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Copper-Catalyzed Tandem Nucleophilic Ring-Opening/Intramolecular Oxidative Amidation of *N*-Tosylaziridines and Hydrazones under Aerobic Conditions

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ABSTRACT



A novel and efficient copper-catalyzed tandem reaction of *N*-tosylaziridines and hydrazones under aerobic conditions to afford the functionalized tetrahydrotriazines is described. The process involves a nucleophilic ring-opening and an intramolecular oxidative amidation.

Carbon-nitrogen bond formation is one of the most useful and fundamental reactions in both academic and industrial chemistry, due to the high prevalent subunits of nitrogencontaining heterocycles in a variety of biologically active natural products and pharmaceuticals.¹ Of course, the majority of methods for installation of an amine functionality involve reaction of a nitrogen-based nucleophile with an electrophilic carbon center. With the emergence of the concepts of atom economy² and green chemistry,³ new methods to introduce C–N functionality by direct C–H activation are both important and highly desirable because of its conciseness and atom economy. Although there were a lot of excellent results about C–N bond formation through C–H activation,⁴ examples of the reactions under coppercatalyzed aerobic conditions are rare.⁵

In the past decades, much attention has been attracted to tandem reactions because tandem reaction is a powerful synthetic method for the construction of complex chemical frameworks from readily available materials.⁶ This strategy allows the formation of two or more bonds in a one-pot reaction without the isolation of intermediates and greatly

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For reviews on carbon-nitrogen bond formation reactions, see: (a) Trost, B. M.; Vranken, D. L. Chem. Rev. **1996**, *96*, 395-422. (b) Johannsen, M.; Jorgensen, K. A. Chem. Rev. **1998**, *98*, 1689–1708. (c) Müller, P.; Fruit, C. Chem. Rev. **2003**, *103*, 2905–2919. (d) Bolm, C.; Legros, J.; Paih, J. L.; Zani, L. Chem. Rev. **2004**, *104*, 6217–6254. (e) Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. Acc. Chem. Res. **1997**, *30*, 364–372.

^{(2) (}a) Trost, B. M. Acc. Chem. Res. 2002, 35, 695–705. (b) Trost, B. M. Angew. Chem., Int. Ed. 1995, 34, 259–281. (c) Trost, B. M. Science 1991, 254, 1471–1477.

⁽³⁾ Winterton, N. Green Chem. 2001, 3, G73.

⁽⁴⁾ For selected recent reports on catalytic intramolecular C-H aminations, see: (a) Davies, H. M. L.; Long, M. S. Angew. Chem., Int. Ed. 2005, 44, 3518-3520. (b) Wasa, M.; Yu, J. Q. J. Am. Chem. Soc. 2008, 130, 14058-14059. (c) Brasche, G.; Buchwald, S. L. Angew. Chem., Int. Ed. 2008, 47, 1932-1934. (d) Inamoto, K.; Hasegawa, C.; Hiroya, K.; Doi, T. Org. Lett. 2008, 10, 5147-5150. (e) Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. J. Am. Chem. Soc. 2005, 127, 14198-14199. For selected recent reports on catalytic intermolecular C-H aminations, see: (g) Hamada, T.; Ye, X.; Stahl, S. S. J. Am. Chem. Soc. 2008, 130, 833-834. (h) Chen, X.; Hao, X.-S.; Goodhue, C. E.; Yu, J.-Q. J. Am. Chem. Soc. 2006, 128, 6791-6792. (i) Li, Z.; Capretto, D.; Rahaman, R.; He, C. Angew. Chem., Int. Ed. 2007, 46, 5184-5186. (j) Reed, S.; White, M. C. J. Am. Chem. Soc. 2008, 130, 3316-3317. (k) Kalita, B.; Nicholas, K. M. Tetrahdron Lett. 2005, 46, 1451-1454. (l) Aburel, P. S.; Zhuang, W.; Hazell, R. G.; Jorgensen, K. A. Org. Biomol. Chem. 2005, 3, 2344-2347.

enhances synthetic efficiency. Aziridines are widely used building blocks in organic synthesis,⁷ and many excellent examples about nucleophilic ring-opening reaction of aziridines have been reported.⁸ As a part of our continuing program on development of tandem reactions of aziridines,⁹ we herein report an efficient and general approach to tetrahydrotriazines via the copper-catalyzed tandem reaction of *N*-tosylaziridines with hydrazones.

An exhaustive study of the reaction conditions for the synthesis of **3a** from phenylaziridine **1a** with hydrazone **2a** was conducted (Table 1). A screening of the catalysts showed that 0.1 equiv of Cu(OTf)₂ was the most efficient catalyst for this transformation (Table 1, entries 3-9).

When the copper loading was reduced to 5 mol %, a low yield of 3a was obtained. Interestingly, when other catalysts, such as AgOTf, Yb(OTf)₃, and Sc(OTf)₃ were used, only a simple nucleophilic ring-opening reaction occurred, and β -hydrazinylamine **3aa** was isolated in moderate yield and product **3a** was not observed (Table 1, entries 1-3). Other metal salts, such as CuI, CuBr₂, and FeCl₃, could not catalyze this reaction (Table 1, entries 10-12). Solvent also highly affected this reaction and toluene was the most suitable solvent, whereas both THF and 1,2-dichloroethane (DCE) provided mainly the product **3aa** (Table 1, entries 8 and 9). Further screening of the catalytic reaction conditions revealed that the reaction products largely depended on the reaction temperature. When the reaction was conducted under aerobic conditions at room temperature for 24 h, only the product 3aa was isolated in 60% yield (Table 1, entry 7). It was noteworthy that **3aa** could also be converted into **3a** in 83% yield via Cu(OTf)2-catalyzed intramolecular C-H amination

(6) (a) Meijere, A. D.; Zezschwitz, P. V.; Bräse, S. Acc. Chem. Res. 2005, 38, 413–422. (b) Hussain, M. M.; Walsh, P. J. Acc. Chem. Res. 2008, 41, 883–893. (c) Sun, X. L.; Tang, Y. Acc. Chem. Res. 2008, 41, 937–948. (d) Wasike, J.-C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. Chem. Rev. 2005, 105, 1001–1020. (e) Enders, D.; Hütl, M. R. M.; Grondal, C.; Rabbe, G. Nature 2006, 441, 861–863. (f) Multicomponent Reactions; Zhu, J., Bienayme, H., Eds.; Wiley-VCH: Weinheim, Germany, 2005. (g) Pinto, A.; Neuville, L.; Zhu, J. Angew. Chem. 10, 12, 4005, 43291–3295. (h) Chai, D. I.; Lautens, M. J. Org. Chem. 2009, 74, 3054–3061. (i) Chapman, C. J.; Frost, C. G. Synthesis 2007, 1–21. (j) Trost, B. M.; Gutierrez, A. C.; Livingston, R. C. Org. Lett. 2009, 11, 2539–2542. (k) Trost, B. M.; Frontier, A. J. J. Am. Chem. Soc. 2000, 122, 11727–11728. (l) Trost, B. M. J. Am. Chem. Soc. 2000, 122, 11727–11728. (l) Trost, B. M. J. Am. Chem. Soc. 2000, 39, 3168–3210. (n) Ramon, D. J.; Yus, M. Angew. Chem., Int. Ed. 2005, 44, 1602–1634.

(7) (a) Watson, I. D. G.; Yu, L.; Yudin, A. K. Acc. Chem. Res. 2006, 39, 194–206. (b) Sweeney, J. B. Chem. Soc. Rev. 2002, 31, 247–258.

(8) (a) Tanner, D. Angew. Chem., Int. Ed. 1994, 33, 599–619. (b) Savoia,
D.; Alvaro, G.; Fabio, R. D.; Gualandi, A. J. Org. Chem. 2007, 72, 3859.
(c) Wang, L.; Liu, Q.; Sheng, D.; Li, X.; Han, X.; Xiao, W.; Zhou, Y. Org. Lett. 2009, 11, 1119–1122. (d) Han, H.; Base, I.; Yoo, E. J.; Lee, J.; Do,
Y.; Chang, S. Org. Lett. 2004, 6, 4109–4112. (e) Hou, X.; Fan, R.; Dai,
L. X. J. Org. Chem. 2002, 67, 5295–5300. (f) Sureshkumar, D.; Koutha,
S. M.; Chandrasekaran, S. J. Am. Chem. Soc. 2005, 127, 12760–12761.

(9) (a) Wang, S. Y.; Zhu, Y. X.; Wang, Y. G.; Lu, P. Org. Lett. 2009, 11, 2615–2618. (b) Cui, S. L.; Wang, J.; Wang, Y. G. Org. Lett. 2008, 10, 13–16. (c) Cui, S. L.; Wang, J.; Wang, Y. G. Org. Lett. 2007, 9, 5023–5025.



Pr Me	$ \begin{array}{c} $	Me. at. (10 mol %) air	Ts ^{-N} -3a	Me N ^{Ph} + Ph	H-N H-N Ts 3aa	`N ^{∕Ph}
					yield	^b (%)
entry	catalyst	temp (°C)	solvent	t (h)	3a	3aa
1	AgOTf	80	toluene	10	0	65
2	Yb(OTf)3	80	toluene	10	0	60
3	$Sc(OTf)_3$	80	toluene	10	0	57
4	$Cu(OTf)_2$	80	toluene	4	58	0
5	$Cu(OTf)_2$	80	toluene	10	50^c	0
6	$Cu(OTf)_2$	50	toluene	10	35	26
7	$Cu(OTf)_2$	\mathbf{RT}	toluene	24	0	60
8	$Cu(OTf)_2$	60	THF	15	5	53
9	$Cu(OTf)_2$	80	DCE	10	5	49
10	CuI	80	toluene	15	Ν	R
11	$CuBr_2$	80	toluene	15	Ν	R
12	FeCl_3	80	toluene	15	Ν	R

^{*a*} Reaction conditions: **1a** (1 mmol), **2a** (1 mmol), catalyst (0.1 mmol), and solvent (8 mL). ^{*b*} Yield of the isolated product. ^{*c*} Catalyst (0.05 mmol).



reaction under 1 atm of air at 80 °C for 4 h (Scheme 1). However, no reaction occurred for **3aa** under air-free conditions. These reults indicated that the β -hydrazinylamine **3aa** is the key intermediate to tetrahydrotriazine **3a**. Thus, the most suitable reaction conditions for the formation of **3a** were established, and optimal conditions featured 10 mol % Cu(OTf)₂, toluene, 80 °C, and 1 atm of air as oxidant (Table 1, entry 4).

Since hydrazones are readily available, then, we extended the substrate scope to various hydrazones 2 using the optimized reaction conditions (Table 2). As shown in Table 2, a wide range of hydrazones could react with 1a and resulted in tetrahydrotriazines 3 in moderate to good yields (50-76%). The reaction tolerated substrates 2 with both electron-donating and electron-withdrawing aryl substituents under the present reaction conditions (Table 2, entries 1-7and 12-15). Furthermore, the structure of compound **3f** was unambiguously confirmed by single-crystal X-ray analysis (Figure 1). Phenylallyl hydrazone 2j and naphthyl hydrazone 2k were also transformed into tetrahydrotriazines 3j and 3k in 74% and 57% yields, respectively (Table 2, entries 10 and 11). We were happy to observe that the alkyl-substituted hydrazones 2h, 2i, and 2p also reacted well under the standard conditions (Table 2, entries 8-9 and 16).

^{(5) (}a) Monguchi, D.; Fujiwara, T.; Furukawa, H.; Mori, A. Org. Lett.
2009, 11, 1607–1610. (b) Tsang, W. C. P.; Munday, R.; Brasche, G.; Zheng, N.; Buchwald, S. L. J. Org. Chem. 2008, 73, 7603–7610. (c) Wang, D.; Mei, T.; Yu, J. Q. J. Am. Chem. Soc. 2008, 130, 17676–17677. (d) Hamada, T.; Ye, X.; Stahl, A. S. J. Am. Chem. Soc. 2008, 130, 833–835. (e) Stahl, S. S. Science 2005, 309, 1824–1826. (f) Wu, L.; Qiu, S.; Liu, G. Org. Lett. 2009, 11, 2707–2710. (g) Stahl, S. S. Angew. Chem., Int. Ed. 2004, 43, 3400–3420. (h) Tsang, W.; Zheng, N.; Buchwald, S. L. J. Am. Chem. Soc. 2005, 127, 14560–14561.

Table 2. Copper-Catalyzed Tandem Reaction of **1a** and Hydrazones 2^{a}



entry	R^{1}/R^{2}	<i>t</i> (h)	product	yield ^{b} (%)
1	$4\text{-}CH_3C_6H_4/Ph~(\textbf{2a})$	4	3a	58
2	$4\text{-}CH_3OC_6H_4\!/Ph~(\textbf{2b})$	20	3b	50
3	Ph/Ph (2c)	8	3c	60
4	$4\text{-}BrC_6H_4/Ph~(\textbf{2d})$	8	3d	63
5	$4\text{-NO}_2C_6H_4\!/Ph~(2e)$	20	3e	70
6	$3\text{-}NO_2C_6H_4\!/Ph(\mathbf{2f})$	4	3f	68
7	$2\text{-ClC}_6\text{H}_4/\text{Ph}(2g)$	4	3g	69
8	<i>i</i> -Pr/Ph (2h)	1	3h	73
9	$n-C_9H_{19}/Ph$ (2i)	1	3i	76
10	$C_6H_5CH=CH/Ph(2j)$	30	3j	74
11	2-naphthyl/Ph ($2k$)	20	3k	57
12	$Ph/4\text{-}CH_{3}OC_{6}H_{4}\left(\boldsymbol{2l}\right)$	20	3l	55
13	$Ph/4\text{-}CH_3C_6H_4\;(\boldsymbol{2m})$	48	3m	70
14	$Ph/4\text{-}NO_2C_6H_4~(2n)$	2	3n	72
15	$Ph/4\text{-}ClC_6H_4\;(\textbf{2o})$	6	30	67
16	$Ph/C_{6}H_{5}CH_{2}\;(\boldsymbol{2p})$	4	3p	61
11 12 13 14 15 16	2-naphthyl/Ph $(2k)$ Ph/4-CH ₃ OC ₆ H ₄ $(2l)$ Ph/4-CH ₃ C ₆ H ₄ $(2m)$ Ph/4-CH ₃ C ₆ H ₄ $(2m)$ Ph/4-NO ₂ C ₆ H ₄ $(2n)$ Ph/4-ClC ₆ H ₄ $(2o)$ Ph/C ₆ H ₅ CH ₂ $(2p)$	20 20 48 2 6 4	3k 3 <i>l</i> 3m 3n 3o 3p	57 55 70 72 67 61

^{*a*} Reaction conditions: **1a** (1 mmol), **2** (1 mmol), Cu(OTf)₂ (0.1 mmol), and toluene (8 mL). ^{*b*} Yield of the isolated product.



Figure 1. Crystal structure of compound 3f.

Further investigations into the scope of various *N*-tosylaziridines **1** were then carried out with hydrazone **2c** under the same reaction conditions as above, and representative results are listed in Table 3. The desired products **3c** and **3q**-**t** were obtained in moderate to good yields (50-80%). Significantly, 1-tosylaziridine (**1e**) also worked well to afford the corresponding product **3t** as a single product in 80% yield under the present reaction conditions (Table 3, entry 5).

We proposed a possible mechanism for this tandem reaction as shown in Scheme 2. The first step is most likely the copper-catalyzed regioselective nucleophilic ring-opening reaction of *N*-tosylaziridines and hydrazones, which leads to a β -hydrazinylamine-type intermediate **3aa**. Two possible **Table 3.** Copper-Catalyzed Tandem Reaction of **1** and Hydrazone $2c^a$

$R \xrightarrow{I}_{1} 2c \xrightarrow{I}_{2} Cu(OTf)_{2} (10 \text{ mol }\%) \xrightarrow{Ph}_{N \text{ r}} \xrightarrow{Ph}_{R}$						
entry	R	<i>t</i> (h)	product	yield ^{b} (%)		
1	Ph (1a)	8	3c	60		
2	$4\text{-}ClC_{6}H_{4}\left(\mathbf{1b}\right)$	4	3q	65		
3	$4\text{-}CH_{3}C_{6}H_{4}\left(\mathbf{1c}\right)$	4	3r	75		
4	$C_{6}H_{5}CH_{2}\left(\boldsymbol{1d}\right)$	4	3s	50		
5	H (1e)	4	3t	80		

^{*a*} Reaction conditions: **1** (1 mmol), **2c** (1 mmol), Cu(OTf)₂ (0.1 mmol), and toluene (8 mL). ^{*b*} Yield of the isolated product.

Scheme 2. Possible Mechanism for the Formation of 3



reaction pathways were possible to convert linear adduct **3aa** to final product **3a**: (1) copper-catalyzed direct oxidative amidation (pathway A)^{4g,5a} and (2) nucleophilic addition of tosylamide to hydrazone followed by copper-mediated oxidation of the resulting hexahydrotriazines (pathway B). However, **3aa** could not be converted into **3a** or the nonoxidative cyclization product **5** in the presence of Cu(OTf)₂ under air-free conditions. We also treated **3aa** with NaH, but **5** was not observed and all of **3aa** was recovered. These results suggest that **5** is not an intermediate. Therefore, pathway A is a possible route to **3a**.

1,2,4-Triazine and its derivatives are a well-known class of heterocycles, most of them having biological activities.¹⁰ They are also useful synthetic intermediates.¹¹ Consequently, a number of synthetic approaches have been set up for

^{(10) (}a) Carling, R. W.; Russell, M. G. N.; Moore, K. W.; Mitchinson,
A.; Guiblin, A.; Smith, A.; Wafford, K. A.; Marshall, G.; Atack, J. R.;
Street, L. J. *Bioorg. Med. Chem. Lett.* 2006, *16*, 3550–3554. (b) Fink, B. E.;
Vite, G. D.; Mastalerz, H.; Kadow, J. F.; Kim, S.-H.; Leavitt, K. J.; Du,
K.; Crews, D.; Mitt, T.; Wong, T. W.; Hunt, J. T.; Vyas, D. M.; Tokarski,
J. S. *Bioorg. Med. Chem. Lett.* 2005, *15*, 4774–4779. (c) Hay, M. P.; Hicks,
K. O.; Pchalek, K.; Lee, H. H.; Blaser, A.; Pruijn, F. B.; Anderson, R. F.;
Shinde, S. S.; Wilson, W. R.; Denny, W. A. J. Med. Chem. 2008, *51*, 6853–6865. (d) El-Sayed Ali, T. *Eur. J. Med. Chem.* 2009, *44*, 4385–4392.

^{(11) (}a) Shi, B. L.; Lewis, W.; Campbell, I. B.; Moody, C. J. Org. Lett.
2009, 11, 3686–3688. (b) Catozzi, N.; Wasnaire, P.; Taylor, R. J. K. Tetrahedron 2008, 49, 2865–2868.

constructing this important heterocyclic system.¹² An example for the formation of tetrahydrotriazine from aziridine and nitrilimines was reported by Tsuge and co-workers.¹³ Compared with the published methods, the present tandem method is more efficient and general and should be very attractive to medicinal chemists as well as organic synthetic chemists.

In conclusion, we have developed a single-step approach to tetrahydrotriazines via the Cu(II)-catalyzed tandem reaction of *N*-tosylaziridines and hydrazones under aerobic conditions. The process is thought to involve a copper-catalyzed nucleophilic ring-opening reaction and a copper-

catalyzed intramolecular C-H amidation. The use of inexpensive Cu catalyst and air as the ideal oxidant is a significant practical advantage. The synthetic applications of this new methodology are under investigation.

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Supporting Information Available: Detailed experimental procedures, characterizaton data, copies of ¹H and ¹³C NMR spectra for all products, and a crystallographic information file (CIF) for compound **3f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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^{(12) (}a) Winternitz, P. *Helv. Chim. Acta* **1978**, *61*, 1175–1185. (b) Buscemi, S.; Pace, A.; Palumbo Piccionello, A.; Pibiri, I.; Vivona, N.; Giorgi, G.; Mazzanti, A.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 8106–8113.

⁽¹³⁾ Tsuge, O.; Watanabe, H.; Kiryu, Y. Bull. Chem. Soc. Jpn. 1979, 52, 3654–3658.