SYNLETT Spotlight 471

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

Compiled by Shanyan Mo

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-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 method² on a large scale from inexpensive phenylurea and *p*-toluenesulfonyl chloride with pyridine as solvent² (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 cyanide⁵, 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.

(C) *Cyanation of Indoles and Pyrroles Catalyzed by a Lewis Acid:* Wang described a direct cyanation of indoles and pyrroles by NCTS with $\text{BF}_3 \cdot \text{OEt}_2$ as catalyst.⁷ The protocol does not involve a transition-metal catalyst and achieves excellent regioselectivity, providing access 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 $[\text{Cp}^*\text{RhCl}_2]_2$ -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 $[\text{Cp}^*\text{RhCl}_2]_2$ -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: $[\text{RhCp}^*(\text{MeCN})_3](\text{SbF}_6)_2$, Ag_2CO_3 , dioxane, 120 °C
 DG = oxime, isoquinoline, pyrazine, pyrimidine, dihydroimidazole, dihydrooxazole
 Anbarasan's work: $[\text{Cp}^*\text{RhCl}_2]_2$, Ag_2SbF_6 , toluene, 120 °C
 DG = pyridine derivatives, pyrazine, pyrimidine
 Gu's work: $[\text{Cp}^*\text{RhCl}_2]_2$, 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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