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Deoxycyanamidation of Alcohols with *N*-Cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS)

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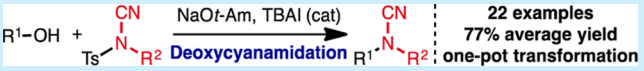
Supporting Information

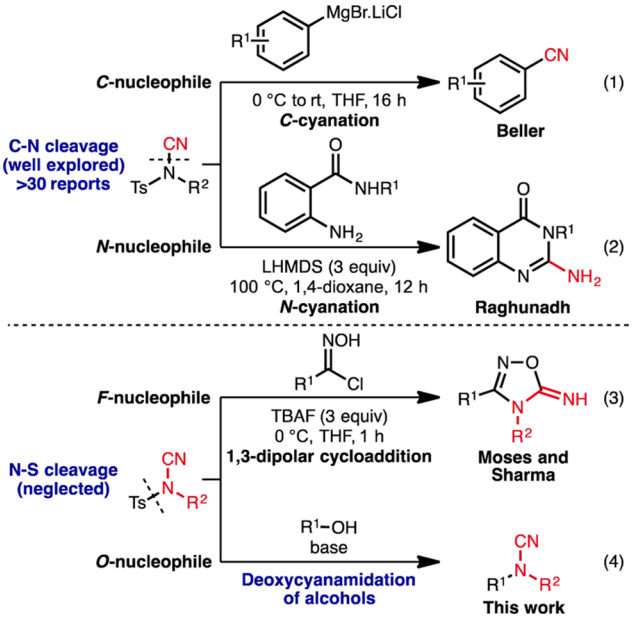
ABSTRACT: The first one-pot deoxycyanamidation of alcohols has been developed using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) as both a sulfonyl transfer reagent and a cyanamide source, accessing a diverse range of tertiary cyanamides in excellent isolated yields. This approach exploits the underdeveloped desulfonylative (N−S bond cleavage) reactivity pathway of NCTS, which is more commonly employed for electrophilic *C*- and *N*-cyanation processes.



The nitrile functional group holds a privileged position within synthetic chemistry and is a common motif within natural products, agrochemicals, and pharmaceuticals.[1] As such, a diverse array of synthetic methodologies have been developed to access nitrile-containing compounds. Electrophilic cyanation describes the reaction of *C*-, *N*-, *O*-, and *S*-based nucleophiles with electrophilic nitrile sources "$^{+}$CN".[2] Traditionally, cyanogen halides have been employed for this purpose,[3] but their high associated toxicity has driven the development of alternative electrophilic cyanating reagents including cyanates (O−CN),[4] thiocyanates (S−CN),[5] cyanamides (N−CN),[6] nitriles (C−CN),[7] and hypervalent iodine reagents (I−CN).[8]

In 2011, Beller employed *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS),[9] as an electrophilic cyanating reagent for the *C*-cyanation of aryl Grignards (Scheme 1, eq 1).[10] Easily accessible in one step from inexpensive phenylurea, NCTS has subsequently attracted widespread interest from the synthetic community and has been applied to a diverse range of *C*-cyanation processes.[11] In 2015, Raghunadh reported the use of NCTS in *N*-cyanation, accessing quinazolinones upon intramolecular cyclization of a cyanamide intermediate (Scheme 1, eq 2).[12] In comparison to the use of NCTS as an electrophilic *C*- and *N*-cyanating reagent, the alternative desulfonylative pathway, via N−S bond cleavage, has been largely overlooked.[13] In 2016, Moses and Sharma reported the desulfonylative formation of cyanamide anions from NCTS via treatment with tetrabutylammonium fluoride.[14] An intermolecular cyclizative capture of the released cyanamide anion with nitrile oxides enabled the synthesis of various oxadiazol-5-imines (Scheme 1, eq 3). Taking inspiration from these reports, we envisaged a deoxycyanamidation of alcohols, proceeding via an initial *N*- to *O*-sulfonyl transfer, followed by a recombination of the resulting cyanamide anion and alkyl sulfonate to access biologically relevant and synthetically useful cyanamide products (Scheme 1, eq 4).[15] The approach would expand the reactivity profile of NCTS to include *O*-nucleophiles, permitting access to a diverse range of bespoke cyanamide products through variation of the alcohol and sulfonamide starting materials. Herein, we report the successful implementation of this strategy and describe the first one-pot deoxycyanamidation protocol of primary and secondary alcohols.

Scheme 1. Previous Work and Outline of the Deoxycyanamidation Strategy



In order to test our hypothesis, we selected 2-fluorobenzyl alcohol **1** and NCTS **2** (1.1 equiv) in bench-grade THF as a model system, cognizant of the opportunity to monitor reaction progress using in situ ^{19}F NMR (Table 1).[16] We were

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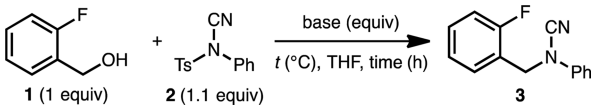
Table 1. Optimization of Deoxycyanamidation Protocol[a]



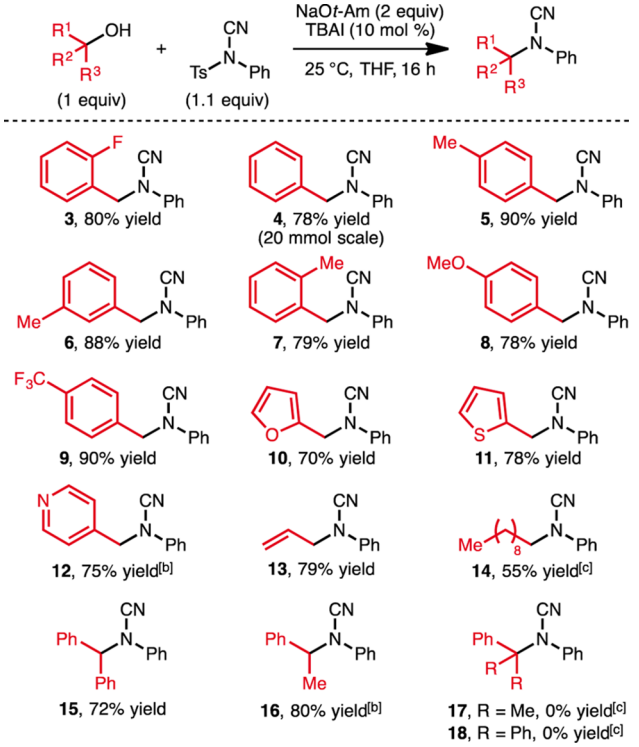
entry	base (equiv)	t (°C)	time (h)	yield[b] (%)
1	NaH (3)	50	0.5	84
2	NaH (2)	rt	6	80
3	DBN (2)	rt	6	0
4	DBU (2)	rt	6	60
5	TBD (2)	rt	6	32
6	KO*t*-Bu (2)	rt	6	85
7	NaO*t*-Am (2)	rt	6	85
8[c]	**NaO*t*-Am (2)**	**rt**	**3**	**100 (80)**
9[c]	NaO*t*-Am (1.1)	rt	23	80

[a]Reactions performed using 1 mmol of alcohol **1** and bench-grade THF. [**1**] = 0.2 M. [b]Yield as determined by ^{19}F NMR analysis of crude reaction mixture with 1,3,5-trifluorobenzene as the internal standard. Isolated yield given in brackets. [c]With tetrabutylammonium iodide (10 mol %).

encouraged to observe 84% conversion to cyanamide **3** using sodium hydride (3 equiv) as a base at 50 °C (Table 1, entry 1). The reaction could be performed at 25 °C, and the quantity of base reduced to 2 equiv without any significant drop in conversion (Table 1, entry 2). Considering the inherent safety concerns associated with using NaH, particularly on a large scale,[17] we searched for alternative bases. Treatment of **1** and **2** (1.1 equiv) with 2 equiv of amidine (DBN and DBU) and guanidine (TBD) bases all gave reduced conversion to cyanamide **3** (Table 1, entries 3–5). To our delight, potassium *tert*-butoxide and sodium *tert*-pentoxide are effective substitutes for NaH, giving comparable conversions to **3** (Table 1, entries 6 and 7).[18] These reactions are typically heterogeneous, and it was found that using TBAI (10 mol %) as an additive with sodium *tert*-pentoxide (2 equiv) gave complete conversion to cyanamide **3** after 1 h at 25 °C with an 80% isolated yield (Table 1, entry 8).

For the purposes of assessing the scope of this protocol, the reaction time was extended to 16 h to ensure full conversion across a range of substrates (Scheme 2). Under these conditions, a variety of aryl substituted primary alcohols were readily converted to the corresponding aryl/alkyl cyanamides in excellent yields (products **3**–**12**, 70–90% yield). The reaction performs well upon scale-up, with the formation of cyanamide **4** successfully carried out on a 20 mmol scale in 78% yield to provide 3.23 g of product. Within the aryl unit, 4-Me, 3-Me, and 2-Me substitution was tolerated in addition to electron-donating (4-OMe) and electron-withdrawing (4-F and 4-CF_3) substituents. Heteroaryls (2-furyl, 2-thiophenyl, and 4-pyridyl) can be present within the alcohol, although the reaction using 4-pyridinemethanol required heating at 100 °C in 1,4-dioxane with 2 equiv of NCTS to achieve a full conversion, giving cyanamide **12** in 75% yield. Allyl alcohol performed well, accessing aryl/allyl substituted cyanamide **13** in 79% yield. Simple alkyl substituted primary alcohols (e.g., 1-decanol) required extended reaction times and more forcing reaction conditions and gave cyanamide **14** in 55% yield.[19] Secondary alcohols were also readily tolerated, giving cyanamides **15** and **16** in 72% and 80% yield, respectively. The stereospecificity of the process was investigated using (*R*)-1-phenylethanol. Under standard reaction conditions, cyanamide (*S*)-**16** was formed in

Scheme 2. Alcohol Scope[a]



[a]Reactions performed using 1 mmol of alcohol starting material. All yields are isolated yields after chromatographic purification. [b]NCTS (2 equiv) in 1,4-dioxane at 100 °C for 16 h [c]NCTS (2 equiv) in 1,4-dioxane at 100 °C for 48 h.

74% e.e. (80% e.e. in the absence of TBAI) indicative of competing S_N1 and S_N2 pathways.[20] A substrate limitation was identified upon testing tertiary alcohols 2-phenyl-2-propanol and triphenylmethanol. These hindered alcohols did not react with NCTS to give cyanamides **17** and **18** even after heating for prolonged reaction times, with starting materials returned.[21]

Having successfully demonstrated deoxycyanamidation with a variety of primary and secondary alcohols, we next investigated the reaction scope with respect to the sulfonamide (Scheme 3). Under the standard reaction conditions with benzyl alcohol it was found that a range of *N*-aryl substituents within the sulfonamide could be incorporated, giving aryl/alkyl cyanamides in excellent yields (products **4** and **19**–**25**, 72–89% yield). Aryl substitution at the 4-, 3-, and 2-position was tolerated in addition to electron-donating (4-OMe) and electron-withdrawing (4-F, 4-Cl, and 4-CF_3) substituents. An *N*-butyl sulfonamide was used to afford alkyl/alkyl cyanamide **26** in 52% yield. The effect of electronics within the *S*-substituent of the sulfonamide was also probed. Both 4-$OMeC_6H_4$ and 4-$NO_2C_6H_4$ *S*-substituents resulted in lower isolated yields of cyanamide **4** (62% and 63% respectively). Furthermore, employing a sulfonamide bearing a thiomethyl substituent resulted in a complex reaction mixture, giving **4** in only 19% yield. The commonly reported tosyl sulfonamides (e.g., NCTS) gave the highest yields for this protocol.

With respect to the mechanism of this process, we propose an initial *N*- to *O*-sulfonyl transfer between NCTS and sodium alkoxide (generated in situ from 2-fluorobenzyl alcohol and NaO*t*-Am), to give 2-fluorobenzyl tosylate, which has been directly observed using in situ ^{19}F NMR during optimization studies (Scheme 4, eq 5).[22] Subsequent alkylation of the

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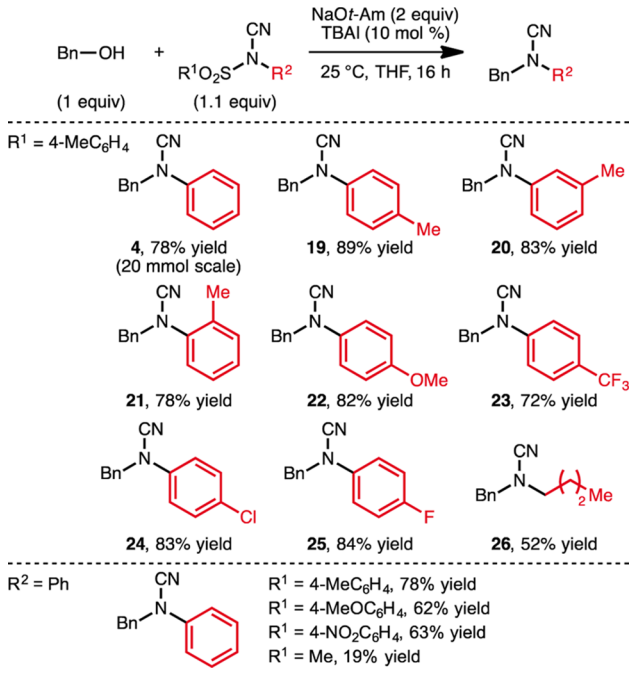
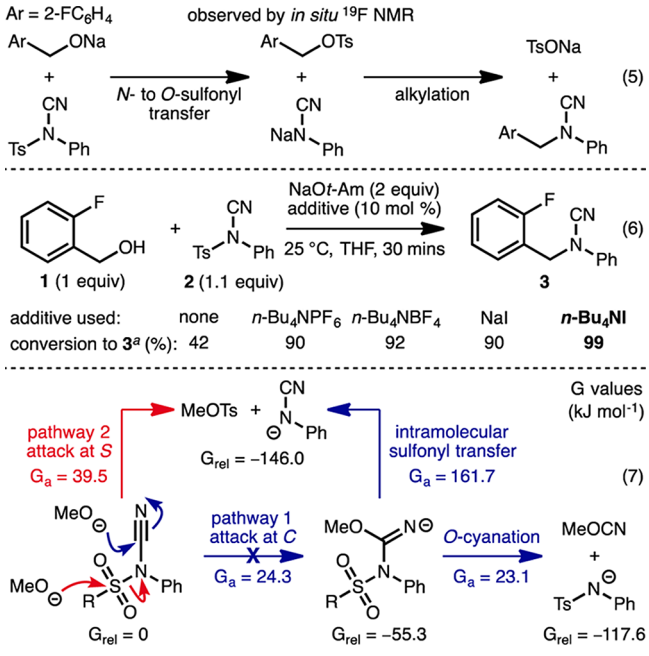
Scheme 3. Sulfonamide Scope[a]



[a]Reactions performed using 1 mmol of alcohol starting material. All yields are isolated yields after chromatographic purification.

Scheme 4. Mechanistic Considerations[a]



[a]As determined by ^{19}F NMR analysis of crude reaction mixture with 1,3,5-trifluorobenzene as the internal standard.

cyanamide anion with alkyl tosylate affords the tertiary cyanamide product. The role of the additive in this reaction was also investigated (Scheme 4, eq 6). In the absence of any additives, 42% conversion to cyanamide **3** was observed after 30 min using the standard reaction conditions. The conversion increased to 90% and 92% upon addition of *n*-Bu_4NPF_6 (10 mol %) and *n*-Bu_4NBF_4 (10 mol %), respectively, indicating rate enhancement via cation exchange.[23] An increase in conversion to 90% was also observed when NaI (10 mol %) was used as an additive, indicative of in situ conversion of the alkyl tosylate to a more reactive alkyl iodide.[24] These effects are combined when using *n*-Bu_4NI (10 mol %) as an additive, giving 99% conversion to cyanamide **3** after just 30 min at 25 °C. We envisaged two possible mechanistic pathways for the observed *N*- to *O*-sulfonyl transfer (Scheme 4, eq 7): (1) alkoxide attack at *C* followed by intramolecular *N*- to *O*-sulfonyl transfer; (2) intermolecular *N*- to *O*-sulfonyl transfer via direct attack of alkoxide at *S*. Computational experiments revealed that nucleophilic attack at *C* (pathway 1), forming a carbamimidate intermediate, was approximately 15 kJ mol^{-1} lower in energy than attack at *S* (pathway 2).[25] However, the large energy barrier associated with intramolecular *N*- to *O*-sulfonyl transfer to phenyl cyanamide and methyl tosylate (G_a = 161.7 kJ mol^{-1}) is unlikely to be overcome at 25 °C. Furthermore, the lack of any observable products resulting from *O*-cyanation (the lowest energy pathway from the carbamimidate intermediate) suggests that the observed sulfonyl transfer proceeds via direct attack at *S* (pathway 2).[26]

In conclusion, we have developed a new operationally simple one-pot protocol for the deoxycyanamidation of primary and secondary alcohols using *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS), accessing a diverse array of tertiary cyanamide products in excellent yields. This process exploits the underdeveloped desulfonylative (N−S bond cleavage) reactivity pathway of NCTS, which is more commonly employed for *C*- and *N*-cyanation processes. Ongoing studies are focused on further applications of NCTS in synthesis, and these results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01710.

Optimization data, experimental procedures, characterization of new compounds, and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

Information about the data that underpins the results presented in this article, including how to access them, can be found in the Cardiff University data catalogue at http://doi.org/10.17035/d.2017.0038300689 (accessed Jun 28, 2017).

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(18) Using KO*t*-Bu as a base produced some minor impurities in the $^{19}F\{^{1}H\}$ NMR spectra that were not observed when using NaO*t*-Am. Hence, optimization was continued using NaO*t*-Am as a base.

(19) The remaining mass balance was unreacted 1-decanol.

(20) A control experiment revealed that enantiomerically pure cyanamide (*S*)-**16** did not epimerize under these reaction conditions.

(21) Using NaH (2 equiv) as a base at 100 °C in 1,4-dioxane for 16 h also returned starting materials, with no observable conversion to **17** or **18**.

(22) The validity of 2-fluorobenzyl tosylate as an intermediate was further probed via its reaction with phenylcyanamide (1.1 equiv) and NaO*t*-Am (2 equiv) at 25 °C in THF for 16 h, giving the expected cyanamide **3** in 77% isolated yield.

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(25) See Supporting Information for full details of the computational investigation of the reactivity of *N*-cyano-*N*-phenyl-*p*-methylbenzenesulfonamide (NCTS) towards *O*-based nucleophiles.

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