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Copper-Catalyzed Aminohalogenation Using the 2-NsNCl$_2$/2-NsNHNa Combination as the Nitrogen and Halogen Sources for the Synthesis of *anti*-Alkyl 3-Chloro-2-(*o*-nitrobenzenesulfonamido)-3-arylpropionates

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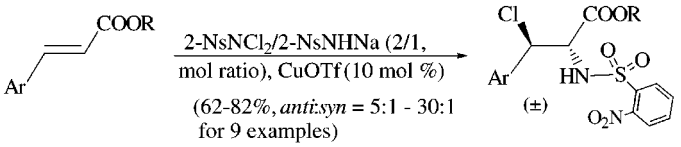
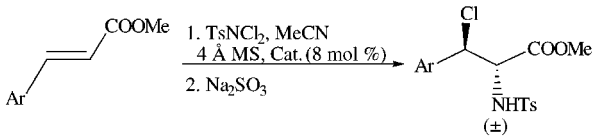
ABSTRACT



New regio- and stereoselective aminohalogenation of cinnamic esters has been developed using the combination of 2-NsNCl$_2$/2-NsNHNa as the nitrogen and chlorine sources and copper(I) triflate as the catalyst. The new procedure provides an efficient synthesis of *anti*-alkyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate derivatives. Nine examples are presented with good yields (62–82%) and stereoselectivity ((5:1)–(30:1)).

The vicinal haloamine derivatives are important building blocks in modern organic and medicinal chemistry.[1] The development of highly regioselective and stereoselective synthetic approaches to this functionality has been attempted for several decades but still remains important and challenging.[2,3] In actuality, this synthetic area has not been well-documented in the past 15 years. Very recently, we developed the aminohalogenation of cinnamic esters by using *N*,*N*-dichloro-*p*-toluenesulfonamide (TsNCl$_2$) as the nitrogen and chlorine sources and the transition-metal compounds ZnCl$_2$ and Cu(OTf)$_2$ as the catalysts (Scheme 1).[4] In the continuing study of this reaction, we anticipated that the replacement of *N*,*N*-dichloro-*p*-toluenesulfonamide with the analogous nitrogen/chlorine sources *N*,*N*-dichloro-*p*-nitro and *o*-nitro-

Scheme 1



(1) Kemp, J. E. G., In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; Vol. 3, pp 471−513.

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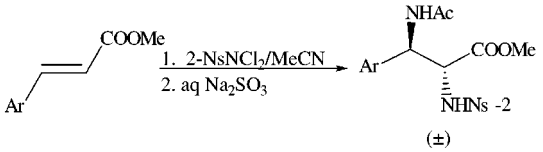
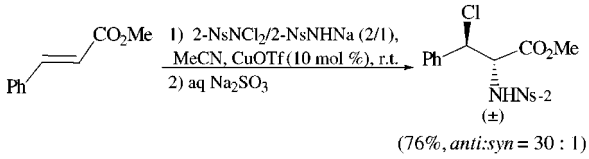
benzenesulfonamide (2-$NsNCl_2$ and 4-$NsNCl_2$) under similar conditions could result in *anti*-alkyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate derivatives. The advantage of such a modification is that the *N*-nitrobenzenesulfonyl protecting group of the resulting products can be readily cleaved by $PhSH/K_2CO_3$ in DMF at room temperature.[5] However, our attempts to react $NsNCl_2$ with methyl cinnamate under the conditions we previously developed failed to give the desired haloamine product. Instead, *anti*-methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate was determined to be the predominant product (Scheme 2).[6]

Scheme 2



While the study of diamination is ongoing in our laboratories, we concurrently have been searching for new conditions to direct the reaction toward the formation of *N*-nosyl haloamine derivatives. We found that *N*-nosyl group-based aminohalogenation of cinnamic esters can be achieved by using $NsNCl_2$−NsNHNa (1:2 mole ratio) as the nitrogen and chlorine sources in the presence of copper(I) triflate as the catalyst. In this report, we describe the preliminary results of this new reaction system, which is represented in Scheme 3; the results are summarized in Table 1.

Scheme 3



(76%, *anti:syn* = 30 : 1)

The reaction can be conducted in a convenient vessel of appropriate size without the need of inert-atmosphere protection which is similar to the case for the previous $TsNCl_2$-based reaction system. 2-$NsNCl_2$ was prepared by treating *o*-nitrobenzenesulfonamide with commercial bleach, followed by CH_3COOH acidification.[4] Interestingly, 2-$NsNCl_2$ showed greater stability than *p*-$TsNCl_2$. In fact, it can be stored at room temperature for a few months without nitrogen protection. The 2-NsNHNa salt was obtained by deprotonating 2-$NsNH_2$ with sodium hydroxide in methanol/water solution and subsequently drying overnight under high vacuum prior to use. An excess amount of 2-$NsNCl_2$ (1.5 equiv) and 2-NsNHNa (3.0 equiv)[7] was found to be necessary for optimal yields and complete consumption of cinnamic ester starting materials. The surplus 2-$NsNH_2$, after the reaction was quenched with aqueous Na_2SO_3, can be readily recovered because of its high polarity and low solubility in several organic solvents such as $CHCl_3$, CH_2Cl_2, etc. Copper(I) triflate was the first catalyst found effective for this process. In the absence of this triflate, no reaction occurred between methyl cinnamate and 2-$NsNCl_2$/2-NsNHNa even after more than 3 h. Later on, copper(II) triflate and copper(I) chloride were also proven to be efficient catalysts for this reaction, giving similar results. Less than 10 mol % of catalyst can be utilized, but the reaction takes longer. The concentration of reactants should also be maintained around the amount shown in the typical procedure.[8] In actuality, when the reaction mixture was diluted to half of the current concentration, only a trace amount of haloamine product was observed after the reaction was performed over 20 h.

Examination of the results listed in Table 1 reveals that cinnamic esters with either electron-donating or electron-

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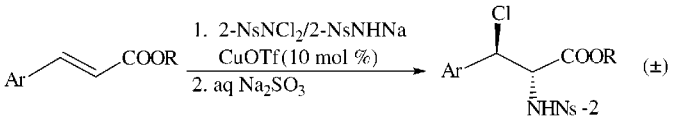
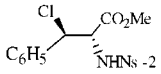
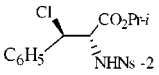
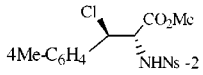
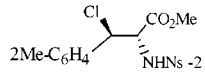
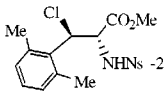
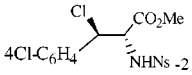
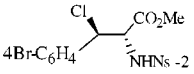
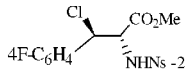
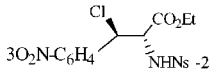
(7) The mixture of $NsNCl_2$/NsNHNa has been previously utilized as the nitrogen source to react with selenium for the formation of diimidoselenium compounds: Bruncko; M.; Khuong, T.-A. V.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 454.

(8) Typical procedure: CuOTf-catalyzed aminochlorination reaction of methyl *trans*-cinnamate with 2-$NsNCl_2$/2-NsNHNa as described in Scheme 1. Into a dry vial was added methyl cinnamate (162 mg g, 1.00 mmol) and freshly distilled acetonitrile (3 mL). The reaction vial was immersed in a room-temperature bath, and 2-$NsNCl_2$ (407 mg, 1.50 mmol), 2-NsNHNa (672 mg, 3.00 mmol), and copper(I) trifluoromethanesulfonate benzene complex (50.3 mg, 0.10 mmol, 10 mol %) were added. The resulting dark brown solution in the capped vial was stirred at room temperature for 20 h without argon protection. As the reaction proceeded to completion over the course of 20 h, the color of the solution changed from dark brown to light green and finally to yellow. The reaction was quenched by dropwise addition of saturated aqueous Na_2SO_3 solution (2 mL). The phases were separated, and the aqueous phase was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous magnesium sulfate, and concentrated to dryness. Purification by flash chromatography (3/7 EtOAc/hexane, v/v) provided *anti*-methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate (**1**; 303 mg, 76% yield) as a colorless oil. ^1H NMR data (Table 1; 200 MHz, $CDCl_3$; *J* values in Hz): **1**, δ 8.04−7.87 (m, 2H), 7.92−7.87 (m, 1H), 7.74−7.69 (m, 2H), 7.35−7.29 (m, 5H), 6.12 (d, J = 9.61, 1H), 5.28 (d, J = 6.12, 1H), 4.74 (dd, J = 6.12, 9.61, 1H), 3.62 (s, 3H); **3**, δ 8.03−7.86 (m, 2H), 7.72−7.68 (m, 2H), 7.21−7.17 (m, 2H), 7.09−7.05 (m, 2H), 6.08 (d, J = 9.72, 1H), 5.22 (d, J = 6.30, 1H), 4.72 (dd, J = 6.30, 9.72, 1H), 3.58 (s, 3H); **4**, δ 7.95−7.85 (m, 2H), 7.73−7.67 (m, 2H), 7.44−7.39 (m, 1H), 7.17−7.07 (m, 3H), 6.25 (d, J = 9.9.56, 1H), 5.41 (d, J = 7.41, 1H), 4.73 (dd, J = 7.41, 9.56, 1H), 3.54 (s, 3H), 2.38 (s, 3H); **6**, δ 7.98−7.87 (m, 2H), 7.76−7.69 (m, 2H), 7.30−7.20 (m, 4H), 6.14 (d, J = 9.73), 1H), 5.19 (d, J = 6.78, 1H), 4.71 (dd, J = 6.78, 9.73, 1H), 3.62 (s, 3H); **7**, δ 7.97−7.87 (m, 2H), 7.76−7.69 (m, 2H), 7.40−7.36 (m, 2H), 7.22−7.18 (m, 2H), 6.13 (d, J = 9.76, 1H), 5.17 (d, J = 6.87, 1H), 4.70 (dd, J = 6.87, 9.76, 1H), 3.61 (s, 3H); **8**, δ 8.01−7.88 (m, 2H), 7.78−7.70 (m, 2H), 7.36−7.27 (m, 2H), 7.01−6.93 (m, 2H), 6.14 (d, J = 9.77, 1H), 5.23 (d, J = 6.55, 1H), 4.71 (dd, J = 6.55, 9.77, 1H), 3.58 (s, 3H); **9**, δ 8.22−8.16 (m, 2H), 8.07−8.03 (m, 1H), 7.93−7.89 (m, 1H), 7.82−7.72 (m, 3H), 7.61−7.53 (m, 1H)6.30 (d, J = 9.38, 1H), 5.38 (d, J = 6.11, 1H), 4.73 (dd, J = 6.11, 9.38, 1H), 4.05 (m, 2H), 1.12 (t, J = 7.19, 3H). ^{13}C NMR data (Table 1; 50 MHz, $CDCl_3$): **1**, δ 168.3, 147.4, 135.5, 134.1, 133.7, 133.0, 130.5, 129.4, 128.8, 127.6, 125.6, 63.1, 61.3, 52.8; **3**, δ 168.4, 147.3, 139.3, 134.3, 133.5, 132.9, 132.4, 130.5, 129.4, 127.4, 125.6, 63.1, 61.1, 52.8, 21.2; **4**, δ 168.5, 147.2, 135.7, 133.9, 6.5, 125.6, 61.6, 57.8, 52.6, 19.2; **6**, δ 168.3, 147.3, 135.3, 134.2, 134.1, 133.7, 133.0, 130.3, 129.1, 128.9, 125.6, 62.9, 60.5, 52.9; **7**, δ 168.3, 147.3, 134.8, 134.1, 133.7, 133.1, 131.9, 130.3, 129.4, 125.6, 123.5, 62.8, 60.5, 52.9; **8**, δ 168.3, 165.4, 160.5, 147.4, 134.1, 133.7, 133.0, 131.5, 131.5, 130.4, 129.6, 129.5, 125.6, 116.0, 115.6, 63.0, 60.5, 52.9; **9**, δ 167.2, 148.1, 147.5, 138.1, 134.0, 133.9, 133.8, 133.0, 130.4, 129.8, 125.7, 124.1, 123.0, 62.8, 60.6, 13.8.

Table 1. Results of CuOTf-Catalyzed Aminochlorination of Cinnamic Esters



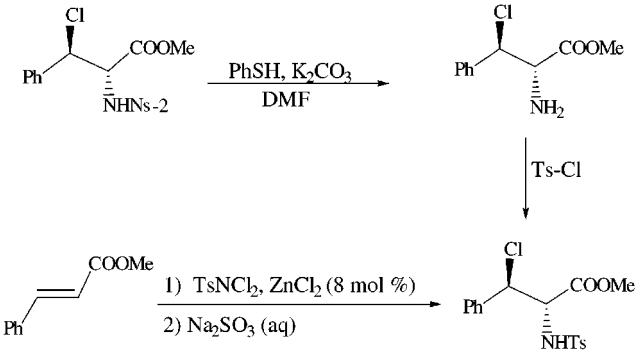
entry	Ar	R	product (±)	stereoselectivty (*anti*:*syn*)[a]	yield (%)[b]
1	C_6H_5	Me		30:1	76
2[c]	C_6H_5	*i*-Pr		15:1	82
3	4-Me-C_6H_4	Me		20:1	75
4	2-Me-C_6H_4	Me		25:1	71
5[c]		Me		5:1	72
6	4-Cl-C_6H_4	Me		30:1	63
7	4-Br-C_6H_4	Me		25:1	79
8	4-F-C_6H_4	Me		28:1	77
9	3-NO_2-C_6H_4	Et		10:1	62

[a] Estimated by crude ^{1}H NMR determination. [b] The yields after purification via column chromatography. [c] The combined yield of two isomers which were difficult to separate by column chromatography.

withdrawing groups on their aromatic rings can be subjected to this reaction. So far, only cinnamic esters have been used as the reaction substrates simply because of the convenience of TLC monitoring. Preliminary results showed that aliphatic α,β-unsaturated carboxylic esters can also be employed as the starting materials. For all of the aromatic substrates we examined, the regioselectivity has been completely controlled. Excellent *anti/syn* stereoselectivity was realized for most of the examples we studied. Only in two cases, **5** and **9**, was modest stereoselectivity obtained (*anti*:*syn* = 5:1 and 10:1, respectively).

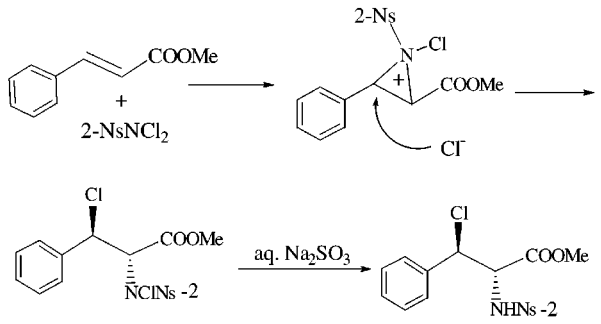
Structure determination was carried out by the conversion of product **1** in Table 1 to a known sample (Scheme 4). In this determination, the deprotection of the N^{α}-Ns group was performed by using Fukuyama's method[5] followed by the protection of the free amine product with *p*-toluenesulfonyl chloride in pyridine. The resulting *anti*-methyl 3-chloro-2-(*p*-toluenesulfonamido)-3-phenylpropionate was proven to be identical with the product synthesized from the $TsNCl_2$-based aminohalogenation procedure.[4]

Scheme 4



It is reasonable to suggest that this aminohalogenation proceeds through the formation of an unprecedented *N*-nosyl-*N*-chloroaziridinium intermediate at the initial step rather than the chloronium ion as previously proposed (Scheme 5).[4] This

Scheme 5



hypothesis is supported by the new diamination results.[6] In this diamination process, the existence of an *N*-nosyl-*N*-chloroaziridinium intermediate was proven by its reaction with acetonitrile to give *anti*-methyl N^{α}-nosyl-N^{β}-acetyldiaminophenylpropionate after quenching the reaction with aqueous Na_2SO_3 solution.[6] The copper catalysts help to remove the chlorine anion from *N*,*N*-dichloro-*o*-nitrobenzenesulfonamide, which is beneficial in forming "Ns$-N^{+}-$Cl" electrophilic species for the electrophilic addition. The nearby copper-associated "Cl^{-}" around the aziridinium intermediate acts as the nucleophile to open the three-membered ring. An S_N2 mechanism for this opening is responsible for the high *anti* stereoselectivty. The regioselectivity can be explained by the fact that the β-position of the aziridinium intermediate has more positive charge than the α-position because of the stabilization effect from the phenyl ring. At this early stage, it is not clear why Cl^{-} is the dominant nucleophile over other species which coexist with Cl^{-} in the reaction system.

In summary, highly regio- and stereoselective aminohalogenation of cinnamic esters has been developed using the 2-$NsNCl_2$/2-NsNHNa combination as the nitrogen and chlorine sources and copper(I) triflate as the catalyst. This new process provides a novel approach to *ant*-methyl 3-chloro-2-(*o*-nitrobenzenesulfonamido)-3-phenylpropionate derivatives. The *N*-nosyl protecting group of the resulting products can be readily cleaved under mild conditions. The unprecedented *N*-nosyl-*N*-chloroaziridinium intermediate generated during this new process could find more applications in organic synthesis by reactions with various other nucleophiles.

Acknowledgment. We acknowledge the Robert A. Welch Foundation and the South Plains Foundation for generous support. We thank Mr. David W. Purkiss for assistance in NMR spectroscopic analysis.

Supporting Information Available: Figures giving ^{1}H and ^{13}C NMR spectra for all pure products. This material is available free of charge via the Internet at http://pubs.acs.org.

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