CHEMISTRY
A EUROPEAN JOURNAL

COMMUNICATION

DOI: 10.1002/chem.201200763

Synthesis of Acrylonitriles through an $FeCl_3$-Catalyzed Domino Propargylic Substitution/*Aza*-Meyer–Schuster Rearrangement Sequence

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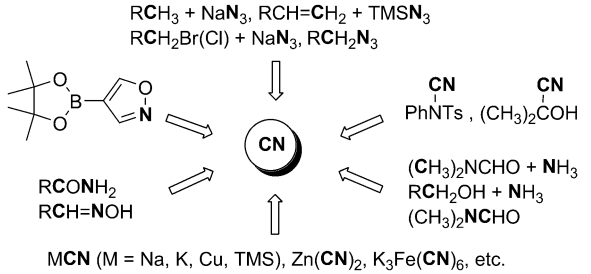
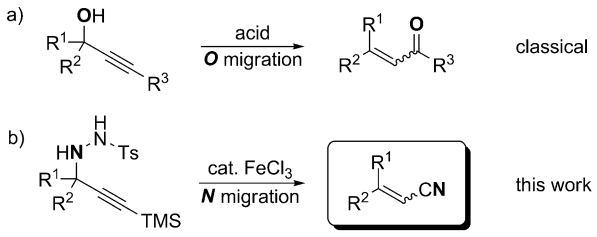
Nitrile and acrylonitrile scaffolds constitute a key component of numerous compounds, including dyes, natural products, agrochemicals, and pharmaceuticals.[1] The cyano group may also be transformed into a variety of functional groups consisting of amines, aldehydes, amidines, and amides. Accordingly, considerable effort has been invested in their syntheses. The cyano group is generally constructed from sources containing whole cyano units, such as metal cyanides (CuCN, KCN, NaCN, $Zn(CN)_2$, $K_3[Fe(CN)_6]$, TMSCN) and cyano-containing organic compounds,[2] and yet this type of cyanation method suffers from the high toxicity of cyano sources. Alternatively, this group may be formed by the dehydration of precursors, including primary amides and aldoximes.[3] Very recently, a new strategy for generating a cyano group by direct transformation of one precursor or a combined cyano source has been revealed by the groups of Jiao, Chang, Schmalz, Cheng, and Mizuno.[4] By these methods, cyanation can be achieved through cyano generation from simple reagents, such as DMF, ammonia, and azides (Scheme 1). Despite these pioneering methodologies, the further development of new cyano sources generated in situ from simple, low-toxicity, readily available reagents is still an extremely attractive, yet challenging task.

During recent years, the transition-metal-catalyzed transformation of propargylic alcohols has received considerable attention.[5] Particularly intriguing is the reactivity of these easily accessible compounds in the context of iron catalysis,[6] which has been reflected in the development of a variety of diverse and elegant transformations leading to an array of complex organic molecules. Herein, we wish to report an unprecedented $FeCl_3$-catalyzed synthesis of acrylonitriles by employing propargylic alcohols and *para*-tolylsulfonohydrazide as a combined cyano source through a domino propargylic substitution/*aza*-Meyer–Schuster rearrangement route.



Scheme 1. Various cyano sources for cyanation reactions (TMS = trimethylsilyl; Ts = tosyl).

In the field of propargylic alcohol chemistry, the classical acid-catalyzed Meyer–Schuster rearrangement plays a very important role[7] because a wide range of α,β-unsaturated carbonyl compounds can be easily synthesized by this named reaction. In addition, the rearrangement may serve as a strategy for double-bond construction. It is generally proposed that the propargylic alcohols rearrange to the corresponding α,β-unsaturated carbonyl compounds through a formal [1,3] shift of the hydroxyl moiety (Scheme 2a).[8]



Scheme 2. The Meyer–Schuster rearrangement and its *aza* analogue.

However, to the best of our knowledge, an *aza*-Meyer–Schuster rearrangement in which the nitrogen atom migrates has not yet been disclosed (Scheme 2b).

In the course of our studies on propargylic substitution,[9] we became interested in the employment of readily available and inexpensive reagents, such as *para*-tolylsulfonohydrazide (**2a**). When we carried out the reaction between 1,1-

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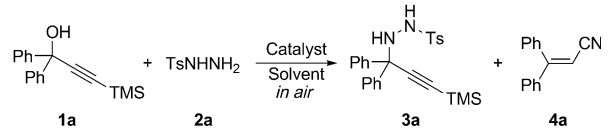
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201200763.

diphenyl-3-(trimethylsilyl)propargylic alcohol (**1a**) and **2a**, in addition to the main substitution product **3a**, the acrylonitrile compound **4a** was obtained as a byproduct in 27% yield (Table 1, entry 1). To obtain **4a** selectively, different

Table 1. Screening of reaction parameters.[a]



1a 2a 3a 4a

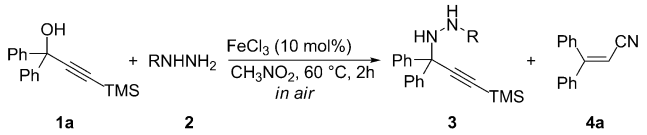
Entry	Catalyst (10 mol%)	Solvent	T [°C]	t [h]	Yield **3a**/**4a** [%][b]
1	$FeCl_3$	CH_3CN	60	5	68:27
2	$FeCl_3$	DCE	60	1	0:93
3	$BiCl_3$	DCE	60	2	0:42
4	$InCl_3$	DCE	60	2	0:76
5	$AuCl_3$	DCE	RT	2	18:0[c]
6	$ZnCl_2$	DCE	60	2	0:25
7	$ZnBr_2$	DCE	60	2	0:23
8	AgOTf	DCE	60	2	42:40
9	$In(OTf)_3$	DCE	60	2	0:57
10	$Cu(OTf)_2$	DCE	60	2	0:82
11	*p*-TSA·H_2O	DCE	60	2	5:0[d]
12	TfOH	DCE	60	2	0:88
13	$FeCl_3$	$PhCH_3$	60	2	0:68
14	$FeCl_3$	THF	60	2	85:0
15	**$FeCl_3$**	**CH_3NO_2**	**60**	**2**	**0:99**
16	$FeCl_3$	CH_3NO_2	RT	4	99:0[e]
17	$FeCl_3$	1,4-dioxane	100	2	complex mixture
18	$FeCl_3$	CH_2Cl_2	40	1	0:90
19	$FeCl_3$	DMF	100	5	0:0[f]
20[g]	$FeCl_3$	CH_3NO_2	60	2	9:89
21	-	CH_3NO_2	60	2	0:0
22[h]	**$FeCl_3$**	**CH_3NO_2**	**60**	**2**	**0:99**

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), catalyst (10 mol%) in solvent (3 mL) in air (DCE = dichloroethane; Tf = triflyl; *p*-TSA = *para*-toluenesulfonic acid). [b] Isolated yields. [c] 72% of **1a** was recovered. [d] 77% of **1a** was recovered. [e] After being heated at 60°C for 2 h, **3a** transformed into **4a** in nearly quantitative yield. [f] 96% of **1a** was recovered. [g] 5 mol% $FeCl_3$ was used. [h] Run on a 5 g scale.

parameters were carefully screened and the optimal reaction conditions were determined to be $FeCl_3$ (10 mol%) in nitromethane at 60°C for an appropriate time (Table 1, entry 15). In contrast, reactions performed in THF at reflux or in nitromethane at room temperature exclusively led to the substitution product **3a** (Table 1, entries 14 and 16), and the latter gave a nearly quantitative yield. Decreasing the catalyst loading made the reaction sluggish (Table 1, entry 20), and performing the reaction without using the catalyst gave neither products (Table 1, entry 21). We also examined the potential of scaling up this novel cyanation; the reaction of **1a** and **2a** was run on a 5 g scale in air, and a remarkably clean cyanation reaction was observed, producing **4a** in 99% isolated yield (Table 1, entry 22).

Very interestingly, the examination into the use of different substituted hydrazines showed that only *para*-tolylsulfonohydrazide (**2a**) worked in the cyanation reaction. Reactions with other substituted hydrazines under the standard

Table 2. Screening of different substituted hydrazines.[a]



1a 2 3 4a

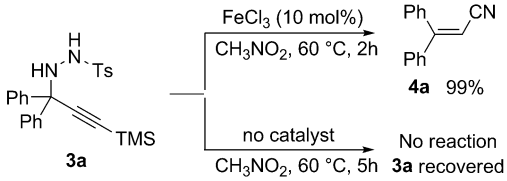
Entry	**2**	Yield **3**/**4a** [%][b]	Recovered **1a** [%][b]
1	**2a**: $TsNHNH_2$	0:99	0
2	**2b**: $BocNHNH_2$	0:0	98
3	**2c**: $PhCONHNH_2$	0:0	93
4	**2d**: $PhNHNH_2$	0:0	98
5	**2e**: $AcNHNH_2$	0:0	96
6	**2f**: *t*$BuCONHNH_2$	0:0	95

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.75 mmol), $FeCl_3$ (10 mol%) in CH_3NO_2 (3 mL) at 60°C for 2 h in air (Boc = *tert*-butoxycarbonyl). [b] Isolated yields.

conditions gave neither substitution products **3** nor acrylonitrile **4a** (Table 2, entries 2–6). We reasoned that the catalytic activity of $FeCl_3$ was suppressed by the stronger alkalinity of the alternative substituted hydrazines.

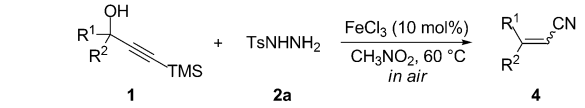
Next, we probed the substrate scope of this $FeCl_3$-catalyzed synthesis of acrylonitriles under the optimized conditions (Table 3). Moderate to excellent yields were obtained in most cases examined, and a range of functionalities could be tolerated. We began our investigation by examining the cyanation of symmetrical propargylic alcohols ($R^1 = R^2$). Substrates with both electron-rich and -poor substituents reacted very well, providing compounds **4** in good to excellent yields (Table 3, examples **4a**–**4d** and **4n**). The asymmetric propargylic alcohols ($R^1 \neq R^2$) investigated also gave good yields. It should be noted that a single isomer was observed in the cases of **4f**, **4g**, **4k**, **4l**, **4m**, and **4o**. In comparison with the similar compounds **4k** and **4l**, a lower yield was obtained for **4p**.[10] Although a wide range of propargylic alcohols could be employed, dialkyl-substituted and monoaryl-substituted propargylic alcohols proved to be uniquely challenging partners and none of the desired products were detected (Table 3, examples **4s** and **4t**).

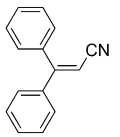
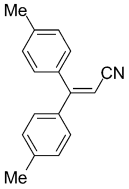
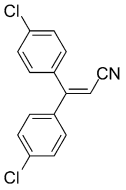
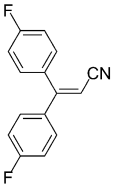
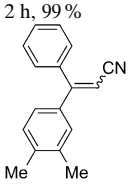
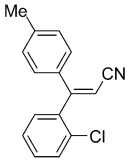
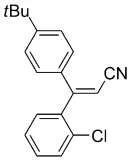
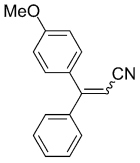
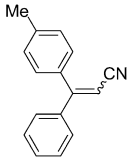
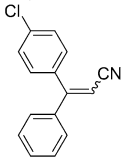
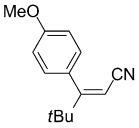
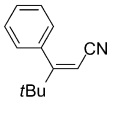
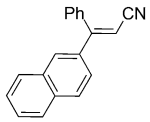
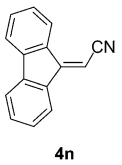
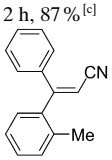
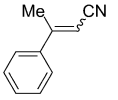
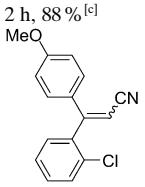
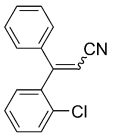
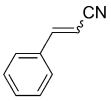
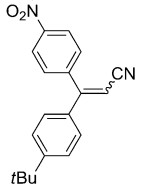
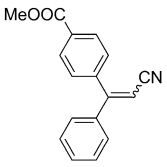
To probe the mechanism of this reaction, we first isolated the substitution product **3a** under the reaction conditions shown in Table 1, entry 16. Then, by using **3a** as the substrate, two reactions were carried out (Scheme 3). Under the optimized reaction conditions, the desired 3,3-diphenylacrylonitrile **4a** was obtained in 99% isolated yield (Scheme 3). However, it was found that **3a** did not react at all without the added $FeCl_3$ catalyst (Scheme 3).



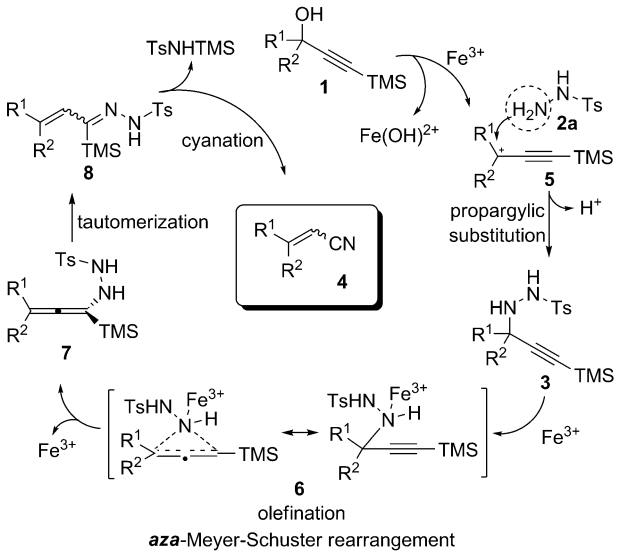
Scheme 3. Direct cyanation of substitution product **3a**.

Table 3. $FeCl_3$-catalyzed syntheses of acrylonitriles.[a]



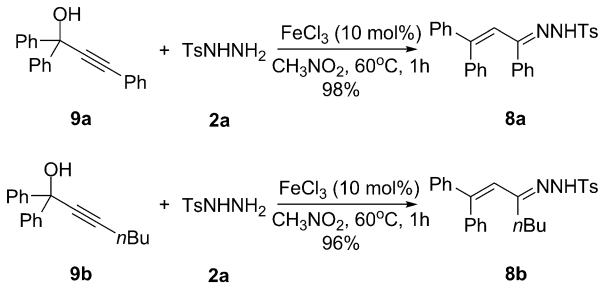
 **4a**	 **4b**	 **4c**	 **4d**
2 h, 99 %	2 h, 99 %	3 h, 92 %	2 h, 88 %
 **4e**	 **4f**	 **4g**	 **4h**
2 h, 99 %[b]	3 h, 91 %[c]	3 h, 81 %[c]	2 h, 99 %[b]
 **4i**	 **4j**	 **4k**	 **4l**
2 h, 99 %[b]	3 h, 94 %[b]	2 h, 87 %[c]	24 h, 73 %[c]
 **4m**	 **4n**	 **4o**	 **4p**
2 h, 88 %[c]	3 h, 63 %	2 h, 96 %[c]	20 h, 53 %[d]
 **4q**	 **4r**	 **4s**	 **4t**
2 h, 97 %[d]	3 h, 92 %[d]	24 h, 0 %	24 h, 0 %
 **4u**	 **4v**		
2 h, 85 %[d]	2 h, 82 %[d]		

[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.75 mmol), $FeCl_3$ (10 mol %) in CH_3NO_2 (3 mL) in air for an appropriate time. Isolated yields based on **1**. The isomeric ratio of **4** was determined by ^1H NMR spectroscopy. [b] A 1:1 ratio of olefin isomers. [c] A single olefin isomer was observed and the double-bond geometry was determined by NOE experiment. [d] The olefin isomer ratios of **4p**, **4q**, **4r**, **4u**, and **4v** are 55:45, 75:25, 89:11, 62:38, and 57:43, respectively.



Scheme 4. Plausible mechanism for the cyanation reaction.

Consequently, we propose the following plausible mechanism for this cyanation reaction (Scheme 4). First, propargylic alcohol **1** reacted under iron catalysis to yield propargylic cation **5**. Next, the propargylic substitution occurs regioselectively by attack of the terminal nitrogen atom ($-NH_2$) of **2a**, resulting in the substitution product **3**. Then, compound **3** experiences an $FeCl_3$-mediated [1,3] shift of the -NHNHTs group to generate allene intermediate **7** via transition states **6** (*aza*-Meyer–Schuster rearrangement, an olefination process). Finally, allene **7** transforms into the final product **4** through rapid tautomerization and subsequent elimination of TsNHTMS (cyanation process). To further clarify the mechanism, we performed the reactions of 1,1,3-triphenylprop-2-yn-1-ol (**9a**) and 1,1-diphenylhept-2-yn-1-ol (**9b**) with *para*-tolylsulfonohydrazide (Scheme 5). The two analogues **8** (**8a** and **8b**) were observed and isolated in excellent yields.



Scheme 5. Isolation of analogues **8**.

In summary, we have developed a highly efficient and practical $FeCl_3$-catalyzed domino synthesis of acrylonitriles by using propargylic alcohols and *para*-tolylsulfonohydrazide as a combined cyano source, which avoids the use of highly toxic metal cyanides. This novel cyanation reaction

proceeds through a domino regioselective propargylic substitution/*aza*-Meyer–Schuster rearrangement route. To the best of our knowledge the rearrangement process described herein is reported for the first time, which is of both theoretical and practical significance. The gram-scale experiment performed in air indicates the potential of this type of reaction for practical and large-scale applications. Further studies are currently in progress in our laboratory.

Experimental Section

General procedure for the syntheses of acrylonitriles 4: Propargylic alcohol **1** (0.5 mmol, 1.0 equiv), *para*-tolylsulfonohydrazide **2a** (0.75 mmol, 1.5 equiv), and nitromethane (3 mL) were successively added to a flame-dried flask (10 mL) equipped with a magnetic stirring bar. The mixture was stirred until **2a** was completely dissolved. Subsequently, $FeCl_3$ (10 mol%, 0.05 mmol) was added. The reaction mixture was stirred at room temperature in air for about 15 min, that is, until the reaction system became homogeneous. Then, the mixture was put in an oil bath (60 °C) for an appropriate time, and monitored periodically by thin-layer chromatography. Upon completion of the reaction, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel to afford the acrylonitrile.

Acknowledgements

We thank the NSFC (No. 21072159), the 973 Projects (No. 2011CB935901), the NFFTBS (No. J1030415), and the Science & Technology Bureau of Xiamen (No. 3502Z20093007) for financial support of this project.

Keywords: acrylonitriles · cyanides · domino reactions · iron · propargylic substitution · rearrangement

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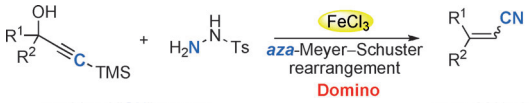
[10] The relatively low yield of **4p** may be ascribed to the competing elimination of propargylic cation intermediate **5**, shown in Scheme 4, producing trimethyl(3-phenylbut-3-en-1-ynyl)silane.

Received: March 7, 2012
Published online: ■■ ▮▮, 0000



Nontoxic cyanide source: An unprecedented route to acrylonitriles by employing propargylic alcohols and *para*-tolylsulfonohydrazide as a combined cyano source has been developed (see scheme). This efficient and practical cyanation reaction proceeds through an $FeCl_3$-catalyzed domino propargylic substitution/*aza*-Meyer–Schuster rearrangement sequence, the rearrangement process of which is reported for the first time.

Cyanation

*L. Hao, F. Wu, Z.-C. Ding, S.-X. Xu, Y.-L. Ma, L. Chen, Z.-P. Zhan** ..... ▮▮▮▮–▮▮▮▮

Synthesis of Acrylonitriles through an $FeCl_3$-Catalyzed Domino Propargylic Substitution/*Aza*-Meyer–Schuster Rearrangement Sequence