of **4d** (Fig. S2, ESI†) and **4w** (Fig. S4, ESI†).

Pyrene-based propargylamine **3c′** (10 μM) displayed a λ_{max} = 353 nm. When an aliquot from the completed reaction mixture of **3c′** and TsN_3 (Table 2, entry 29) was diluted suitably (to obtain ~10 μM concentration of **4c′**) in HEPES buffer (10 mM, pH = 7.4), the resulting solution exhibited a λ_{max} = 375 nm (*i.e.* 22 nm red shift) due to the formation of more conjugated **4c′** (Fig. 2A). Formation of more conjugated **4c′** was also marked by the change in fluorescence from cyan to green (Fig. 2B).

In conclusion, we have demonstrated a new reaction of ketenimine bearing a tethered amino group facilitating its 1,3-migration. The methodology portrays rapid reactions of *N,N*-disubstituted propargylamines with tosylazide under CuCl catalytic, open air conditions to synthesize acrylamidines. For propargylamines with an alkyl/aryl substituent at the C_1-position, products were isolated in moderate to excellent yields. However, for *N,N*-cyclic substituted propargylamines, reactions were slower and isolated yields were also affected. The 1,3-migration of amine was predicted *via* a 4-*exo*-*dig* cyclization followed by an E1cB elimination type ring opening step. With a pyrene chromophore at the C_1-position, the formation of a more conjugated product was demonstrated by 22 nm red shift of λ_{max} and change in fluorescence from cyan to green.

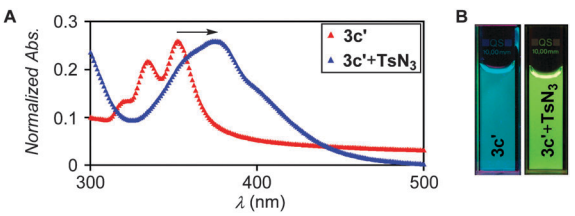


Fig. 2 UV-visible spectra of **3c′** (10 μM) in the absence and in the presence of 10 μM TsN_3 (A); images of cuvettes containing either **3c′** (50 μM) or [**3c′** + TsN_3] taken under the hand-held UV (λ_{ex} = 365 nm) lamp (B).

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Notes and references

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