SYNLETT
Spotlight 445

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

Toluenesulfonyl Cyanide (TsCN)

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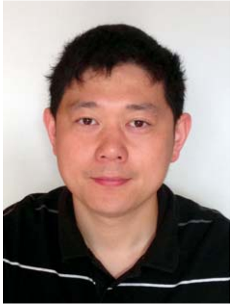

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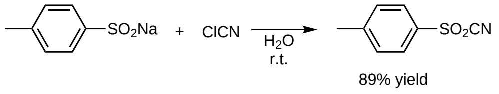
Introduction

Toluenesulfonyl cyanide (TsCN) is a convenient and versatile cyanide source that has great potential in organic synthesis. It displays useful reactivity for electrophilic cyanation of aromatic compounds,[1] carbonyl compounds,[2] and other types of organic compounds.[3] It has been used in radical-mediated cyanation[4] and hydrocyanation[5] reactions. Furthermore, TsCN has been reported to be a good component for [4+2][6] and [3+2][7] cycloaddition reactions. The sulfonyl tetrazoles produced from 1,3-dipolar cycloaddition of TsCN with azides can be further elaborated using nucleophilic aromatic substitution (S_NAr). This two-step process represents an interesting ligation strategy that probably warrants greater exploration in chemical biology.[8] Other uses of TsCN in the recent literature include reactions with allylic alcohols to make allyl sulfones,[9] and palladium-catalyzed C–H activation of arenes to synthesize diaryl sulfides.[10]

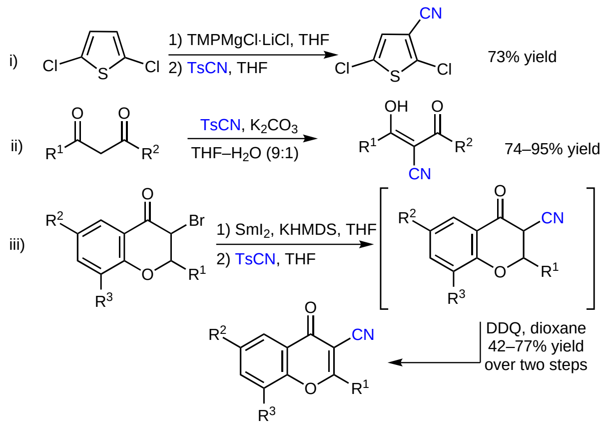
TsCN is a white crystalline solid (mp 49–50 °C) that is available from dozens of commercial sources. It can be readily prepared in the lab by several methods (Scheme 1).[11] Compared to other commonly used CN^+ equivalents, such as cyanogen bromide [LD_{50} (rats, orally) = 25–50 mg/kg],[12] TsCN is less toxic [LD_{50} (rats, orally) = 800–1000 mg/kg][13] and has a longer shelf life. Hence, TsCN will likely continue to serve as an important and versatile reagent for organic synthesis.



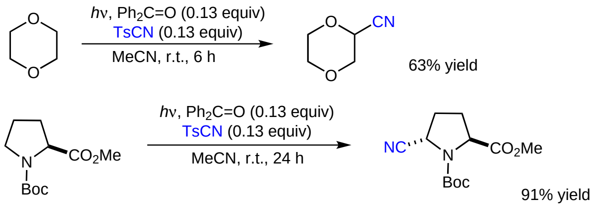
Scheme 1 Cox and Ghosh's synthesis of toluenesulfonyl cyanide[11b]

Abstracts

(A) *CN^+ Source for Electrophilic Cyanation*
The Knochel group has utilized TsCN as an electrophilic reagent to trap a variety of organomagnesium compounds. Notably: i) Magnesiation of 2,5-dichlorothiophene followed by reaction with TsCN provides the aryl nitrile in 73% yield.[1] α-Cyanation of ketones has been one important application of TsCN; ii) Under mildly basic conditions, 1,3-dicarbonyl compounds can be expeditiously α-cyanated using TsCN. Both cyclic and acyclic substrates undergo this transformation well, giving good to excellent yields;[2a] iii) To realize α-cyanation of more sensitive ketones or esters, Hilmersson and coworkers have developed a SmI_2/KHMDS-mediated Reformatsky-type cyanation.[2b] TsCN is found to be the 'most suitable' cyanating agent for a putative heteroleptic RSmI(HMDS) complex. The resulting 3-cyano-chroman-4-ones are further oxidized to the more stable chromone derivatives in up to 77% yield over the two steps.



(B) *CN• Source for Free-Radical Cyanation*
Direct C(sp^3)–H cyanation is achieved via a photoinduced radical generation process. The photosensitizer benzophenone is applied to generate carbon radicals from alkanes, benzylic compounds, alcohols, ethers, and amines. Trapped in situ by TsCN, these radicals yield the corresponding nitriles in moderate to excellent yields. Protected L-proline is cyanated in a highly regio- and diastereoselective manner at the δ-position in 91% yield (based on added TsCN).[4]



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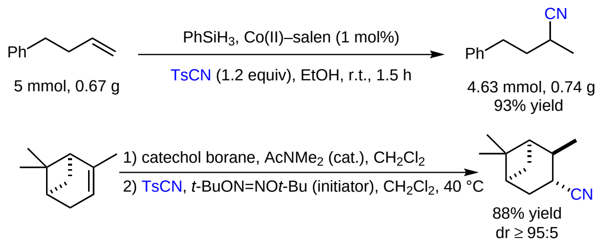
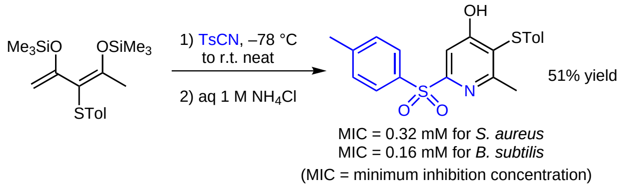
(C) *$\mathrm{CN}^\bullet$ Source for Hydrocyanation*

Carreira and co-workers have disclosed a unique hydrocyanation of unactivated olefins, using tosyl cyanide and phenylsilane under the catalysis of Co(II)–salen complexes. This practical method displays a broad substrate scope and excellent Markovnikov selectivity.[5a] Alternatively, a sequential hydroboration–cyanation process converts olefins into cyano compounds in an anti-Markovnikov fashion.[5b]



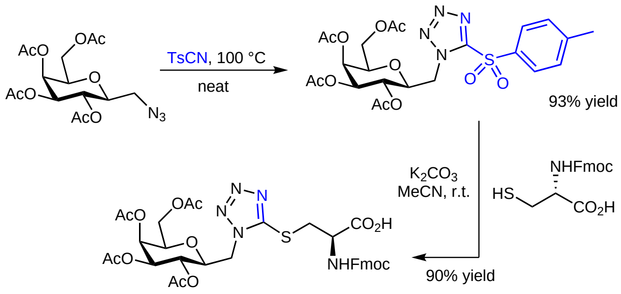
(D) *Dienophile for [4+2] Hetero-Diels–Alder (DA) Reaction*

Hetero-DA reactions of tosyl cyanide and 1,3-bis(trimethylsiloxy)-1,3-butadienes have recently been studied by Langer and co-workers.[6] After acidic work-up, the reactions afford a series of 2-(arylsulfonyl)-4-hydroxypyridines, among which the 5-tolylthio-substituted compound shows promising antibiotic activity against Gram-positive bacteria.



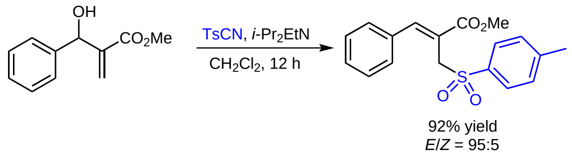
(E) *Dipolarophile for [3+2] Huisgen Cycloaddition*

The 1,3-dipolar cycloaddition of TsCN and azides was first introduced by Sharpless and Demko as a 'click chemistry' strategy.[7a] A Cu(I)-promoted version was later reported under mild conditions.[7b] Recently, the Dondoni group have employed this cycloaddition–$\mathrm{S_NAr}$ sequence to make novel glycoconjugates.[8] Noteworthy, thermal cycloaddition of β-azidomethyl galactoside and TsCN produces 1-alkyl-5-sulfonyl tetrazole in excellent yield (93%). Treatment with *N*-Fmoc cysteine under basic conditions provides tetrazole-tethered *C*-galactosyl cysteine, an unnatural *C*-glycosylated amino acid suitable for automated peptide synthesis.



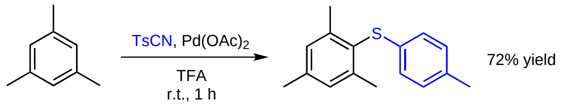
(F) *Sulfonyl Source for Synthesis of Allyl Sulfones*

In an unprecedented organic transformation, TsCN reacts with allylic alcohols to form allyl cyanate intermediates under basic conditions. The expelled *p*-tolyl sufinate then attacks in an $\mathrm{S_N2'}$ fashion, with elimination of HOCN, affording trisubstituted allyl sulfones in high yield (80–92%).[9]



(G) *Sulfur Source for Synthesis of Diaryl Sulfides*

A direct reductive thiolation of arenes is reported exploiting TsCN as the key sulfur source.[10] This Pd(II)-catalyzed procedure produces thioethers in 37–76% yield with excellent chemoselectivity and moderate regioselectivity.



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