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Efficient Copper-Catalyzed Benzylic Amidation with Anhydrous Chloramine-T

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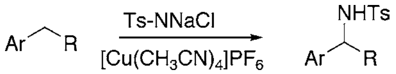
ABSTRACT



Benzylic hydrocarbons are selectively converted to the corresponding sulfonamides by the [Cu(CH_3CN)$_4$]PF_6-catalyzed reaction with anhydrous TolSO$_2$NNaCl (chloramine-T). Under the same conditions, representative ethers are also α-amidated; olefins produce allyl sulfonamides, aziridines, and/or *β*-chloro sulfonamides.

The direct N-functionalization of hydrocarbons via the activation of C−H and C═C bonds is a synthetically attractive transformation which is receiving increasing attention, in part because of the tremendous value of the product amines. The most well-developed and successful of such reactions are the transition metal catalyzed hydroamination,[1] aziridination,[2] and allylic amination[3] of alkenes. In contrast, reactions that effect benzylic C−H amination have received relatively little attention. Here, the imido reagents, ArI═NTs, have been most commonly employed in combination with rhodium−carboxylate,[4] ruthenium−porphyrin,[5] manganese−Schiff base,[6] silver−phenanthroline,[7] or copper−pyrazolylborate[8] catalysts. Moderate to good chemical yields and regioselectivities have been achieved in these reactions with a limited set of substrates. Practical limitations include the use of a noncommercial reagent and the production of PhI as a coproduct; improvements which generate the imido reagent in situ from ArSO$_2$NH$_2$/PhI(OAc)$_2$ have been reported.[9] Benzylic amidation and imidation have also been accomplished with limited efficiency employing aryl azides with Co(porphyrin) catalysts[10] and sulfonimidamides with rhodium catalysts.[11]

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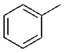
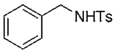
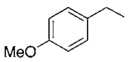
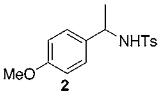
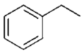
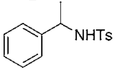
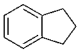
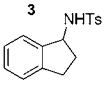
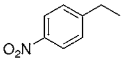
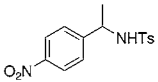
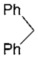
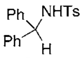
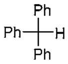
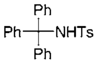
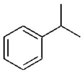
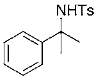
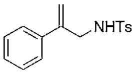
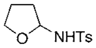
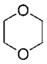
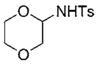
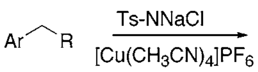
Table 1. Copper-Catalyzed Amidation with Anhydrous Chloramine-T

entry	substrate	product	time (h)	yield (%)[a]
1		 **1**	10	54
2		 **2**	5	77
3		 **3**	6	69
4		 **4**	10	64
5		 **5**	48	15
6		 **6**	10	65
7		 **7**	15	64
8		 **8**  **9**	12	55 **8 : 9** (2.5 : 1)[b]
9		 **10**	10	55
10		 **11**	15	61

[a] Isolated yield after chromatography. [b] Calculated from the ^{1}H NMR spectrum.

The inexpensive, environmentally benign chloramine-T hydrate ($TolSO_2NNaCl{\cdot}H_2O$) has received some attention as a reagent for olefin aziridination[12] and ether α-amidation under catalysis by CuCl[13] or Cu[tris(pyrazolylborate)].[8] Only a few examples of benzylic amidation with this reagent have been reported, with modest yields and variable regioselectivity.[14,8] In search of more efficient and economical systems for the selective amidation of C−H bonds, we have examined the copper-catalyzed reactions of *anhydrous* chloramine-T with representative benzylic and allylic hydrocarbons and ethers. We report here that commercial $[Cu(CH_3CN)_4]PF_6$ effectively catalyzes these reactions with generally good to excellent chemo- and regioselectivity.

Screening experiments were first conducted using anhydrous chloramine-T[15] with toluene and 4-methoxyethylbenzene as test substrates and several commercial copper salts and complexes as potential catalysts to establish reaction viability and to select the preferred catalyst and reaction conditions. From these experiments, it was found that high conversions and good yields of amidation products **1** and **2**[16] were obtained employing 10 mol % of $[Cu(CH_3CN)_4]PF_6$ as the catalyst in acetonitrile at 70 °C with a slight excess of chloramine-T (1.3:1.0 hydrocarbon) with 4 Å molecular sieves (eq 1, Table 1). Small amounts of $TolSO_2NH_2$ were produced as the only significant byproduct.[17]



(1)

1 (Ar = Ph, R = H)
2 (Ar = *p*-$MeOC_6H_4$, R = Me)

Because chloramine-T *trihydrate* has been reported to give modest yields of benzylic amidation products in Cu-promoted reactions with toluene and tetralin,[14] we compared the relative efficiency of the hydrated and anhydrous reagents for the amidation of toluene and 4-methoxyethylbenzene under identical conditions (CH_3CN, 70 °C) with $[Cu(CH_3CN)_4]PF_6$ as catalyst. In both cases, the yield (by NMR analysis) of the benzylic sulfonamide was substantially higher with the anhydrous reagent, and less $TolSO_2NH_2$ was formed: **1**/$TolSO_2NH_2$, 57%/33% (anh.) vs 24%/64% (hyd.); and **2**/$TolSO_2NH_2$, 71%/18% (anh.) vs 65%/23% (hyd.).

The scope and selectivity of the reaction was then investigated with a range of benzylic substrates under the established conditions. The results are summarized in Table 1. Entries 1−8 demonstrate that benzylic substrates with 1°, 2°, and 3 °C−H bonds are all amidated, with a qualitative order of reactivity: 2° > 1° > 3°. A semipreparative scale reaction with 1 g of 4-methoxyethylbenzene gave a comparable yield of **2** (75%). In all but the cumene case, the

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[12] Jain, S. L.; Joseph, J. K.; Sain, B. *J. Mol. Catal. A* **2006**, *256*, 16. Kumar, G. D. K.; Baskaran, S. *Chem. Commun.* **2004**, 1026. Gullick, J.; Taylor, S.; McMorn, P.; Bethell, D.; Page, P. C. Bulman, H. F. E.; King, F.; Hutchings, G. *J. Mol. Catal. A* **2002**, *180*, 85. Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089. Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S.; Derrick, A. M. *J. Org. Chem.* **1998**, *63*, 9569. Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

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[14] Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569.

[15] Commercial chloramine-T trihydrate was dried in a drying pistol over refluxing toluene under (0.1 mm) for 4−5 h. Although a small explosion from dried chloramine-T has once been noted (Klundt, I. L. *Chem. Eng. News* **1977**, *55*, 56), several other studies, including ours, have found no instability during or after drying chloramine-T; e.g.: Kitagawa, H.; Mukaiyama, T. *Chem. Pharm. Bull.* **2002**, *50*, 1276. Barton, D. H. R.; Hay-Motherwell, R. S.; Motherwell, W. B. *J. Chem. Soc., Perkin 1* **1983**, 445. Ando, T.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* **1998**, *39*, 309. Sharpless, K. B.; Hori, T.; Truesdale, L. K.; Dietrich, C. O. *J. Am. Chem. Soc.* **1976**, *98*, 269.

[16] All products were characterized by NMR, MS, and mp and by comparison with reported data.

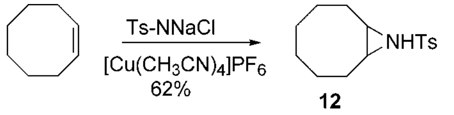
[17] Representative procedure: Anhydrous chloramine-T (1.3 mmol), $Cu(CH_3CN)_4PF_6$ (0.10 mmol), and dry CH_3CN (6 mL) were added to an oven-dried test tube containing molecular sieves (4 Å, 30 mg) under a nitrogen atmosphere. To the well-stirred suspension was added the substrate (1.0 mmol). The reaction mixture was stirred at 65−70 °C (oil bath temperature) for the specified time (Table 1). The mixture was cooled to room temperature and filtered through a short plug of silica followed by washing with 50 mL of chloroform. The solvent was evaporated from the filtrate under reduced pressure. The residue was purified by preparative TLC (6:1, $CHCl_3$/hexane). The products were characterized by ^{1}H and ^{13}C NMR, MS, and mp and by comparison with authentic samples or the literature data; see Supporting Information for full experimental and characterizational details.

reactions were highly regioselective (>95%) with only the benzylic sulfonamide being detected. Curiously, the amidation of cumene (entry 8) afforded a mixture of the expected tertiary amide **8** and the unsaturated amide **9** (ca. 2.5:1).[18] A moderate electronic substrate effect in the reaction is indicated by comparing the conversion rates and ratio of amidation product to $TolSO_2NH_2$ among the three ethyl benzenes (entries 2, 3, and 5), the electron-poor *p*-nitro substrate being only partially converted to **5** after 48 h. We note that the anhydrous chloramine-T/$[Cu(CH_3CN)_4]PF_6$ system provides not only substantially improved amidation yields relative to chloramine-T trihydrate[14] but also greater C−H regioselectivity *vis a vis* the [tris(pyrazolyl)borate]Cu-catalyzed reactions of ArI═NTs and chloramine-T.[8]

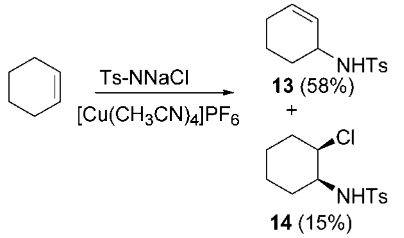
The effectiveness of anhydrous chloramine-T/$[Cu(CH_3CN)_4]PF_6$ for ether amidation was briefly tested with tetrahydrofuran and dioxane as substrates under the same conditions. Moderate yields of the corresponding α-sulfonamido ethers **10** and **11** were obtained (Table 1) along with small amounts of $TolSO_2NH_2$. Comparable results have been reported from the chloramine-T trihydrate/CuCl[13] and [tris(pyrazolyl)borate]Cu-[8]promoted reactions.

Three olefinic substrates were also examined for reactivity toward anhydrous chloramine-T/$[Cu(CH_3CN)_4]PF_6$ with unexpected and contrasting results. Under the standard conditions (12 h) *cis*-cyclooctene afforded a single olefin-derived product that proved to be the corresponding *N*-tosyl aziridine **12** (62%, eq 2). On the other hand, cyclohexene was largely converted to the 3-cyclohexenyl sulfonamide **13** (58%) along with a small amount (15%) of a second product that was identified as *cis*-2-chloro-cyclohexyl-*p*-toluenesulfonamide (**14**) and confirmed by X-ray diffraction (eq 3). With 1-octene as the substrate in the chloramine-T/$[Cu(CH_3CN)_4]PF_6$ reaction, the 2-chloro-*N*-octyl sulfonamide **15** was the only amination product isolated (35%, eq 4). Although both aziridine and allyl amine derivatives are typical products of nitrenoid/cyclic olefin reactions,[2,3,14] the high, substrate-dependent chemoselectivity found here is extraordinary as is the formation of the chloroamine derivatives **14** and **15**. The pathway leading to the latter products is unclear, but the *cis*-stereochemistry of **14** and the 1,2-regiochemistry of **15** are inconsistent with their formation via Cl^--assisted opening of the corresponding aziridines.[19]

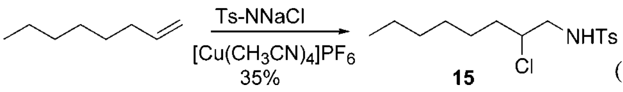
The nature of the active amidating reagent in the present system, like that in most other reported metal-catalyzed amidation reactions, is presently unknown. Although the product selectivities observed in these reactions are suggestive of the intermediacy of a metal−N−Ts complex rather than the free nitrene,[20] identification of the reactive species involved awaits the outcome of ongoing experiments.



(2)

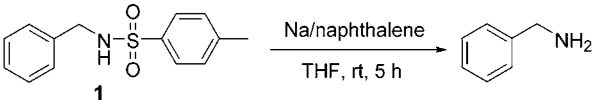


(3)



(4)

Finally, the value of the present reaction as a general entry to benzyl amines is supported by the mild, efficient reductive deprotection of *N*-benzyl sulfonamide **1** (85%, eq 5).[21]



(5)

In conclusion, readily available anhydrous chloramine-T is an effective and selective reagent for the Cu-catalyzed amidation of benzylic hydrocarbons and ethers. Continued studies of the scope, selectivity, and mechanism of these amination reactions are underway.

Acknowledgment. The financial support provided by the National Science Foundation is appreciated. We thank Dr. Douglas Powell for determination of the X-ray structure of **14**.

Supporting Information Available: Detailed experimental procedures and characterization data, including product NMR spectra and X-ray crystallographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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[18] α-Methylstyrene was not detected as an impurity in the cumene by ^1H NMR.

[19] Chloride-induced aziridine opening exhibits the opposite regioselectivity (refs a−c), hence a Cu-assisted pathway may be involved. (a) Das, B.; Krishnaiah, M.; Venkateswarlu, K. *Chem. Lett.* **2007**, *36*, 82. (b) Sabitha, G.; Babu, R. S.; Rajkumar, M.; Reddy, C. S.; Yadav, J. S. *Tetrahedron Lett.* **2001**, *42*, 3955. (c) Cenini, S.; Penoni, A.; Tollari, S. *J. Mol. Catal. A* **1997**, *124*, 109.

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