**SPOTLIGHT**

**SYNLETT Spotlight 313**

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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**N-Chlorosuccinimide (NCS)**

Compiled by Pankaj Chauhan

Pankaj Chauhan was born in 1984 in Rohru, India and received his B.Sc. Degree from Himachal Pardesh University Shimla, in 2004. After completing his master degree from Guru Nanak Dev University, Amritsar in 2007, he commenced his Ph.D. studies under the supervision of Dr. Swapandeep Singh Chimni. His research interests include asymmetric organocatalysis particularly the asymmetric synthesis of new chiral entity by the application of bifunctional organocatalysts and green chemistry.

Department of Chemistry, Guru Nanak Dev University, Amritsar 143005, India
E-mail: pukch89@gmail.com

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**Introduction**

N-Chlorosuccinimide (NCS) is a very powerful chlorinating reagent, which also finds applications as mild oxidizing agent. This colourless, commercially available, inexpensive solid is thermally stable to some extent. It is least toxic as well as highly selective compared to chlorinating agents, such as 1,3-dichloro-5,5-dimethylhydantoin (NDDH) and trichloroisocyanuric acid (TCCA). In the last two decades, it has emerged as a useful mediator or catalyst for many chemical reactions, such as functional groups replacement, halocyclization, formation of heterocyclic systems, carbon–carbon bond formation, rearrangement, deprotections, and functional group transformations.\(^1\) NCS also possess some bacteriostatic and anti-bactericidal activity as it forms hypochlorous acid upon slow hydrolysis with water.\(^2\) NCS is soluble in carbon tetrachloride at room temperature while its conjugate product succinimide is not, which leads to easy separation from the reaction mixture.

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**Preparation**

NCS was firstly prepared by Bender in 1886 by chlorination of succinimide with chlorinated lime.\(^3\) It can also be prepared by the chlorination of succinimide with potassium hypochlorite or \(\text{Cl}_2\) in aqueous sodium hydroxide.\(^4\)

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**Abstracts**

(A) Håkansson and co-workers have discovered the absolute asymmetric synthesis of 1-chloroindene in 87–89% ee and 78–97% yield utilizing NCS and a single crystal of novel diindenylzinc reagent \([\text{Zn(ind)}_2(\text{pic})_2]\).\(^5\)

(B) The application of NCS and an organophosphine reagent for the synthesis of polychlorinated hydrocarbon motifs with multiple sp\(^3\) C–Cl bonds arranged in a regularly spaced pattern with proper stereochemical configuration has been developed by Tanaka and co-workers.\(^6\)

(C) Nasim and Crooks have utilized the oxidative power of NCS for the convenient synthesis of pharmacologically important 1,2,4-thiadiazolidine-3,5-diones (TDZD) via an oxidative condensation of isothiocyanate and isocyanate.\(^7\) This method provides a safe and easy alternate method for the synthesis of thiadiazolidinones to the classical reagents like chlorine gas or \(\text{SO}_2\text{Cl}_2\).

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(D) De Kimpe and co-workers have developed the chlorination of 1-alkyl-3,4-dihydroisoquinolines with NCS to yield 1-chloroalkyl-1-(2,2-dichloroalkyl)-, and 1-(trichloromethyl)-3,4-dihydroisoquinolines which serves as suitable precursors for the synthesis of functionalized isoquinolines by aromatization with alkoxide involving sequential 1,4-dehydrochlorination, tautomerization, and nucleophilic substitution. 1-Vinylisoquinoline and 1-methylisoquinolines could be synthesized selectively depending on the substitution pattern on position 1.18

(E) Yadav et al. have developed a simple, environmentally benign, and practical protocol for the selective synthesis of α-keto thiocarbamates in excellent yields via α-sulfenylation of ketones with thioanisole mediated by NCS.9

(F) The thiourea-catalyzed regioselective synthesis of the chlorohydrins has been developed by Bentley et al. with NCS chlorination of aliphatic olefins, stilbenes, chalcones, and indenes were found tolerable under the reaction conditions.10

(G) α-Thio-β-chloroacrylamide analogues have been synthesized by treatment of α-thioamides with NCS.11 Different substituents, such as aryl and alkylthio as well as primary, secondary and tertiary amides have been employed. In most cases, the chloroacrylamides were formed exclusively as E-stereoisomers; however, with tertiary propanamides or with amides derived from butanoic or pentanoic acid a mixture of E- and Z-isomers were formed.

(H) Michael et al. have explored the application of NCS for the functional group tolerant, exo-selective synthesis of a variety of five-and six-membered ring systems via a mild and facile palladium-catalyzed intramolecular chloramination of unactivated alkenes under mild conditions.12 Various valuable acid sensitive groups were tolerated under the reaction conditions.

(I) A mild approach for the synthesis of benzonitriles from corresponding benzaldehyde oximes substituted with electron-donating groups using NCS and pyridine has been developed by Gucma and Golebiewski.13 However, benzaldehyde oxime and oximes of aliphatic aldehydes are deprotected to the parent aldehydes.

References