



# An efficient synthetic route to substituted tetrahydropyrimidines by Cu(OTf)<sub>2</sub>-mediated nucleophilic ring-opening followed by the [4+2] cycloaddition of *N*-tosylazetidines with nitriles

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## ABSTRACT

A highly efficient strategy for Cu(OTf)<sub>2</sub>-mediated S<sub>N</sub>2 type nucleophilic ring-opening followed by the [4+2] cycloaddition reactions of a number of 2-aryl-*N*-tosylazetidines with nitriles to afford a variety of substituted tetrahydropyrimidines in excellent yields is reported. The resulting tetrahydropyrimidines could easily be transformed into synthetically important 1,3-diamines by acid-catalyzed hydrolysis. The strategy has been extended to the synthesis of enantiomerically pure tetrahydropyrimidines from enantiopure disubstituted azetidines. The reaction proceeds through an S<sub>N</sub>2 type mechanism as proposed by us earlier.

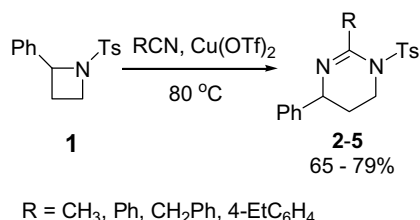
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Small-ring aza-heterocycles are valuable building blocks in organic synthesis.<sup>1</sup> Cycloaddition reactions of four-membered aza-heterocycles with various dipolarophiles are of contemporary interest due to the potential biological activities of the resulting heterocycles.<sup>2</sup> There are only a few successful reports for the cycloaddition of azetidines with different dipolarophiles employing BF<sub>3</sub>·OEt<sub>2</sub> and a Pd(II) complex as the catalysts.<sup>3</sup> We recently reported Zn(OTf)<sub>2</sub>-mediated cycloaddition of 2-aryl-*N*-tosylazetidines with a variety of nitriles to synthesize substituted tetrahydropyrimidines.<sup>4</sup> However, the Zn(OTf)<sub>2</sub>-mediated reaction was found to be sluggish especially with 2-aryl-*N*-tosylazetidines having electron-withdrawing substituents in the aryl ring compared to that of 2-phenyl-*N*-tosylazetidine. We have recently found Cu(OTf)<sub>2</sub> an efficient Lewis acid (LA) to effect the [4+2] cycloaddition of carbonyls with enantiopure 2-phenyl-*N*-tosylazetidine to give non-racemic oxazinanes in moderate to high enantiomeric excess.<sup>5</sup> Based on the experimental results, we proposed an alternative S<sub>N</sub>2 type of mechanism for this transformation in contrast to the earlier proposed mechanism involving a 1,4-dipole.<sup>3a–c</sup> Similar results were obtained for the [3+2] cycloaddition of *N*-sulfonylaziridines with nitriles<sup>6a</sup> and carbonyls.<sup>6b</sup> Cu(OTf)<sub>2</sub> is an efficient catalyst in the organic synthesis for effecting several transformations, for example, oxidations of alkyl radicals,<sup>7</sup> aziridinations,<sup>8</sup>

asymmetric conjugate additions,<sup>9</sup> asymmetric Mannich-type reactions,<sup>10</sup> oxidative couplings,<sup>11</sup> asymmetric Friedel–Craft reactions,<sup>12</sup> and cycloaddition reactions.<sup>13</sup> Moreover, Cu(OTf)<sub>2</sub> can easily be prepared by following a known method,<sup>7</sup> and can be handled in air for quick transfer. In continuation of our research activities in Lewis acid-mediated S<sub>N</sub>2 type ring-opening of small-ring aza-heterocycles, we found Cu(OTf)<sub>2</sub> an efficient LA for the [4+2] cycloaddition reaction of *N*-tosylazetidine with nitriles.<sup>14</sup> We report, herein, Cu(OTf)<sub>2</sub>-mediated S<sub>N</sub>2 type nucleophilic ring-opening followed by [4+2] cycloaddition reactions of a number of 2-aryl-*N*-tosylazetidines with nitriles to afford a variety of substituted tetrahydropyrimidines in excellent yields.

We initially examined the cycloaddition of 2-phenyl-*N*-tosylazetidine **1** with acetonitrile as the solvent in the presence of Cu(OTf)<sub>2</sub>. When **1** was treated with acetonitrile in the presence of 1.0 equiv of Cu(OTf)<sub>2</sub> at 80 °C, the corresponding tetrahydropyrimidine **2** was obtained in excellent yield within 10 mins.<sup>15</sup> The progress of the reaction was comparatively slow when the reaction was performed at lower temperatures, or by taking smaller amounts of LA. Under optimal conditions,<sup>16</sup> **1** was reacted with various nitriles (Scheme 1) to give the corresponding tetrahydropyrimidines **2–5** in good to excellent yields (Table 1). The reaction was studied with an equivalent amount of acetonitrile in DCM, THF, CHCl<sub>3</sub>, and benzene as the solvent. In all these cases, azetidine **1** underwent a competitive ring-opening rearrangement to produce allylamine **6** as a byproduct with a poor yield of cycloaddition

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**Scheme 1.**  $\text{Cu(OTf)}_2$ -mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with nitriles.

product **2** as shown in Scheme 2. The  $\text{Cu(OTf)}_2$ -mediated rearrangement of 2-aryl-*N*-tosylazetidine leading to allylamine has been described in our earlier work.<sup>17</sup>

Further, to study the effect of the 2-aryl group on the  $\text{Cu(OTf)}_2$ -mediated [4+2] cycloaddition with nitriles, a number of azetidines **7–10** with different aryl groups were prepared following our reported procedure<sup>4</sup> and studied for a cycloaddition reaction with nitriles. Under optimal conditions, all azetidines underwent a smooth cycloaddition reaction with nitriles to give tetrahydropyrimidine derivatives **11–17**. The results are shown in Table 2. When 2-(4-methoxyphenyl)-1-(phenylsulfonyl)azetidine **10** (Table 2, entry 7) was reacted with benzonitrile under the same conditions, tetrahydropyrimidine derivative **17** was produced within 1 min or even at rt within 10 min. In contrast, 2-(3-bromophenyl)-1-tosylazetidine **9** (Table 2, entry 5) reacted with acetonitrile slowly under the same conditions to provide tetrahydropyrimidine **15** in 63% yield along with the corresponding allylamine (15%).

Although we have demonstrated earlier that the LA-mediated nucleophilic ring-opening of 2-phenyl-*N*-tosylazetidine follows an

$\text{S}_{\text{N}}2$  pathway,<sup>5</sup> the mechanism of the cycloaddition reaction with nitriles was further investigated. Enantiomerically pure (*S*)-**1** was reacted with acetonitrile as the solvent in the presence of  $\text{Cu(OTf)}_2$  at rt for 1 h to produce non-racemic tetrahydropyrimidine **2** in 38–40% ee with 10% isolated yield (95% brsm). When the reaction was continued for 4 h, **2** was obtained in 23% ee with 60% isolated yield indicating the decrease in ee of **2** with increasing time. These observations are in support of our earlier proposed mechanism for the cycloaddition reaction as shown in Scheme 3.  $\text{Cu(OTf)}_2$  is coordinated to the nitrogen atom of heterocycle **18** and generates a highly reactive species **19**. Subsequently, it undergoes a [4+2] cycloaddition reaction with the nitrile to provide non-racemic tetrahydropyrimidine **22**. We rationalized the reduced enantioselectivity of **2** due to the partial racemization of (*S*)-**1** (through the interconversion of **19** and **21**) before the nucleophilic ring-opening step, as shown in Scheme 3. Convincing evidence to support this mechanistic proposal has been provided in our earlier work.<sup>18</sup>

The cycloaddition products were found to be very labile, and gave hydrolyzed products 1,3-diamines under acidic conditions. Various tetrahydropyrimidines on treatment with 1(N) HCl produced corresponding 1,3-diamines **23–26** in good yields (Table 3).<sup>19</sup> 1,3-diamines are useful intermediates in organic synthesis.<sup>20</sup> Moreover, 1,3-diamines are important structural units present in a number of peptidomimetic inhibitors of the HIV-1 protease, used for the treatment of AIDS.<sup>21</sup>

The scope of the methodology was further extended for the cycloaddition of enantiomerically pure *cis*-disubstituted azetidines<sup>22</sup> **27a–b** with acetonitrile to give highly substituted enantiopure tetrahydropyrimidines **28a–b** and **29a–b** in 80% combined yield with 4,6-*trans* geometry (**28a–b**) as the major diastereomer in both the cases (Scheme 4). The diastereomers **28** and **29** were obtained in pure forms by simple column chromatography. The

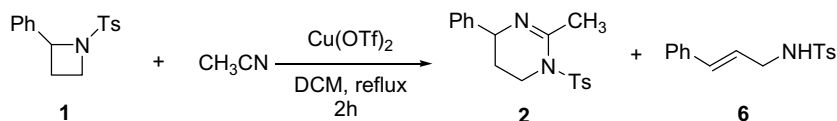
**Table 1**  
 $\text{Cu(OTf)}_2$ -mediated [4+2] cycloaddition of 2-phenyl-*N*-tosylazetidine with different nitriles<sup>a</sup>

Entry	Azetidine	Nitrile	Product (2–5)	Time (min)	Yield <sup>b</sup> (%)
1		$\text{CH}_3\text{CN}$		10	79 (95%) <sup>c</sup>
2		$\text{PhCN}$		10	72
3		$\text{Ph CH}_2\text{CN}$		10	68
4		$4\text{-EtC}_6\text{H}_4\text{CN}$		10	65

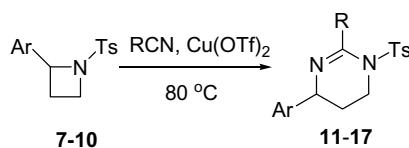
<sup>a</sup> In all the cases nitrile was served as solvent.

<sup>b</sup> Isolated yield after column chromatographic purification.

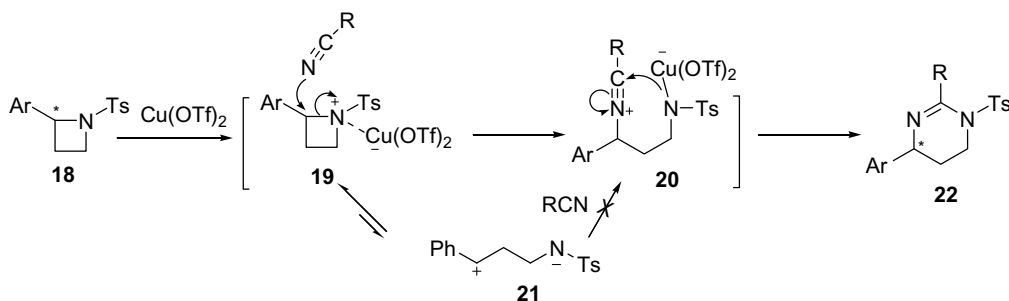
<sup>c</sup> Yield was determined by  $^1\text{H}$  NMR analysis of the crude reaction mixture.



**Scheme 2.** Competitive ring-opening reaction of 2-phenyl-*N*-tosylazetidine with acetonitrile in DCM as a solvent.

**Table 2**Cu(OTf)<sub>2</sub>-mediated [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with acetonitrile and benzonitrile<sup>a</sup>

Entry	Azetidine ( <b>7-10</b> )	Nitrile	Product ( <b>11-17</b> )	Time (min)	Yield <sup>b</sup> (%)
1		CH <sub>3</sub> CN		30	68
2		PhCN		20	62
3		CH <sub>3</sub> CN		10	72
4		PhCN		10	70
5		CH <sub>3</sub> CN		180	63
6		PhCN		20	70
7		PhCN		10 <sup>c</sup>	55

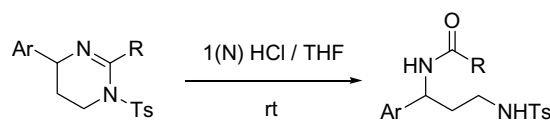
<sup>a</sup> In all the cases nitrile was served as solvent.<sup>b</sup> Isolated yield after column chromatographic purification.<sup>c</sup> Reaction was performed at rt.**Scheme 3.** Proposed mechanism for the [4+2] cycloaddition of 2-aryl-*N*-tosylazetidine with nitriles.

diastereomeric ratio was determined by the isolated yields of both the diastereomers (**28** and **29**) from column chromatography and <sup>1</sup>H NMR of the crude reaction mixture. The relative stereochemistry of the chiral substituted tetrahydropyrimidines (**28a** and **29a**) was determined by NOE measurements. The relative stereochemistry of the starting azetidines **27a–b** at C4 had been inverted in the major cycloaddition products (**28a–b**), which clearly supports the involvement of an S<sub>N</sub>2 type pathway during a cycloaddition reaction.

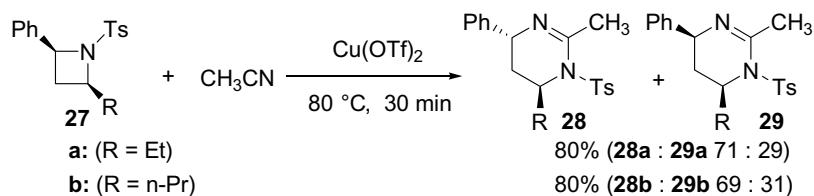
In conclusion, we have demonstrated a novel Cu(OTf)<sub>2</sub>-mediated [4+2] cycloaddition of 2-aryl-*N*-tosyl azetidines with nitriles for a direct one-step synthesis of substituted tetrahydropyrimidines. The cycloaddition reaction proceeds through an S<sub>N</sub>2 type pathway as we proposed earlier. The strategy has been extended for the synthesis of enantiomerically pure tetrahydropyrimidines. Acid-catalyzed hydrolysis of tetrahydropyrimidines leads to the formation of 1,3-diamines. Further synthetic and mechanistic investigations are currently underway in our laboratory.

**Table 3**

Hydrolysis of tetrahydropyrimidines with 1 (N) HCl



Entry	Tetrahydropyrimidine	Time (h)	Product	Yield <sup>a</sup> (%)
1	 2	12	 23	75
2	 3	12	 24	73
3	 12	8	 25	66
4	 14	15	 26	63

<sup>a</sup> Isolated yield after column chromatographic purification.**Scheme 4.** Cycloaddition of 2,4-disubstituted-N-tosylazetidines with acetonitrile.

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- (a) Presented in 2nd J-NOST conference held in Jaipur, India during October 11–14, 2006; (b) Part of the work is included in the Ph.D. thesis of Kalpataru Das (2007, IIT Kanpur, India).
- After screening of several Lewis acids under optimized reaction conditions, Cu(OTf)<sub>2</sub> was found to be a better and more efficient catalyst to effect the reaction.
- Representative experimental procedure: A mixture of 2-phenyl-N-tosylazetidine **1** (0.35 mmol) and acetonitrile (1 mL) was added to anhyd Cu(OTf)<sub>2</sub> (0.35 mmol) under argon and heated at 80 °C for 10 mins. TLC indicated complete consumption of the starting azetidine **1**. Then the reaction mixture was quenched with a saturated aq NaHCO<sub>3</sub> solution (1 mL) and extracted with ethyl acetate three times. The combined organic layers were washed with brine, dried over anhyd Na<sub>2</sub>SO<sub>4</sub>, filtered, and the solvent was removed under vacuum. The crude product was purified by flash column chromatography on deactivated silica gel (deactivated with 1% N<sub>2</sub>Et<sub>3</sub>) using ethyl acetate/petroleum ether to provide the corresponding tetrahydropyrimidine **2**. In cases where higher boiling nitriles were used, a modified purification method was followed. The reaction mixture was directly charged on a deactivated basic alumina column followed by washing with petroleum ether to remove and recover excess nitriles. Pure compounds were obtained using ethyl acetate/petroleum ether as eluent.
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19. *Experimental procedure of the hydrolysis of 2-methyl-4-phenyl-1-tosyl-1,4,5,6-tetrahydropyrimidine (2)*: 1 (N) solution of HCl (0.34 mmol) was added to a solution of **2** (0.17 mmol) in THF (1 mL), and the mixture was stirred at rt overnight. Later, a saturated aq NaHCO<sub>3</sub> solution was added, and the aq layer was extracted with ethyl acetate (3 × 4.0 mL) and dried over anhyd Na<sub>2</sub>SO<sub>4</sub>. The crude product was purified by flash column chromatography on silica gel (230–400 mesh) using 60% ethyl acetate in petroleum ether to provide the pure product **23**. *Characterization data of 23*: <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 1.79–1.97 (m, 2H), 1.89 (s, 3H), 2.33 (s, 3H), 2.71–2.79 (m, 1H), 3.01–3.09 (m, 1H), 4.91–4.97 (m, 1H), 5.81 (br s, 1H, NH), 6.02 (d, *J* = 7.8 Hz, 1H, NH), 7.11–7.26 (m, 7H), 7.66 (d, *J* = 8.3 Hz, 2H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 21.4, 23.0, 36.0, 40.1, 51.0, 126.5, 127.0, 127.9, 128.9, 129.6, 137.3, 140.7, 143.2, 170.7; HRMS (ES<sup>+</sup>) for C<sub>18</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub>S (M+H), calcd 347.1429; found 347.1427.
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