Tetrahedron Letters 54 (2013) 3819–3821

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Nickel-catalyzed cross-coupling reaction of acetylenic sulfones with alkynyl Grignard reagents: a facile method for the preparation of unsymmetrical 1,3-diynes

Kuang Fang, Meihua Xie *, Zhannan Zhang, Peng Ning, Guanying Shu

Key Laboratory of Functional Molecular Solids (Ministry of Education), Anhui Key Laboratory of Molecular Based Materials, College of Chemistry and Materials Science, Anhui Normal University, Wuhu 241000, China

ARTICLE INFO

Article history:
Received 31 January 2013
Revised 28 April 2013
Accepted 10 May 2013
Available online 20 May 2013

Keywords:
Acetylenic sulfone
Grignard reagent
Cross-coupling reaction
1,3-Diyne

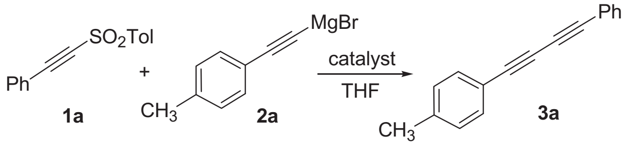
ABSTRACT

The cross-coupling reaction of acetylenic sulfones with acetylenic Grignard reagents was realized by using Ni(acac)$_2$ as catalyst to afford unsymmetrical 1,3-diynes under mild conditions without homocoupling byproducts. By using this method, 1,4-diaryl-1,3-diynes could be obtained in moderate to good yields (59–83%), whereas, the yields for alkyl substituted 1,3-diynes are lower (30–54%).

1,3-Diynes are useful starting materials in organic synthesis[1] and the conjugation functionality is widely occurring in natural products, pharmaceuticals,[2] and carbon-rich materials, such as macrocyclic annulenes, π-conjugated acetylenic oligomers, and polymers.[3] Some compounds containing the 1,3-diyne structure have been recognized for their antitumor, antibacterial, anti-inflammatory, and anti-HIV activities.[4] Consequently, the synthesis of 1,3-diynes has attracted considerable attention for decades. Methods for the synthesis of symmetrical 1,3-diynes have already been well-developed, mainly by transition-metal-catalyzed homo-coupling reaction of terminal alkynes and their derivatives.[5] In contrast, methods for the synthesis of unsymmetrical 1,3-diynes are still under-represented. Until now, the Cadiot–Chodkiewicz reaction, copper-catalyzed cross-coupling of 1-bromoalkynes with terminal alkynes with aliphatic amines as bases, still represents the major protocol for preparing unsymmetrical 1,3-diynes.[6] Lei and co-workers recently reported a Pd-catalyzed version of this cross-coupling.[7] Jiao and co-workers developed a Cu-catalyzed decarboxylative cross-coupling of propiolic acids with terminal alkynes.[8] However, in these reaction systems, the homo-coupling byproducts were formed concomitantly with the desired unsymmetrical diynes, which would inevitably add to the difficulty in the purification of the product.

Acetylenic sulfone has shown great potential in organic synthesis because the sulfone group is strongly electron-withdrawing and has versatile reactivities.[9] We have achieved the stereoselective synthesis of polysubstituted alkenes by the conjugate addition of organometallic reagents to acetylenic sulfones.[10] As an

Table 1
Screening of desulfonylation cross-coupling of acetylenic sulfone **1a** with Grignard reagent **2a**[a]



Entry	Catalyst	Ratio of **1a**:**2a**	T (°C)	Time (min)	Yield[b] (%)
1	None	1:1.2	25	40	45
2	Ni(acac)$_2$	1:1.2	25	40	59
3	Ni(acac)$_2$	1:1.5	25	30	78
4	Ni(acac)$_2$	1:2.0	25	30	80
5	Ni(PPh$_3$)$_2$Cl$_2$	1:1.5	25	40	64
6	FeCl$_3$	1:1.5	25	40	30
7	Ni(acac)$_2$	1:1.5	0	240	71
8	Ni(acac)$_2$	1:1.5	45	20	60
9[c]	Ni(acac)$_2$	1:1.5	25	30	60
10[d]	Ni(acac)$_2$	1:1.5	25	30	70

[a] The reaction was carried out with **1a** (1.0 mmol), **2a,** and 10 mol % catalyst in 5 mL of THF.

[b] Isolated yield based on **1a**.

[c] 5 mol % Ni(acac)$_2$ was used.

[d] 15 mol % Ni(acac)$_2$ was used.

---

* Corresponding author. Tel.: +86 0553 3869310; fax: +86 0553 3883517.
E-mail address: xiemh@mail.ahnu.edu.cn (M. Xie).

http://dx.doi.org/10.1016/j.tetlet.2013.05.049

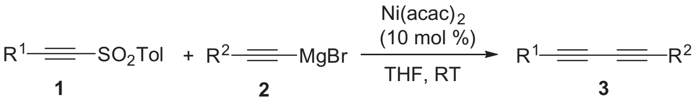
extension of our continued research interest in the synthetic applications of acetylenic sulfone, we report herein the facile synthesis of unsymmetrical 1,3-diynes by nickel-catalyzed desulfonylation cross-coupling of alkynyl Grignard reagent with acetylenic sulfone at room temperature without the formation of homo-coupling byproducts.

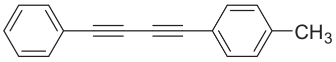
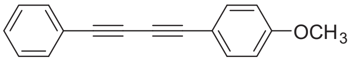
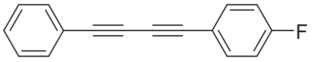
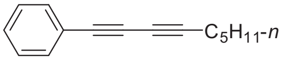
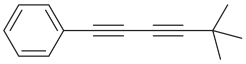
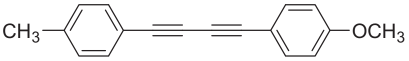
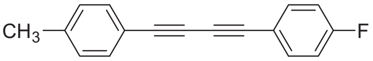
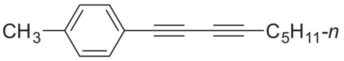
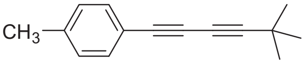
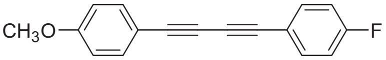
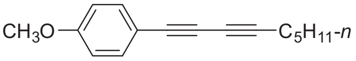
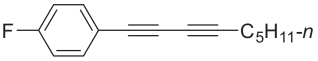
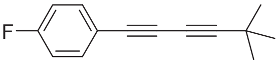
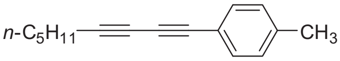
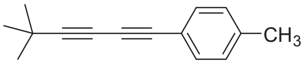
Initially, the reaction of 1-phenyl-2-(*p*-tolylsulfonyl)ethyne (**1a**) and (*p*-tolylethynyl)magnesium bromide (**2a**) in THF was investigated. The results are summarized in Table 1. In the absence of a catalyst, the unsymmetrical 1,3-diyne **3a** could be obtained in 45% yield when **1a** was reacted with 1.2 equiv of **2a** in THF at 25 °C (Table 1, entry 1).[11] The yield of **3a** was improved to 59% when 10 mol % of $Ni(acac)_2$ was added (Table 1, entry 2). When 1.5 equiv of **2a** was used, the yield could be further improved to 78% (Table 1, entry 3). Similar result was obtained when the amount of **2a** was increased to 2.0 equiv (Table 1, entry 4). When $Ni(PPh_3)_2Cl_2$ was used as the catalyst, the yield decreased to 64% (Table 1, entry 5). With $FeCl_3$ as catalyst, only 30% yield of **3a** was isolated (Table 1, entry 6). The reaction proceeded sluggishly at 0 °C (Table 1, entry 7), while a reduction in the yield was observed when the reaction temperature was raised to 45 °C (Table 1, entry 8). Neither reducing the catalyst loading amount to 5 mol % nor increasing it to 15 mol % could improve the yield (Table 1, entries 9 and 10). Notably, in all these cases examined, no homocoupling by-product was detected, though some unidentifiable complex mixtures of polar side products were detected.[12] To summarize, we choose the use of 1.5 equiv of **2a**, 10 mol % $Ni(acac)_2$ in THF at room temperature as the optimized reaction conditions for further study.

Under the optimized reaction conditions, the scope of the cross-coupling reaction was investigated. The results were compiled in Table 2. Using different combinations of acetylenic sulfones and Grignard reagents, a series of unsymmetrical 1,4-disubstituted

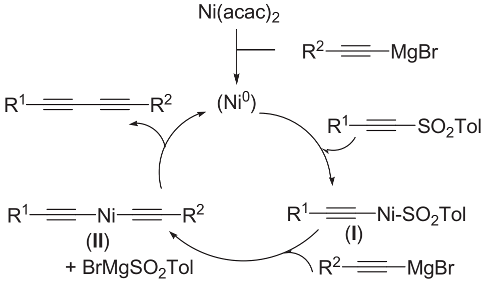
Table 2

The desulfonylation cross-coupling of acetylenic sulfone and Grignard reagent



Entry	1	2	R^1—≡—≡—R^2 (**3**)	Yield[a] (%)
1	**1a**	**2a**	 (**3a**)	78
2	**1a**	**2b**	 (**3b**)	67
3	**1a**	**2c**	 (**3c**)	83
4	**1a**	**2d**	 (**3d**)	42
5	**1a**	**2e**	 (**3e**)	30
6	**1b**	**2b**	 (**3f**)	59
7	**1b**	**2c**	 (**3g**)	66
8	**1b**	**2d**	 (**3h**)	54
9	**1b**	**2e**	 (**3i**)	33
10	**1c**	**2c**	 (**3j**)	63
11	**1c**	**2d**	 (**3k**)	36
12	**1d**	**2e**	 (**3l**)	40
13	**1d**	**2d**	 (**3m**)	35
14	**1e**	**2e**	 (**3h**)	36
15	**1f**	**2a**	 (**3i**)	30

[a] Isolated yield based on **1**.



Scheme 1. A tentative catalytic cycle for the cross-coupling reaction.

1,3-diynes were synthesized in 30–78% yields. When R^1 and R^2 were aryl groups, the desired diyne products were obtained in good yields, regardless of the electronic nature of the substituents on the benzene ring (Table 2, entries 1–3, 6, 7, and 10). However, when either R^1 or R^2 was an alkyl group, the yield dropped significantly (Table 2, entries 4, 5, 8, 9, 11–15), and the reaction failed to produce the desired 1,3-diynes when both R^1 and R^2 were alkyl groups.

The catalytic mechanism for this cross-coupling might be similar to that of the previously reported Ni-catalyzed cross-coupling of aryl sulfone and arylmagneusium bromide.[13] A tentative catalytic cycle is shown in Scheme 1. First, in the presence of Grignard reagents, $Ni(acac)_2$ would be reduced to Ni(0) species, which would undergo oxidative addition to the acetylenic sulfone to form intermediate (I). Subsequent transmetallation with the Grignard reagent would give intermediate (II) followed by reductive elimination to furnish the diyne products and regenerate the catalytic active Ni(0) species.

In conclusion, we have developed a facile method for the synthesis of unsymmetrical 1,3-diynes by nickel-catalyzed desulfonylation cross-coupling reactions of acetylenic sulfones with Grignard reagents. The cross-coupling reaction could be run at room temperature, and no homo-coupling byproduct was detected. Further studies on the reaction are ongoing in our laboratory.

Acknowledgments

The authors are grateful to the National Natural Science Foundation of China (Nos. 20772001 and 21272004) for financial support of this work. We are also grateful to Professor Jiping Hu, Professor Gaosheng Yang and Dr. Zhuo Chai for their helpful assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.05.049.

References and notes

1. (a) Wang, L. G.; Yu, X. Q.; Feng, X. J.; Bao, M. *Org. Lett.* **2012**, *14*, 2418; (b) Santana, A. S.; Carvalho, D. B.; Casemiro, N. S.; Hurtado, G. R.; Viana, L. H.; Kassab, N. M.; Barbosa, S. L.; Marques, F. A.; Guerrero, P. G., Jr.; Baroni, A. C. M. *Tetrahedron Lett.* **2012**, *53*, 5733; (c) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758.
2. (a) Kanokmedhakul, S.; Kanokmedhakul, K.; Kantikeaw, I.; Phonkerd, N. *J. Nat. Prod.* **2006**, *69*, 68; (b) Christensen, L. P.; Brandt, K. *J. Pharm. Biomed. Anal.* **2006**, *41*, 683; (c) Shi Shun, A. L. K.; Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 1034; (d) Yun, H. D.; Chou, T. C.; Dong, H. J.; Tian, Y.; Li, Y. M.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10375.
3. (a) Gholami, M.; Tykwinski, R. R. *Chem. Rev.* **2006**, *106*, 4997; (b) Baxter, P. N. W.; Dali-Youcef, R. *J. Org. Chem.* **2005**, *70*, 4935; (c) Kim, C.; Lee, S. J.; Lee, I. H.; Kim, K. T.; Song, H. H.; Jeon, H. J. *Chem. Mater.* **2003**, *15*, 3638.
4. (a) Stavri, M.; Mathew, K. T.; Gibson, T.; Williamson, R. T.; Gibbons, S. *J. Nat. Prod.* **2004**, *67*, 892; (b) Lerch, M. L.; Harper, M. K.; Faulkner, D. J. *J. Nat. Prod.* **2003**, *66*, 667; (c) Zeni, G.; Panatieri, R. B.; Lissner, E.; Menezes, P. H.; Braga, A. L.; Stefani, H. A. *Org. Lett.* **2001**, *3*, 819.
5. (a) Niu, X. J.; Li, C. J.; Li, J.; Jia, X. S. *Tetrahedron Lett.* **2012**, *53*, 5559; (b) Cheng, Z. W.; Jiang, H. F.; Wang, A. Z.; Yang, S. R. *J. Org. Chem.* **2010**, *75*, 6700; (c) Paixão, M. W.; Weber, M.; Braga, A. L.; de Azeredo, J. B.; Deobald, A. M.; Stefani, H. A. *Tetrahedron Lett.* **2008**, *49*, 2366; (d) Nishihara, Y.; Okamoto, M.; Inoue, Y.; Miyazaki, M.; Miyasaka, M.; Takagi, K. *Tetrahedron Lett.* **2005**, *46*, 8661; (e) Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.; Mori, A.; Hiyama, T. *J. Org. Chem.* **2000**, *65*, 1780.
6. (a) Wang, S. H.; Yu, L.; Li, P. H.; Meng, L. G.; Wang, L. *Synthesis* **2011**, 1541; (b) Jiang, H. F.; Wang, A. Z. *Synthesis* **2007**, 1649; (c) López, S.; Fernández-Trillo, F.; Midón, P.; Castedo, L.; Saá, C. *J. Org. Chem.* **2006**, *71*, 2802; (d) Marino, J. P.; Nguyen, H. N. *J. Org. Chem.* **2002**, *67*, 6841; (e) Chodkiewicz, W.; Cadiot, P. C. R. *Hebd. Seances Acad. Sci.* **1955**, *241*, 1055.
7. (a) Weng, Y.; Cheng, B.; He, C.; Lei, A. W. *Angew. Chem., Int. Ed.* **2012**, *51*, 9547; (b) Shi, W.; Luo, Y. D.; Luo, X. C.; Chao, L.; Zhang, H.; Wang, J.; Lei, A. W. *J. Am. Chem. Soc.* **2008**, *130*, 14713.
8. Yu, M.; Pan, D. L.; Jia, W.; Chen, W.; Jiao, N. *Tetrahedron Lett.* **2010**, *51*, 1287.
9. (a) García Ruano, J. L.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A. *Angew. Chem., Int. Ed.* **2012**, *51*, 2712; (b) Back, T. G.; Clary, K. N.; Gao, D. T. *Chem. Rev.* **2010**, *110*, 4498; (c) Back, T. G. *Tetrahedron* **2001**, *57*, 5263.
10. (a) Xie, M. H.; Lin, G. F.; Zhang, J. H.; Li, M.; Feng, C. Y. *J. Organomet. Chem.* **2010**, *695*, 882; (b) Xie, M. H.; Wang, J. L.; Zhang, W.; Wang, S. W. *J. Organomet. Chem.* **2009**, *694*, 2258; (c) Xie, M. H.; Wang, J. L.; Gu, X. X.; Sun, Y.; Wang, S. W. *Org. Lett.* **2006**, *8*, 431.
11. For a related direct reaction between aryl lithium reagents and arylsulfonylacetylenes without any transition metal catalysts, see: Ruano, J. L. G.; Alemán, J.; Marzo, L.; Alvarado, C.; Tortosa, M.; Díaz-Tendero, S.; Fraile, A. *Angew Chem., Int. Ed.* **2012**, *51*, 2712.
12. ^1H NMR analysis of these mixtures suggested the probable presence of products derived from the conjugate addition of the Grignard reagent to the acetylenic sulfone. For a relevant report, see: Cheng, C. Y.; Isobe, M. *Tetrahedron* **2011**, *67*, 9957.
13. (a) Clayden, J.; Julia, M. *J. Chem. Soc., Chem. Commun.* **1993**, 1682; (b) Clayden, J.; Cooney, J. J. A.; Julia, M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 7.