Transformations of *N*-Allyl-*N*-(phenylethynyl)arenesulfonamides into 2,2-Disubstituted 4-Pentenenitriles through Aza-Claisen Rearrangement that Follows Carbomagnesiation

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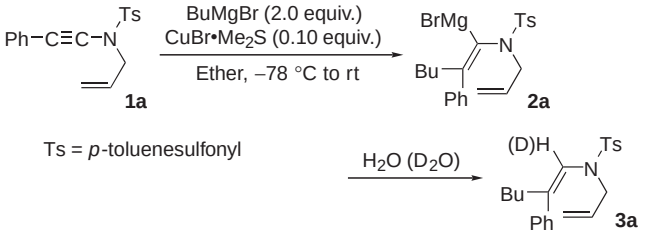
Treatment of *N*-allyl-*N*-(phenylethynyl)arenesulfonamides with Grignard reagents under copper catalysis resulted in carbomagnesiation across the alkynyl parts. The carbomagnesiations yielded 2-magnesio-3-aza-1,5-hexadienes, which underwent the aza-Claisen rearrangement upon heating. The rearrangement followed by elimination of the arenesulfonyl groups provided 2,2-disubstituted 4-pentenenitriles.

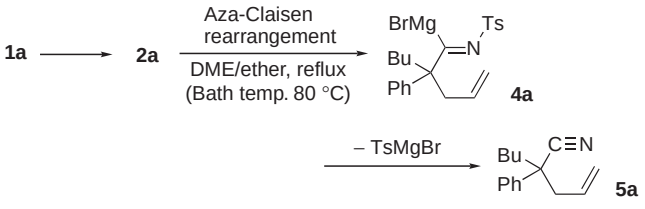
The [3,3]sigmatropic rearrangement reactions of 3-aza-1,5-hexadienes are useful in organic synthesis.[1] We describe herein the aza-Claisen rearrangement reactions triggered by carbomagnesiations of ynamides, specifically *N*-allyl-*N*-(phenylethynyl)-arenesulfonamides.[2] The transformation offers a new repertoire to the synthesis of 4-pentenenitriles.

The initial carbomagnesiation proceeded smoothly by using Grignard reagents and a copper catalyst.[3] Treatment of **1a** with butylmagnesium bromide (2.0 equiv.) in the presence of CuBr•Me_2S (10 mol %) in ether at ambient temperature afforded **3a** in 86% yield after hydrolysis (Scheme 1).[4] Quenching the reaction with deuterium oxide provided the corresponding deuterated product (96%D). Hence, the intermediate **2a** was formed in the reaction flask.

When organomagnesium **2a** was boiled in a 1,2-dimethoxyethane/ether mixed solvent, pentenenitrile **5a** was obtained in 47% yield, along with 34% of **3a** (Scheme 2). The formation of **5a** would proceed as follows. The organomagnesium **2a** undergoes the aza-Claisen rearrangement to afford **4a**. The following elimination of the toluenesulfonyl group provided **5a**. It is worth noting that heating **3a** in boiling DME resulted in complete recovery of **3a**. Carbocupration of **1a** proceeded smoothly by using a combination of 3 equiv. of BuMgBr and 1.5 equiv. of CuI to afford **3a** in 76% yield. However, the 2-cuprio-3-aza-1,5-hexadiene derivative, which would be generated prior to aqueous workup, underwent similar rearrangement much less efficiently. The cuprate-mediated reaction provided **3a** and **5a** in 50 and 34% yields, respectively. These results suggest that the magnesium part would facilitate the rearrangement process.

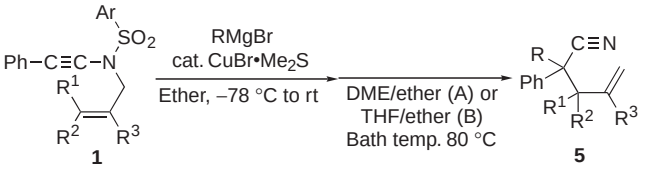


Scheme 1.



Scheme 2.

Table 1. Synthesis of 4-pentenenitriles through carbomagnesiation followed by the aza-Claisen rearrangement



Entry	1	RMgBr	Solvent	Time[a]/h	5	Yield/%
1	**1a**	BuMgBr	A	5	**5a**	47
2	**1a**	EtMgBr	B	4	**5b**	47
3	**1a**	*t*-$BuCH_2MgBr$	B	18	**5c**	46
4	**1a**	PhMgBr	B	4	**5d**	27
5	**1b**	BuMgBr	A	4	**5a**	61
6	**1b**	EtMgBr	B	4	**5b**	50
7	**1b**	*i*-PrMgBr	B	19	**5e**	23
8	**1c**	BuMgBr	B	4	**5f**	48
9	**1d**	BuMgBr	B	4	**5f**	58
10	**1e**	BuMgBr	B	4	**5g**	61
11	**1f**	BuMgBr	B	4	**5h**	49[b]
12	**1g**	BuMgBr	B	5	**5i**	57[c]

[a]Time for the rearrangement. [b]Diastereomer ratio = 1.6:1. [c]Diastereomer ratio = 1.4:1.

Table 1 summarizes the results of the synthesis of 4-pentenenitriles starting from ynamides (Figure 1) and Grignard reagents.[5] Primary alkyl Grignard reagents including a bulky neopentylmagnesium reagent participated in the reaction (Entries 1, 2, and 3). However, yields were much lower when aryl and secondary alkyl Grignard reagents were used (Entries 4 and 7). A more electron-withdrawing *p*-fluorobenzenesulfonyl group improved the yields (Entries 1, 2, 8 vs 5, 6, 9). *N*-Methallyl amides **1c** and **1d** participated in the reaction smoothly (Entries 8 and 9). Owing to the inherent regiospecificity of the aza-Claisen rearrangement, 2,2,3,3-tetrasubstituted 4-pentenenitrile **5g** was obtained in the reaction of *N*-prenyl amide **1e** (Entry 10).

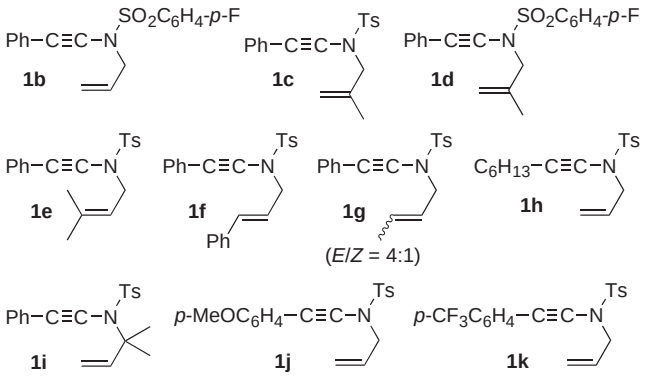


Figure 1. Structures of substrates **1**.

Such a sterically congested nitrile is difficult to synthesize by the conventional nitrile synthesis. The reactions of *N*-cinnamyl and *N*-crotyl amides **1f** and **1g** afforded mixtures of diastereomers (Entries 11 and 12).

The phenyl group at the acetylenic terminus proved to be indispensable for the success of the reaction. A similar reaction of *N*-allyl-*N*-(1-octynyl)-*p*-toluenesulfonamide (**1h**) resulted in formation of a complex mixture containing 6% of the anticipated nitrile and 31% of *N*-allyl-*p*-toluenesulfonamide. The low yield is attributed to the inefficient initial carbometalation of **1h**, which provided the corresponding enamide in only 33% yield. The methyl groups at the allylic position of **1i** completely suppressed the carbometalation reaction. The reactions of **1j** and **1k** with butylmagnesium bromide in the solvent system B for 4 h resulted in lower yields of the corresponding nitriles **5j** and **5k** in 33 and 34% yields, respectively.

In summary, we have devised a new route to 4-pentenenitriles through a sequence of carbomagnesiation of ynamides and metallo-aza-Claisen rearrangement. The synthesis of **5g** having two adjacent quaternary carbons features the advantage of the new route. The aza-Claisen rearrangement generally requires high temperature such as 300 °C. Acidic catalysis or quaternization of the nitrogen atom allows for much milder reaction conditions.[2,6] The present results suggest that metalation at the 2 position also facilitates the aza-Claisen rearrangement.

Dedicated to Prof. Teruaki Mukaiyama on the occasion of his 80th birthday.

References and Notes

1 A. M. M. Castro, *Chem. Rev.* **2004**, *104*, 2939; S. Jolidon, H.-J. Hansen, *Helv. Chim. Acta* **1977**, *60*, 978; S. Blechert, *Synthesis* **1989**, 71; R. P. Lutz, *Chem. Rev.* **1984**, *84*, 205; G. B. Bennett, *Synthesis* **1977**, 589.

2 Synthesis of ynamides was performed according to the literature. Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz, E. L. Vera, *Org. Lett.* **2004**, *6*, 1151.

3 Carbometalation reactions of ynamides were reported: H. Chechik-Lankin, S. Livshin, I. Marek, *Synlett* **2005**, 2098.

4 The *syn* mode of the addition was determined according to the literature. See Ref. 3.

5 Typical experimental procedure: $CuBr \cdot SMe_2$ (6 mg, 0.03 mmol) and *N*-allyl-*N*-phenylethynyl-*p*-fluorobenzenesulfonamide (**1b**) (95 mg, 0.30 mmol) were placed in a 20-mL reaction flask under argon. Diethyl ether (3 mL) was added. A solution of butylmagnesium bromide (0.53 mL, 1.13 M diethyl ether solution, 0.60 mmol) was added at −78 °C. The mixture was stirred at room temperature for 1 h. DME (5 mL) was added, and the reaction mixture was refluxed for 4 h (bath temp, 80 °C). A saturated solution of NH_4Cl (2 mL) was added. The organic compounds were extracted with a mixture of ethyl acetate and hexane twice. The combined organic part was dried over Na_2SO_4 and concentrated in vacuo. Chromatographic purification on silica gel afforded **5a** (39 mg, 0.18 mmol) in 61% yield. 2-Butyl-2-phenyl-4-pentenenitrile (**5a**): IR(neat): 2933, 2863, 2236, 1495, 1449, 924, 699, 519 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 0.85 (t, $J = 7.5$ Hz, 3H), 1.09–1.45 (m, 4H), 1.89 (dt, $J =$ 13.5, 4.5 Hz, 1H), 2.00 (dt, $J = 13.5$, 4.5 Hz, 1H), 2.67 (d, $J = 7.0$ Hz, 2H), 5.11–5.15 (m, 2H), 5.64 (ddt, $J = 17.0$, 10.0, 7.0 Hz, 1H), 7.30–7.33 (m, 1H), 7.37–7.41 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.96, 22.72, 27.43, 39.87, 45.55, 48.20, 120.05, 122.35, 126.23, 127.85, 128.98, 132.06, 138.34. Anal. Calcd for $C_{15}H_{19}N$: C, 83.92; H, 9.55%. Found: C, 83.84; H, 9.25%.

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