JOC*Note*

Synthetic Utility of Ammonium Salts in a Cu-Catalyzed Three-Component Reaction as a Facile Coupling Partner

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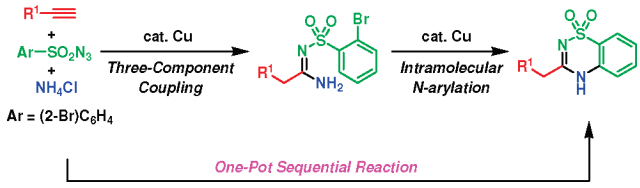

Ammonium salts were found to be a convenient and inexpensive reagent in the Cu-catalyzed three-component reaction with terminal alkynes and sulfonyl or phosphoryl azides leading to N-unprotected amidines. Thus obtained amidines bearing 2-bromobenzenesulfonyl moiety were efficiently cyclized by the Cu-catalyzed intramolecular N-arylation to give an important pharmacophore skeleton of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides. Conveniently, two tandem catalytic procedures could be readily operated in one pot.

Although gaseous ammonia is the simplest nitrogen source in chemical processes,[1] it is less frequently used as an efficient reagent in organic syntheses compared to substituted amines,[2] mainly owing to practical problems with respect to safety and convenience. On the other hand, ammonium salts (e.g., NH_4Cl, NH_4OH, NH_4OAc, or NH_4BF_4) are employed in some synthetic procedures as a facile and inexpensive equivalent to ammonia because of their ease of handling.[3]

In this context, we recently reported an example of utilizing ammonium salts in Cu-catalyzed N-arylation.[4] We found that, by the action of CuI/proline catalyst, NH_4Cl or NH_4OH react readily with aryl halides under mild conditions to afford primary arylamines in high yields. One of the attractive features of using ammonium salts turned out to be excellent functional group tolerance presumably due to the low nucleophilicity of the reagent. On the basis of the N-arylation results, we envisioned that ammonium salts could also be employed as an ammonia surrogate in the Cu-catalyzed three-component reaction to make N-unprotected amidines.

Recently, we have developed the Cu-catalyzed three-component reaction of terminal alkynes, sulfonyl azides, and primary or secondary amines, leading to amidines under mild conditions.[5] This reaction is revealed to proceed via a ketenimine intermediate, generated in situ by the Cu-catalyzed coupling of 1-alkynes and sulfonyl azides upon release of N_2.[6] The mechanistic description is further evidenced by the successful incorporation of diverse nucleophiles such as alcohol,[7] water,[8] or pyrrole.[9] Synthetically interesting applications have been also achieved on the basis of the same approach.[10,11] Herein, we disclose the fruitful utilization of ammonium salts in the coupling reactions and its application in the synthesis of a biologically important pharmacophore of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides.

Using ammonium salts, we first investigated the Cu-catalyzed three-component reaction with phenylacetylene and *p*-toluenesulfonyl azide (Table 1). To our delight, the reaction with NH_4Cl took place smoothly at room temperature to give 2-phenyl-*N*-(*p*-toluenesulfonyl) acetamidine, and it was found that its yields varied depending on the conditions employed. While CH_2Cl_2 turned out to be the most effective solvent, the equivalent of Et_3N additive was also important for the reaction efficiency. The reaction could be carried out under ambient conditions, thus not requiring inert atmosphere and dried solvents (compare entries 3 and 7). As in our recent example in the Cu-catalyzed N-arylation of aryl halides,[4] aqueous ammonia solution (28% aqueous NH_3) was also a highly effective nitrogen source in this case. In fact, reaction efficiency was even higher with aqueous NH_3 solution compared to that with NH_4Cl, and side products such as amides were not observed.[8]

It was interesting to compare the relative initial reaction rates among various nucleophiles in the Cu-catalyzed three-compo-

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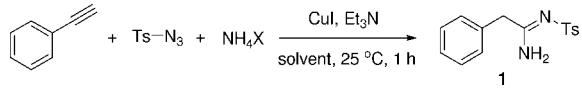
TABLE 1. Screen of Reaction Conditions in the Cu-Catalyzed Three-Component Couplings with Ammonium Salts[a]



1

entry	NH_4X	Et_3N (equiv)	solvent	yield (%)[b]
1	NH_4Cl	2.0	$CHCl_3$	68
2	NH_4Cl	2.0	CH_2Cl_2	85
3	NH_4Cl	1.5	CH_2Cl_2	84
4	NH_4Cl	0.5	CH_2Cl_2	62
5	NH_4Cl	2.0	THF	58
6	NH_4Cl	2.0	DMSO	25
7[c]	NH_4Cl	1.5	CH_2Cl_2	87
8[c]	NH_3 (aq)[d]	1.5	CH_2Cl_2	89
9[c]	NH_3 (aq)[d]	2.0	$ClCH_2CH_2Cl$	88
10[c]	NH_3 (aq)[d]	2.0	THF	63

[a] Phenylacetylene (0.5 mmol), *p*-toluenesulfonyl azide (0.5 mmol), Et_3N, NH_4X (0.5 mmol), and CuI (0.05 mmol) in the indicated solvent (1.0 mL) at 25 °C under N_2. [b] ^1H NMR yield (internal standard 1,1,2,2-tetrachloroethane). [c] Run open to the air. [d] Aqueous 28% solution.

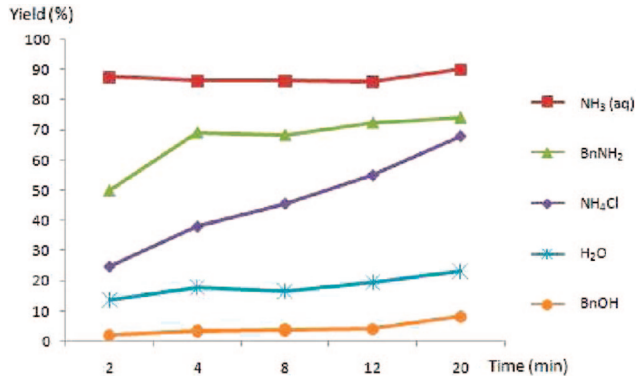


FIGURE 1. Reaction profile in the Cu-catalyzed three-component couplings of phenylacetylene and *p*-toluenesulfonyl azide with NH_3 (aq), benzylamine, NH_4Cl, water, or benzyl alcohol.

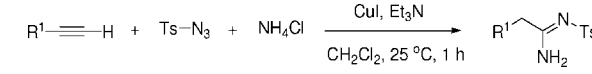
nent reactions (Figure 1).[12] It was revealed that aqueous ammonia solution displayed the highest initial rates followed by benzylamine and NH_4Cl. On the other hand, reactions with water or benzyl alcohol proceeded with much slower initial rates.

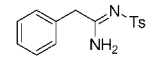
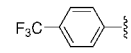
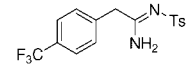
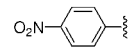
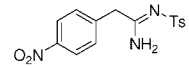
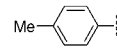
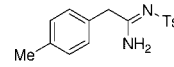
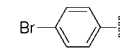
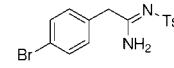
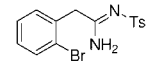
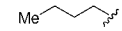
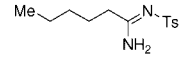
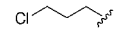
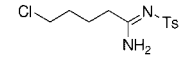
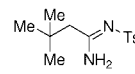
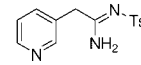
Under the optimized reaction conditions with ammonium salts, the scope of terminal alkynes was next investigated using *p*-toluenesulfonyl azide as a representative coupling partner (Table 2). We were pleased to see that a wide range of aromatic alkynes underwent the reaction with excellent efficiency irrespective of their electronic and steric properties (entries 1−6). It should be noted that employment of aqueous ammonia solution, in general, provides similar or slightly higher yields of amidine products compared to those with NH_4Cl. Aliphatic alkynes were also readily utilized to provide the corresponding amidines with satisfactory yields (entries 7−9). Heteroaromatic alkynes underwent the three-component reaction without difficulty (entry 10).

It is interesting to note that double bond character in the generated amidines is delocalized over two C−N bonds as evidenced by the solid state structure analysis of an isolated amidine **2** (Figure 2).[12] We then examined the scope of azides substituted with various sulfonyl or phosphoryl groups in the Cu-catalyzed three-component coupling with ammonium salts

(12) See Supporting Infomation for the reaction profile and X-ray crystallographic data.

TABLE 2. Three-Component Reactions of Various Alkynes with *p*-Toluenesulfonyl Azide and Ammonium Salts[a]



Entry	R^1	Product	Yield (%)[b]
1			90 89[c]
2			66 80[c]
3			94
4			84
5			75 91[c]
6			80
7			81
8			72 90[c]
9			61 54[c]
10			92

[a] Alkyne (0.5 mmol), *p*-toluenesulfonyl azide (0.5 mmol), Et_3N (0.75 mmol), NH_4Cl (0.5 mmol), and CuI (0.05 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C for 1 h. [b] Isolated yield. [c] NH_3 (28% aqueous, 0.5 mmol) was employed instead of NH_4Cl.

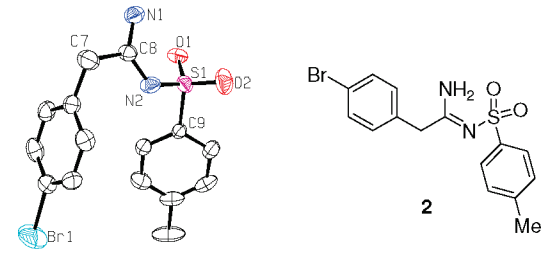
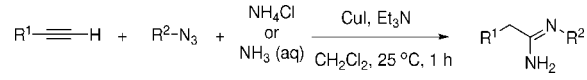


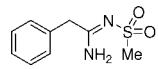
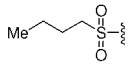
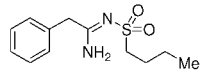
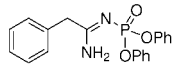
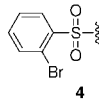
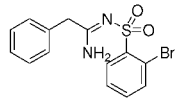
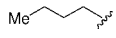
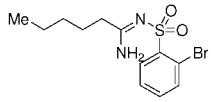
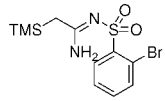
FIGURE 2. Selected bond lengths (Å) of an amidine **2**: C7−C8, 1.515(8); C8−N1, 1.295(7); C8−N2, 1.306(7); N2−S1, 1.590(5); S1−O2, 1.432(4); S1−O1, 1.446(4); S1−C9, 1.756(6).

(Table 3). Not only arene- but also alkanesulfonyl azides were found to be facile reactants, giving amidines in high yields under the optimized conditions (entries 1 and 2). However, phosphoryl azides were less effective for the coupling reaction (entry 3). With the subsequent intramolecular N-arylation in mind (vide infra), when 2-bromobenzenesulfonyl azide was allowed to react with a range of 1-alkynes, the corresponding amidines could be obtained in satisfactory yields (entries 4−6).

The synthetic utility of N-unsubstituted amidines was then investigated in the subsequent conversion to interesting heterocycles. 2*H*-1,2,4-Benzothiadiazine 1,1-dioxide is a biologically important pharmacophore, and various derivatives bearing the

TABLE 3. Three-Component Reactions with Ammonium Salts[a]



Entry	R^1	R^2	Product	Yield (%)[b]
1	 **3**			73 89[c]
2	**3**			83 95[c]
3	**3**			39[d] 15[c]
4	**3**	 **4**		90
5		**4**		87
6		**4**		50

[a] Alkyne (0.5 mmol), azide (0.5 mmol), Et_3N (0.75 mmol), NH_4Cl (0.5 mmol), and CuI (0.05 mmol) in CH_2Cl_2 (1.0 mL) at 25 °C. [b] Isolated yield. [c] NH_3 (28% aqueous, 0.5 mmol) was employed. [d] For 12 h.

key moiety are known to show antihypertensive or antimicrobial activities.[13] For instance, 1-butyl-3-(1,1-dioxido-2*H*-1,2,4-benzothia-diazin-3-yl)-4-hydroxy-(1*H*)-quinolinone and its derivatives were revealed to be potent HCV polymerase inhibitors.[14] Therefore, a range of efficient synthetic routes to the pharmacophore have been developed.[15] Since we queried that the key molecular skeleton of 2*H*-1,2,4-benzothiadiazine 1,1-dioxides could be prepared by the intramolecular N-arylation of the precursors that are obtainable based on our approach, we envisioned to develop a straightforward and convenient route to the important pharmacophore by employing two tandem Cu-catalytic reactions (Scheme 1). The Cu-catalyzed intramolecular

SCHEME 1. Synthetic Strategy to 2*H*-1,2,4-Benzothiadiazine 1,1-Dioxide

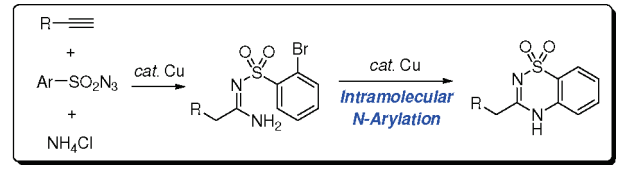
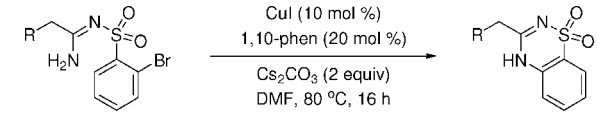
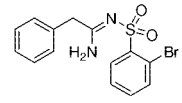
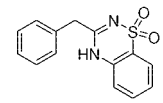
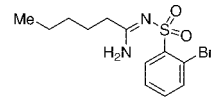
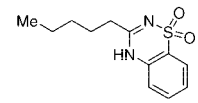
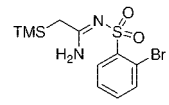
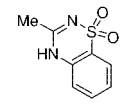


TABLE 4. Intramolecular Catalytic *N*-Arylation of Amidines[a]



Entry	Amidine	Product	Yield (%)[b]
1			75
2			86
3			72

[a] Amidine (0.3 mmol), CuI (0.03 mmol), Cs_2CO_3 (0.6 mmol), and 1,10-phenanthroline (0.06 mmol) in DMF (4.0 mL) at 80 °C for 16 h. [b] Recrystallization yield.

C−N cross-coupling[16] of 2-bromobenzenesulfonyl amidines, which were obtained from the above three-component reactions (Table 3, entries 4−6), was readily achieved by a slight modification of the known catalytic protocol of 1,10-phenanthroline, CuI, and Cs_2CO_3 in DMF (Table 4).[17] Under the employed conditions, a range of 3-substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides were obtained in respectable yields after recrystallization. Interestingly, a TMS group was desilylated in situ under the reaction conditions (entry 3).

Due to the fact that CuI catalyst was employed commonly in both amidine formation and N-arylation reaction, we tried to carry out the two operations in one pot. After the initial three-component coupling reaction, volatile species were removed, and then the intramolecular N-arylation was next attempted by simply adding 1,10-phenanthroline and Cs_2CO_3 in DMF in the same flask. As expected, the one-pot operation of the two catalytic procedures was successfully carried out leading to 3-benzyl-2*H*-1,2,4-benzothiadiazine 1,1-dioxide (**5**) in good overall yield (Scheme 2).

In summary, we have demonstrated that ammonium salts can be readily utilized as a convenient and cheap reagent in a Cu-catalyzed three-component reaction to afford amidines, which were further manipulated to give 2*H*-1,2,4-benzothiadiazine 1,1-dioxides, a biologically important pharmacophore.

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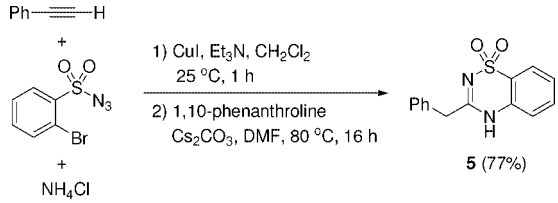
SCHEME 2. One-Pot Synthesis of 3-Benzyl-2*H*-1,2,4-benzothiadiazine 1,1-Dioxide (5)



Experimental Section

Representative Procedure for the Cu-Catalyzed Three-Component Coupling Reaction with Ammonium Salts. To a stirred mixture of NH_4Cl (26.7 mg, 0.5 mmol), CuI (9.5 mg, 0.05 mmol), and phenylacetylene (51.1 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was slowly added triethylamine (0.14 mL, 0.75 mmol) at room temperature. After color changed to yellow, *p*-toluenesulfonyl azide (98.6 mg, 0.5 mmol) was added dropwise. After the reaction was completed, which was monitored with TLC, the reaction mixture was diluted by adding CH_2Cl_2 (2 mL) and aqueous NH_4Cl solution (3 mL). The mixture was stirred for an additional 30 min, and two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 mL × 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude residue was purified by flash column chromatograph on silica gel (ethyl acetate/hexane, 1:1) to afford 2-phenyl-*N*-(*p*-toluenesulfonyl)acetamidine as a white solid (129.8 mg, 90%): mp 115−116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br, 1H), 7.75 (d, J = 8.2 Hz, 2H), 7.30−7.16 (m, 7H), 5.97 (br, 1H), 3.58 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 143.0, 139.0, 133.4, 129.5, 129.3, 129.1, 127.9, 126.3, 43.6, 21.4; IR (NaCl) ν 3327, 3328, 3238, 1654, 1545, 1449, 1414, 1277, 1103, 801 cm^{-1}; HRMS(FAB) *m*/*z* calcd for $C_{15}H_{17}O_2N_2S$ $[M + H]^+$ 289.1011, found 289.1001.

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Supporting Information Available: Detailed experimental procedures, characterization data, copies of ^{1}H and ^{13}C-spectra of new compounds, and a CIF file of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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