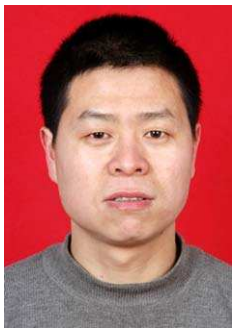
SYNLETT
Spotlight 250

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

N-Hydroxysuccinimide (NHS)

Compiled by Ping'An Wang



Ping'An Wang was born in Shaanxi, P. R. of China. He received his B.Sc. (1999) and M.Sc. (2001) in Organic Chemistry from Northwest University, Xi'an. After his graduation, he joined the research group of Prof. Shengyong Zhang at the Research Center for Chirotechnology, Fourth Military Midecal University (FMMU), Xi'an, P. R. of China. He is currently pursuing his Ph.D. under the supervision of Shengyong Zhang at the same university. His research interests focus on ligand design, asymmetric organocatalysis, and green synthetic methods for organic compounds.

Research Center for Chirotechnology, Fourth Military Medical University, FMMU, Xi'an 710032, P. R. of China
E-mail: ping_an1718@yahoo.com.cn

Introduction

N-Hydroxysuccinimide (NHS, NHSI, or HOSu), a white crystalline solid with a melting point of 99–100 °C, was first introduced by Anderson in peptide synthesis.[1] Since then, NHS has been widely used as activating or protecting reagent in organic and bio-organic synthesis[2] because of its high reactivity, good hydrophilicity, ease of formation of peptide bonds, and commercial availability. Recently, NHS has been exploited for a number of other utilities in synthetic chemistry: it was used as auxiliary for oxidations, activating reagent for selective reductions and coupling reactions of bulky substrates, additive for acceleration of Passerini reactions under aqueous conditions, and efficient ligand for N-arylations. NHS can easily be prepared from equivalent amounts of succinic anhydride and hydroxylamine hydrochloride.[3]

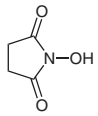
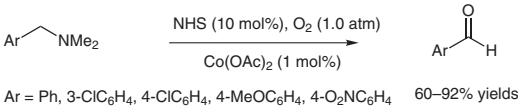


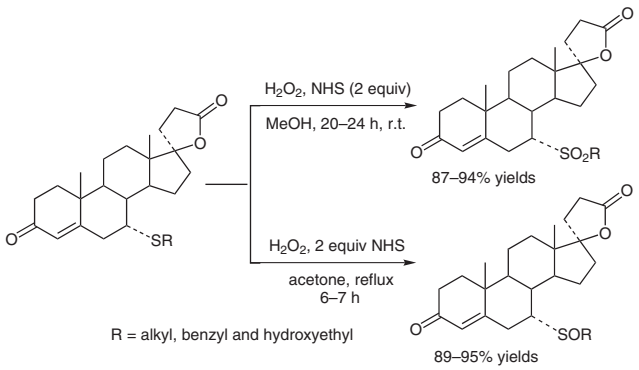
Figure 1 *N*-Hydroxysuccinimide (NHS)

Abstracts

(A) *Oxidation of tertiary benzylamines to aromatic aldehydes:*
Copper(II)-catalyzed aerobic oxidation of tertiary benzylamines in the presence of NHS can produce aromatic aldehydes in good to excellent yields.[4] The mechanism involves a redox chain of a free *N*-oxyl radical between the Co(III) and the Co(II) species. Although the reaction time was prolonged, NHS appears to give higher selectivity than NHPI (*N*-hydroxyphthalimide).

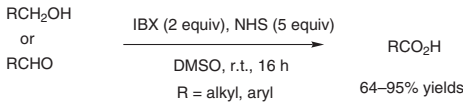


(B) *Selective oxidation of sulfides to sulfoxides and sulfones:*
Hu and co-workers[5] found that spirolactone-related sulfides were selectively oxidized to their corresponding sulfoxides and sulfones by hydrogen peroxide in the presence of NHS. More interestingly, sulfoxides were obtained in acetone under reflux conditions, whereas sulfones were obtained in methanol at room temperature. Many sensitive groups, such as ketones and alkenes, are tolerated in this oxidation process.

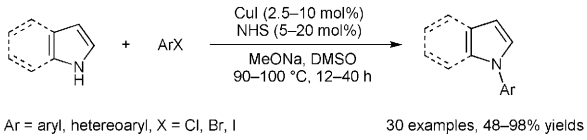


SYNLETT 2008, No. 15, pp 2384–2385
Advanced online publication: 02.07.2008
DOI: 10.1055/s-2008-1067117; Art ID: V25508ST

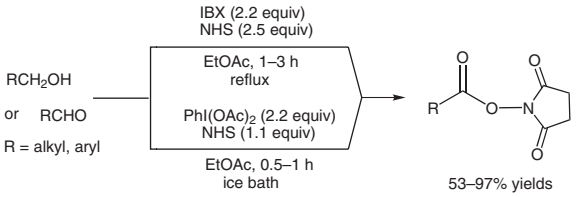
(C) *Oxidation of aldehydes and primary alcohols to carboxylic acids:*
The NHS-mediated oxidation of primary alcohols and aldehydes to form carboxylic acids by using IBX (2-iodoxybenzoic acid) was realized by Giannis and colleagues.[6] The addition of water did not influence the reaction. These methods tolerate a wide variety of functional groups, such as isolated and conjugated double bonds, alkyl halogenides, urethanes, and electron-rich and -poor aromatic compounds. The amino acids can be generated without racemization from the corresponding N-protected α-amino alcohols.



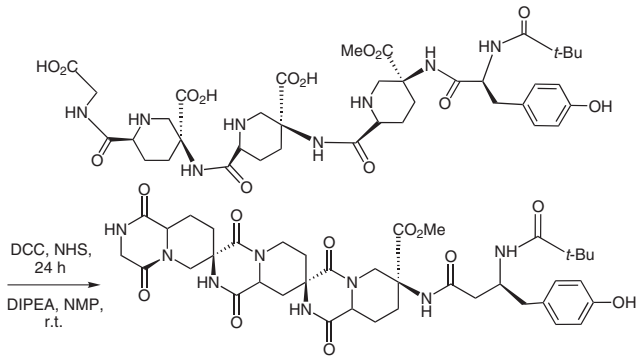
(D) *Copper-catalyzed N-arylation:*
An experimentally simple, efficient, and cheap catalyst system was developed for the N-arylation of pyrroles, indoles, and imidazole with aryl and heteroaryl iodides, bromides, and chlorides in DMSO by using CuI as catalyst, NHS as ligand, and MeONa as base.[7] The coupling reactions tolerated a wide scope of functional groups including nitrile and free NH_2. The high selectivity was also observed in the coupling of N-heterocycles and aryl iodides containing another halide group such as bromine or chlorine.



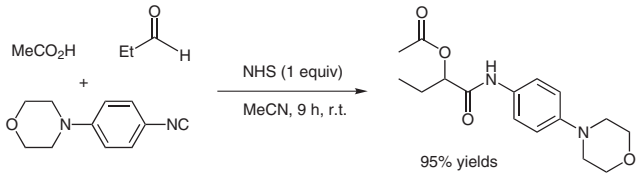
(E) *Promoted oxidation of aldehydes and alcohols to their NHS esters:*
The Pd-free NHS-promoted oxidation of primary alcohols and aldehydes by applying IBX or $PhI(OAc)_2$ to form their corresponding NHS-active esters was developed by Giannis[8] and Liang,[9] respectively. NHS-active esters are valuable intermediates and efficient acylating reagents in peptide synthesis. The reactions were accomplished within 3 hours and the yields ranged from 53% to 97%. NHS does not only act as an esterification partner but also as an activator of the oxidant in the reaction.



(F) *Intramolecular ring-closing amidation:*
Schafmeister and co-workers[10] discovered a novel access to intramolecular ring-closing amidation in the synthesis of spiro-laddered oligomeric peptide. In the presence of NHS, three intramolecular peptide bonds were formed and yielded three six-membered rings in one step.



(G) *Acceleration of the Passerini reaction:*
The Passerini reaction, an isocyanide-based multi-component reaction, was significantly accelerated by addition of 1 equiv of NHS under aqueous conditions at room temperature. The yields of the products were excellent and no side product due to hydrolysis was observed in the process.[11]



References

(1) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1963**, *85*, 3039.
(2) Crimmins, M. T.; DeBaillie, A. C. *J. Am. Chem. Soc.* **2006**, *128*, 4936.
(3) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.
(4) Cecchetto, A.; Minisci, F.; Recupero, F.; Fontana, F.; Pedulli, G. F. *Tetrahedron Lett.* **2002**, *43*, 3605.
(5) Xiong, Z.-G.; Zhang, J.; Hu, X.-M. *Appl. Catal. A* **2008**, *334*, 44.
(6) Mazitschek, R.; Mülbaier, M. M.; Giannis, A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4059.
(7) Ma, H.-C.; Jiang, X.-Z. *J. Org. Chem.* **2007**, *72*, 8943.
(8) Schulze, A.; Giannis, A. *Adv. Synth. Catal.* **2004**, *346*, 252.
(9) Wang, N.-W.; Liu, R.-H.; Xu, Q.; Liang, X.-M. *Chem. Lett.* **2006**, *35*, 566.
(10) Gupta, S.; Das, B. C.; Schafmeister, C. E. *Org. Lett.* **2005**, *7*, 2861.
(11) Mironov, M. A.; Ivantsova, M. N.; Tokareva, M. I.; Mokrushin, V. S. *Tetrahedron Lett.* **2005**, *46*, 3957.