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$Ln[N(SiMe_3)_2]_3/RNH_2$ Catalyzed Monoaddition of Terminal Alkynes to Nitriles: A Novel and Concise Access to the Synthesis of Ynones

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Summary: A mild and highly selective $Ln[N(SiMe_3)_2]_3/n\text{-}BuNH_2$ catalyzed addition of terminal alkynes to nitriles has been established, revealing a novel reactivity pattern of alkynes with nitriles and providing a new, economical, and mild method for the synthesis of conjugated ynones.

The presence of conjugated ynone moieties in natural products and synthetic materials, coupled with the extensive utility of ynone-based reagents in synthetic methodology,[1–4] illustrates the need for efficient and versatile strategies for the construction of such compounds. Among a variety of approaches for their preparation, the coupling of acyl chlorides and terminal alkynes is arguably one of the most versatile and efficient methods.[5] However, such a reaction requires the use of stoichiometric amounts of bases or the initial transformation of alkynes to metal acetylide salts by pretreatment with expensive and/or toxic organometallic reagents, which inevitably produce a stoichiometric amount of salt waste and sometimes require an additional separation step. In addition, the acyl chlorides are commonly water-sensitive and corrosive, which would set limits for the industrial application of this reaction. An alternative strategy for the synthesis of ynones from terminal alkynes is the transition-metal-catalyzed carbonylative three-component coupling reaction of aryl halides with terminal alkynes in the presence of CO.[6,7] Despite the many advantages of this method, it also requires the use of stoichiometric amounts of bases. Consequently, new efficient and catalytic methods for assembling the ynones from alkynes would be valuable.

The cyano group is very common in many organic molecules. The utility of nitriles in organic synthesis has become the subject of intense interest due to their inherent reactivity, stability, low cost, and ready availability as starting materials. Although the reactions between terminal alkynes and nitriles promoted by transition-metal complexes have been explored extensively, in most cases only cocyclotrimerization products are obtained.[8] In a few cases, alkenenitriles are obtained via R−CN cleavage and subsequent addition to the alkynes.[9] To the best of our knowledge, there has been no precedent for the catalytic monoaddition of terminal alkynes to nitriles. On the other hand, readily available homoleptic bis(trimethylsilyl)amides of yttrium and lanthanide metals are currently attracting considerable attention as highly efficient catalysts for various organic transformations. One particular emphasis has been on the activation of carbon−hydrogen and heteroatom−hydrogen bonds, and successful transformations now include the Tishchenko reaction,[10] cross-Aldol reactions,[11] coupling reactions of isocyanides with terminal alkynes,[12] dimerization of terminal alkynes,[13] guanylation of amines,[14] hydroamination,[15] hydrosi-

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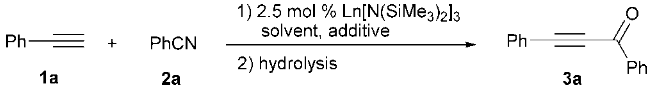
Table 1. Optimization of Catalysts, Additives, and Solvents[a]



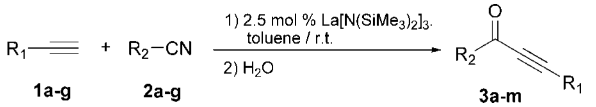
entry	Ln	solvent	additive	yield (%)[b]
1	Nd	toluene		trace
2	Nd	toluene	$PhNH_2$	43
3	Nd	toluene	*n*-$BuNH_2$	59
4	Nd	toluene	*i*-Pr_2NH	13
5	Nd	toluene	Et_3N	5
6	Nd	THF	*n*-$BuNH_2$	12
7	Nd	*n*-C_6H_{14}	*n*-$BuNH_2$	26
8	Nd	CH_2Cl_2	*n*-$BuNH_2$	21
9	La	toluene	*n*-$BuNH_2$	68
10	Sm	toluene	*n*-$BuNH_2$	49
11	Yb	toluene	*n*-$BuNH_2$	35
12	Y	toluene	*n*-$BuNH_2$	27
13[c]	La	toluene	*n*-$BuNH_2$	47
14[d]	La	toluene	*n*-$BuNH_2$	42
15[e]	La	toluene	*n*-$BuNH_2$	69

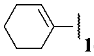
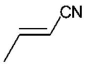
[a] Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), catalyst (0.025 mmol, 2.5 mol %), solvent (5 mL), additive (10 mol %), room temperature. [b] Isolated yield. [c] 70 °C. [d] Reflux. [e] 10 mol % loading of catalyst.

lylation,[16] and hydroalkyoxylation[17] of unsaturated carbon−carbon bonds. On the basis of these promising potentialities, we decided to perform a new study on the reactivity of nitriles with terminal alkynes. Herein we wish to report for the first time a selective monoaddition of terminal alkynes to nitriles catalyzed by $Ln[N(SiMe_3)_2]_3$/primary amine (Ln = yttrium and lanthanide metals) at room temperature, which reveals a novel reactivity pattern of alkynes with nitriles and provides a new method for the synthesis of ynones.

Results and Discussion

Table 2. Addition of Various Terminal Alkynes with Nitriles Catalyzed by $La[N(SiMe_3)_2]_3$/*n*-$BuNH_2$[a]



entry	R_1	R_2	t/h	yield (%)[b]
1	C_6H_5 **1a**	C_6H_5 **2a**	24	**3a,** 68
2	*p*-$CH_3C_6H_4$ **1b**	**2a**	24	**3b**, 51
3[c]	*p*-FC_6H_4 **1c**	**2a**	8	**3c,** 70
4	 **1d**	**2a**	24	**3d**, 55
5	*n*-C_4H_9 **1e**	**2a**	24	**3e,** 57
6	*n*-C_6H_{13} **1f**	**2a**	24	**3f**, 54
7	$(CH_3)_3Si$ **1g**	**2a**	24	**3g,** 55
8	**1a**	*p*-$NO_2C_6H_4$ **2b**	12	**3h,** 71
9	**1a**	*p*-ClC_6H_4 **2c**	20	**3i**, 51
10	**1a**	*p*-BrC_6H_4 **2d**	20	**3j,** 54
11	**1a**	*p*-$CH_3OC_6H_4$ **2e**	24	**3k**, 45
12	**1a**	C_3H_7 **2f**	24	**3l,** 56
13[c]	**1a**	 **2g**	36	**3m,** 57

[a] Reaction conditions: **1a** (1.1 mmol), **2a** (1 mmol), catalyst (0.025 mmol, 2.5 mol %), solvent (5 mL), *n*-$BuNH_2$ (10 mol %). [b] Isolated yield. [c] 5 mol % of catalyst.

The reaction of phenylacetylene and benzonitrile was chosen as a model reaction to find out the optimum reaction conditions. When benzenenitrile (**2a**) was treated with 1.1 molar equiv of phenylacetylene (**1a**) in the presence of $Nd[N(SiMe_3)_2]_3$ (2.5 mol %) for 24 h at room temperature or reflux in toluene and then hydrolyzed, only trace **3a** was obtained (Table 1, entry 1). Remarkably, simply adding 10 mol % aniline to the original system led to a significantly increased yield (Table 1, entry 2). As can be seen in the experiments varying amine additives, the yield of **3a** was dependent on the nature of the amines and increased in the order *i*-Pr_2NH ($pK_a = 11.05$) < $PhNH_2$ ($pK_a = 4.58$) < *n*-$BuNH_2$ ($pK_a = 10.59$) (Table 1, entries 2–4). Tertiary amines such as triethylamine showed no obvious effect (Table 1, entry 5). Among various solvents examined, toluene was most effective for this transformation (Table 1, entries 3 and 6–8). In a comparison of the metal size of the lanthanide catalysts, $La[N(SiMe_3)_2]_3$ gave the highest yield of **3a** (Table 1, entries 3 and 9–12). Notably, the yield of product decreased at elevated temperature (Table 1, entries 13 and 14). In addition, the yield has no obvious improvement with a higher catalyst loading of 10 mol % (Table 1, entry 15).

With the optimum reaction conditions in hand, we subsequently explored the scope of the reaction to various terminal alkynes **1a**−**g** and nitriles **2a**−**g**. Table 2 summarizes the results. The aromatic acetylene **1b**, bearing an electron-donating substituent at the para position, gave the corresponding ynone **3b** in 51% yield (entry 2). However, the aromatic acetylene **1c**, which has an electron-withdrawing substituent at the para position, reacted more quickly and the ynone **3c** was obtained in 70% yield (entry 3). We next examined the reactions of aliphatic acetylenes **1d**−**g** with **2a**. The reactions of **1d**−**g** with **2a** proceeded smoothly to give **3d**−**g** in moderate yields (entries 4–7). The various nitriles **2b**−**g** were also examined, and a tendency similar to that seen above was observed in the case of the phenylacetylene. An electron-donating substituent such

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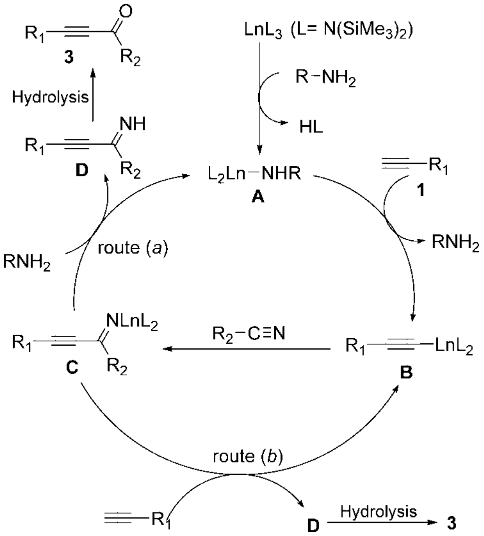
Scheme 1. Possible Mechanism of Addition of Terminal Alkynes to Nitriles



as *p*-methoxybenzonitrile (**2e**) led to a slightly decreased yield (45%), as compared to an electron-withdrawing substituent of **2b** in the same position (71%) (entries 11 vs 8). Aliphatic nitriles such as butanenitrile (**2f**) and (*E*)-but-2-enenitrile (**2g**) also afforded the desirable products in moderate yields (entries 12 and 13). These results indicate that the reaction is tolerant to other functional groups such as halide, nitro, alkoxyl, and carbon−carbon double bonds.

It is well-known that alkynes readily react with nitriles to form the cocyclotrimerization products in the presence of organometallic complexes of transition metals; further, both can undergo self-cyclotrimerization.[18] However, no cyclization product is isolated in the present case. To our knowledge, the present transformation represents the first example of monoaddition of alkynes to nitriles, for which the particular value is to provide a new route to conjugated ynones.

On the basis of the results described above, a plausible reaction pathway for the monoaddition of terminal alkynes to nitriles catalyzed by $Ln[N(SiMe_3)_2]_3$/primary amine is shown in Scheme 1. Terminal alkyne C−H bond activation leads to the formation of lanthanide acetylides (**B**) together with liberation of amine. Coordination and subsequent insertion of one nitrile molecule into the Ln−C bond of **B** gives a key imino lanthanide intermediate (**C**). Then, predominant protonation of **C** with the amine additive affords the addition product (**D**) and regenerates the catalyst (**A**) (route a).[12] Alternatively, the catalytic cycle might be also carried out via route b.[13] Hydrolysis of **D** gives the corresponding ynone. The imine intermediate **D** has been confirmed by ^1H NMR and MS. Consistent with this, the amine additives play an important role as proton sources to abstract the resulting imino ligand and as suitable ligands to activate the rare-earth catalysts in the catalytic cycle. Despite the increasing acidity of primary amine additives being favorable to the liberation of **D**, it is unfavorable to the formation of lanthanide acetylides **B**. Thus, an appropriate acidity of primary amines is required.

Conclusion

In summary, we have demonstrated for the first time that the construction of a conjugated ynone framework can be achieved from nitriles by a hydroalkynylation/hydrolysis sequence. The transformation provides a new, economical, and mild protocol for the synthesis of conjugated ynones and reveals a novel reactivity pattern of alkynes with nitriles.

Experimental Section

All reactions were carried out under a nitrogen atmosphere using standard Schlenk techniques. Ln_2O_3 (Ln = Y, La, Nd, Sm, Yb) are available commercially, and $Ln[N(SiMe_3)_2]_3$ can be prepared according to the literature method.[19] All alkynes were purchased from Aldrich. Solvents were refluxed and distilled over sodium benzophenone ketyl under nitrogen immediately prior to use. Dichloromethane was refluxed in calcium hydride and distilled. ^1H NMR spectra were recorded in $CDCl_3$ with TMS as an internal standard at ambient temperature on a Bruker Avance 400 operating at 400 MHz. GC-MS were obtained on a Hewlett-Packard 6890/5973 instrument.

General Experimental Procedure for the $Ln[N(SiMe_3)_2]_3$/*n*-$BuNH_2$ Catalyzed Addition of Alkynes to Nitriles. To a mixture of benzonitrile (1 mmol), *n*-$BuNH_2$ (10 uL, 0.1 mmol), and alkynes (1.1 mmol) was added a toluene (5 mL) solution of $Ln[N(SiMe_3)_2]_3$ (2.5 mol %). The reaction mixture was stirred at room temperature for 8–36 h and then was quenched with 1 M HCl. The mixture was extracted with ether. The organic layer was separated, dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and purified by flash column chromatography to afford the desired products. All products were identified by comparison with those of authentic samples.

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Supporting Information Available: Text and figures giving experimental details and characterization data for all isolated compounds. The material is available free of charge via the Internet at http://pubs.acs.org.

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