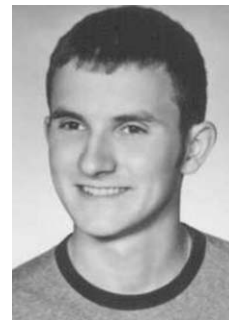


SYNLETT Spotlight 157

N-Iodosuccinimide (NIS)

Compiled by Adam Sniady



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

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Introduction

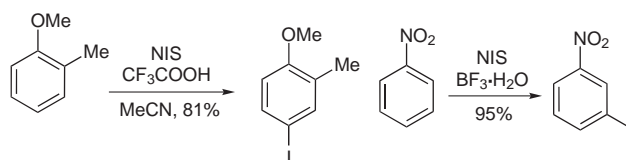
N-Iodosuccinimide (NIS) is a well-known iodination reagent that has found many applications in organic synthesis since it was first reported by Bunge.^{1,2} It is a colorless, stable solid, commercially available, and is widely used in organic transformations. It can be applied for iodination of arenes,^{3,4} halodecarboxylation,^{5,6} iodolysis of the Si–C bond,^{7,8} and chemoselective cleavage of silyl ethers.⁹ Recent reports employ NIS in ring-opening reactions¹⁰ or electrophilic cyclizations to yield substituted furans¹¹ and isoxazolidines.¹² Some of the examples

reported in this article have roots in earlier reactions that have already been reviewed.¹³

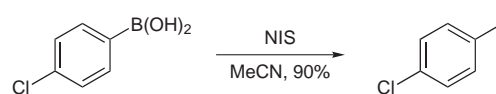
One way to prepare NIS is to combine *N*-silversuccinimide and molecular iodine. The reaction is carried out in dioxane, since in acetone the formation of a lachrymatory side-product was observed.² NIS can also be generated *in situ* from sodium iodide and *N*-chlorosuccinimide in acetonitrile.¹⁴ The use of Na¹²⁵I in the last process leads to isotopically labelled NIS, rendering the reagent useful in medical sciences for the preparation of radiolabelled diagnostic or therapeutic agents.¹⁵

Abstracts

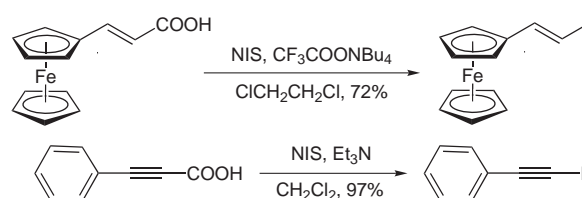
(A) Regioselective iodination of activated aromatic compounds can be achieved using the combination of NIS and catalytic amounts of trifluoroacetic acid.³ The reaction is *para*-directed. Iodine trifluoroacetate is pointed out as the active species for iodination. This highly reactive electrophile facilitates iodination in short reaction times at room temperature. Direct iodination of deactivated aromatics (such as nitrobenzene) can be carried out under mild conditions using NIS in combination with boron trifluoride monohydrate.⁴ Also, 5-iodopyrimidines and their nucleosides can be obtained with the use of NIS in microwave-assisted protocol.¹⁶



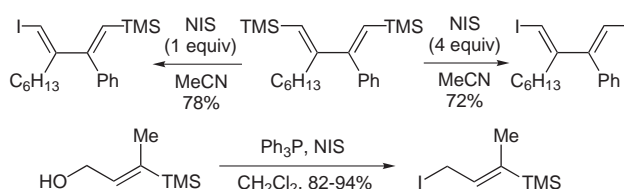
(B) Iodoarenes can also be synthesized from aryl boronic acids and NIS.¹⁴ The procedure may be applied when the presence of strong oxidizing reagents must be avoided. The reaction proceeds usually in a chemoselective manner yielding only the *ipso*-substituted products.



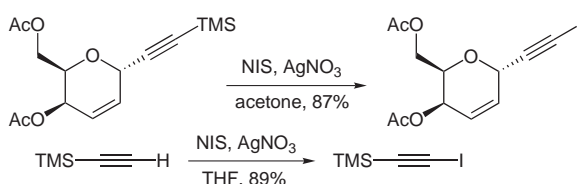
(C) Hunsdiecker-type halodecarboxylation can be applied in metal coordination sphere. Halodecarboxylation of ferrocenylacrylic acid with the use of NIS in the presence of tetrabutylammonium trifluoroacetate (cat.) affords corresponding β -iodovinylferrocene⁵ with retention of *trans*-configuration. The reaction is temperature-dependent: reaction at 35 °C gives the product with only 10% yield, but after reaction at –40 °C, β -iodovinylferrocene is isolated in 72% yield. For the Hunsdiecker reaction of α,β -unsaturated carboxylic acids triethylamine renders the best results as catalyst that accompany NIS.⁶



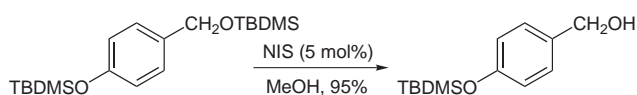
(D) Regioselective iodolysis of the Si–C bond with NIS can also be accomplished.⁷ An equimolar amount of NIS, lower temperature (–50 → 0 °C), and shorter reaction time (6 h) allow to selectively cleave the Si–C bond at the more electron-rich double bond. Excess of NIS (4 equiv) and longer reaction time (24 h) furnishes the corresponding diiodide. However, presence of NIS does not cleave the TMS group during conversion of the allylic alcohol to the corresponding iodide.¹⁷



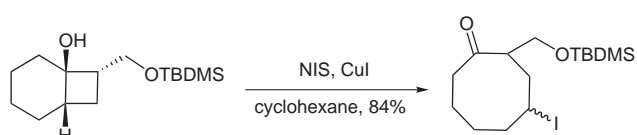
(E) A convenient method for a one-step conversion of trimethylsilylalkynes into haloacetylenes via silver acetylide has been developed.⁸ After addition of NIS, silver is replaced by iodine to furnish alkynyl iodides in high yields. Terminal acetylenes can be converted into haloalkynes also with AgNO₃/NIS.¹⁸ Iodination of trimethylsilyl-acetylene can be carried out in chemoselective manner with iodine exclusively replacing hydrogen.¹⁹



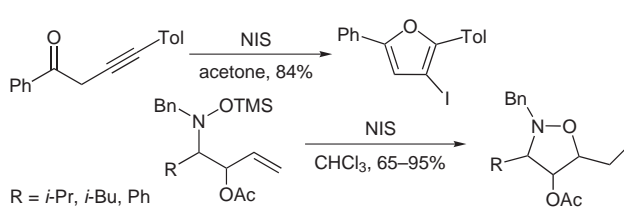
(F) NIS has also found an application in the cleavage of TBDMS ethers of primary, secondary, tertiary, and allylic alcohols.⁹ The protocol does not affect the C=C double bond; also no elimination products were observed during the reaction of TBDMS ethers of tertiary alcohols. Chemoselective deprotection of alkyl TBDMS ethers in the presence of aryl TBDMS ethers is an asset for this procedure.



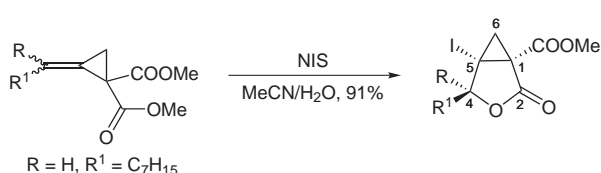
(G) A novel approach for synthesis of medium-sized γ -iodocycloalkanones from bicyclo[n.2.0] substrates has been reported.¹⁰ NIS promotes radical reaction of bicyclic cyclobutanols to give cyclo-octanones in medium to good yields. Addition of a catalytic amount of CuI improves the reaction rate and increases the yield.



(H) Our group developed NIS-triggered 5-*endo-dig* electrophilic cyclization of 1,4-disubstituted but-3-yn-1-ones leading to 2,5-disubstituted 3-iodofurans. This reaction proceeds under mild conditions with excellent regiocontrol and high yields (81–94%).¹¹ Relevant reactions can be carried out when 2-(1-alkynyl)-2-alken-1-ones in the presence of nucleophiles^{20a} or *o*-alkynylanisoles in the presence of BCl₃^{20b} are treated with NIS. A stereospecific 5-*exo-trig* electrophilic cyclization that affords highly substituted isoxazolidines, has been reported.¹²



(I) Highly stereoselective iodolactonization of alkylidenecyclopropyl esters using NIS appears to be more efficient than with I₂ or ICl.²¹ This new route to 3-oxabicyclo[3.1.0]hexan-2-ones gives 1,5-*cis* stereochemistry, while the stereochemical outcome between 4- and 5-position is a consequence of steric hindrance caused by R and R¹ groups, with the bulkier group *trans* to the iodine atom.



References and Notes

- Bunge, N. *Justus Liebigs Ann. Chem.* **1870**, 7, 117.
- Djerassi, C.; Lenk, C. T. *J. Am. Chem. Soc.* **1953**, 75, 3493.
- Castanet, A.-S.; Colobert, F.; Broutin, P.-E. *Tetrahedron Lett.* **2002**, 43, 5047.
- Prakash, G. K. S.; Mathew, T.; Hoole, D.; Esteves, P. M.; Wang, Q.; Rasul, G.; Olah, G. A. *J. Am. Chem. Soc.* **2004**, 126, 15770.
- Naskar, D.; Das, S. K.; Giribabu, L.; Maiya, B. G.; Roy, S. *Organometallics* **2000**, 19, 1464.
- Das, J. P.; Roy, S. *J. Org. Chem.* **2002**, 67, 7861.
- Morita, R.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Org. Biomol. Chem.* **2005**, 3, 1263.
- Nishikawa, T.; Shibuya, S.; Hosokawa, S.; Isobe, M. *Synlett* **1994**, 485.
- Karimi, B.; Zamani, A.; Zareyee, D. *Tetrahedron Lett.* **2004**, 45, 9139.
- Takasu, K.; Nagao, S.; Ihara, M. *Tetrahedron Lett.* **2005**, 46, 1005.
- Sniady, A.; Wheeler, K. A.; Dembinski, R. *Org. Lett.* **2005**, 7, 1769.
- Lombardo, M.; Rispoli, G.; Licciulli, S.; Trombini, C.; Dhavale, D. D. *Tetrahedron Lett.* **2005**, 46, 3789.
- Speicher, A.; Eicher, T. *J. Prakt. Chem.* **1998**, 340, 278.
- Thiebes, C.; Prakash, G. K. S.; Petasis, N. A.; Olah, G. A. *Synlett* **1998**, 141.
- Dewanjee, M. K. *Radioiodination: Theory, Practice, and Biological Applications*; Kluwer Academic Publishers: Boston, **1992**, 115.
- Paolini, L.; Petricci, E.; Corelli, F.; Botta, M. *Synthesis* **2003**, 1039.
- Singletary, J. A.; Lam, H.; Dudley, G. B. *J. Org. Chem.* **2005**, 70, 739.
- Hofmeister, H.; Annen, K.; Laurent, H.; Wiechert, R. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 727.
- Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. *J. Org. Chem.* **1995**, 60, 6829.
- (a) Yao, T.; Zhang, X.; Larock, R. C. *J. Org. Chem.* **2005**, 70, 7679. (b) Colobert, F.; Castanet, A.-S.; Abillard, O. *Eur. J. Org. Chem.* **2005**, 3334.
- Ma, S.; Lu, L. *J. Org. Chem.* **2005**, 70, 7629.