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Spotlight 471

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

N-Cyano-*N*-phenyl-*p*-toluenesulfonamide

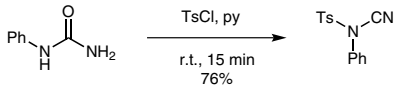
Compiled by Shanyan Mo

Shanyan Mo was born in 1987 and raised in Guiping, Guangxi Zhuang Autonomous Region, P. R. of China. In 2010, he received his B.S. degree from the Beijing University of Chemical Technology. He is currently pursuing his doctoral studies under the supervision of Professor Jiaxi Xu at the same university. From September 2013 to February 2014, he was a visitor student at the University of Hull under the supervision of Professor Carl Redshaw. His research now focuses on the chemospecific intramolecular Büchner reaction, the replacement of precious metals in carbene reactions, and the cascade reaction for the synthesis of 1,4,2,5-dioxadiazines.

State Key Laboratory of Chemical Resource Engineering, Department of Organic Chemistry, Faculty of Science, Beijing University of Chemical Technology, Beijing 100029, P. R. of China
E-mail: moshanyan@gmail.com

Introduction

N-Cyano-*N*-phenyl-*p*-toluenesulfonamide (NCTS) is a bench-stable colorless solid (mp 85–87 °C)[1]. It is commercially available and can be readily synthesized by Kurzer's method[2] on a large scale from inexpensive phenylurea and *p*-toluenesulfonyl chloride with pyridine as solvent[2] (Scheme 1). The preparation of NCTS does not require the use of toxic cyanogen halides; thus, comparing to other cyanating reagent, such as *p*-toluenesulfonyl cyanide,[3] *N*-cyanobenzimidazole,[4] *N*-cyanophthalimide[4b,c] and especially metal cyanide[5], NCTS can be accessed more safely.

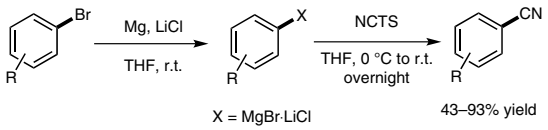


Scheme 1

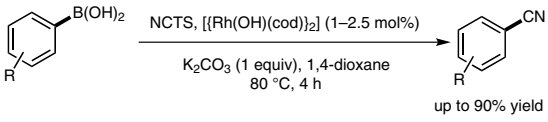
Owing to the *N*–CN bond, NCTS serves as an electrophilic cyanating reagent. In addition, NCTS is employed in the direct C–H cyanation to a variety of (hetero)arenes. The byproduct for the cyanation using NCTS is *N*-phenyl-*p*-toluenesulfonamide, an environmentally benign compound. The cyanation process features the advantages of wide substrate scopes, safe operations, and moderate to excellent yields.

Abstracts

(A) *Cyanation of Aryl and Heteroaryl Bromides through In Situ Generated Grignard Reagents:*
Beller and co-workers disclosed the first use of NCTS as cyanating reagent.[2] (Hetero)aryl bromides were converted into the corresponding Grignard reagents in the presence of LiCl. Subsequent cyanation of the Grignard reagents afforded (hetero)aryl nitriles. Applying this method, several interesting agrochemical and pharmaceutical intermediates, for example, 2-chloro-5-cyanopyridine and 2-(*para*-tolyl)benzonitrile, were synthesized.



(B) *Rhodium-Catalyzed Cyanation of Aryl and Alkenyl Boronic Acids:*
Catalyzed by $[Rh(OH)(cod)]_2$, aryl and alkenyl boronic acids were successfully cyanated by NCTS.[6] The combination of this procedure with the direct borylation of arenes and hydroboration of alkynes yields nitriles in a more straightforward fashion.



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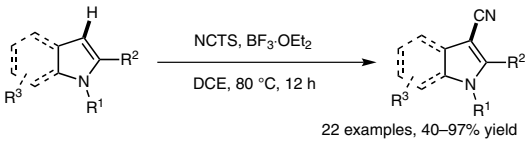
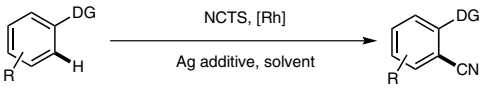
(C) *Cyanation of Indoles and Pyrroles Catalyzed by a Lewis Acid:*
Wang described a direct cyanation of indoles and pyrroles by NCTS with $BF_3{\cdot}OEt_2$ as catalyst.[7] The protocol does not involve a transition-metal catalyst and achieves excellent regioselectivity, providing accesss to various 3-cyanoindoles and 2-cyanopyrroles. Additionally, the cyanation of electron-rich 1,3,5-trimethoxybenzene is also successful, although with low yield.

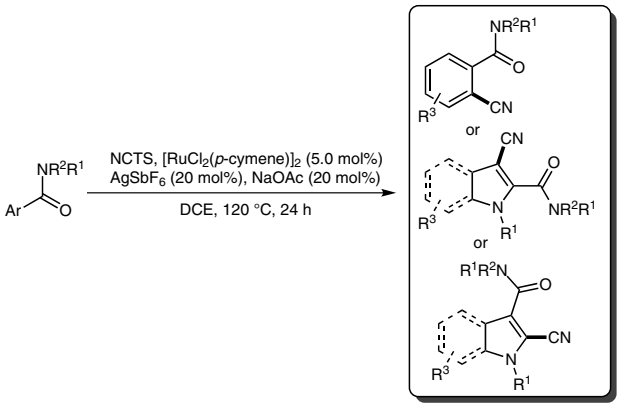


(D) *Rhodium-Catalyzed Directed C–H Cyanation of Arenes:*
Fu and co-workers achieved a $[Cp^*RhCl_2]_2$-catalyzed directed C–H cyanation with NCTS.[8] Many different directing groups, for example, oxime, pyridine and pyrazole can be used in the C–H cyanation process. The substrate can be extended to heteroarenes, such as furan, thiophene, pyrrole and indole. The overall transformation has been identified to involve a C–H activation process via a KIE experiment. Independently, Anbarasan and colleagues also reported a $[Cp^*RhCl_2]_2$-catalyzed directed C–H cyanation with NCTS, but with different additives, solvent, and directing groups.[9] Both groups developed their methods to synthesize intermediates for some important pharmaceuticals. Most recently, using the same catalytic system, Gu et al. accomplished the directed C–H cyanation of dialkyl phosphoryl directing arenes.[10]



Fu's work: $[RhCp^*(MeCN)_3](SbF_6)_2$, Ag_2CO_3, dioxane, 120 °C
DG = oxime, isoquinoline, pyrazine, pyrimidine, dihydroimidazole, dihydrooxazole
Anbarasan's work: $[Cp^*RhCl_2]_2$, Ag_2SbF_6, toluene, 120 °C
DG = pyridine derivatives, pyrazine, pyrimidine
Gu's work: $[Cp^*RhCl_2]_2$, Ag_2SbF_6, DCE, 120 °C
DG = phosphoryl

(E) *Ruthenium(II)-Catalyzed C–H Cyanations of (Hetero)aryl Formamide:*
Employing a robust ruthenium(II) catalyst, Liu and Ackermann achieved a direct cyanation of arenes and heteroarenes with amide as directing group.[11] A high site-selectivity was obtained for the heteroarene substrates. Mechanistic studies indicate a reversible C–H metalation mechanism involving a cationic ruthenium(II) complex.



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