ORGANIC LETTERS

2010
Vol. 12, No. 16
3674−3677

Sulfur-Assisted Propargyl−Allenyl Isomerizations and Electrocyclizations for the Convenient and Efficient Synthesis of Polyfunctionalized Benzenes and Naphthalenes

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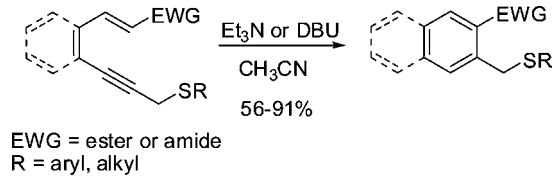
Received June 28, 2010

ABSTRACT

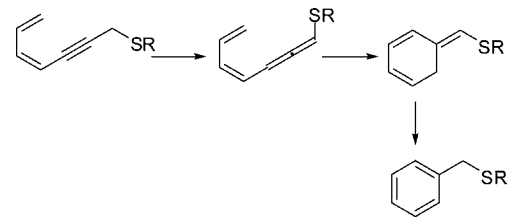


A facile and efficient electrocyclization for the synthesis of polyfunctionalized benzene and naphthalene derivatives was reported. As a result of the ready availability of starting materials and simple operation, this type of reaction has potential utility in organic synthesis.

The benzenoid aromatic compounds might be the most ubiquitous in nature and the laboratory among all cyclic compounds. Thus, the preparation of polyfunctionalized benzenes has been of interest for the organic community over the past century. Besides direct functionalization to benzene, construction of a new benzene ring using building blocks represents an efficient way to access polysubstituted benzenes from simple, readily available starting materials.

Allene-mediated cyclization reactions have attracted much attention by organic chemists, and the electrocyclization of diene−allenes were used as a key step to construct a benzene ring because of the unstable properties of the cyclization product isotoluene.[1] Recently, our group reported the sulfur-assisted Nazarov cyclization,[2a] thio-Claisen rearrangement,[2b] and Diels−Alder cycloaddition.[2c] On the basis of the understanding of sulfur-assisted propargyl−allenyl isomerization,[3] it may be reasonably envisioned that the sulfur-assisted propargyl diene could undergo cycloaddition via a diene−allene intermediate to give cyclic compounds (Scheme 1).

Scheme 1

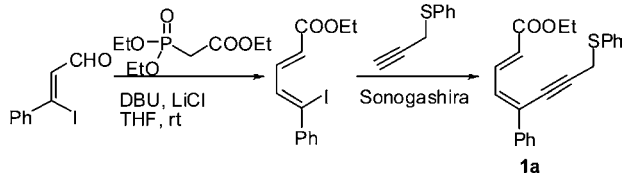


As a first attempt, we chose (2*E*,4*Z*)-ethyl 5-phenyl-8-(phenylthio)octa-2,4-dien-6-ynoate (**1a**)[4] as the starting material, which could be easily prepared via a Sonogashira reaction with (2*E*,4*Z*)-ethyl 5-iodo-5-phenylpenta-2,4-dienoate and phenyl(prop-2-ynyl)sulfane (Scheme 2).

(1) (a) Nakamura, I.; Zhang, D.; Terada, M. *J. Am. Chem. Soc.* **2010**, *132*, 7884. (b) Cabaleiro-Lago, E. M.; Rodriguez-Otero, J.; Garcia-Lopez, R. M.; Pena-Gallego, A.; Hermida-Ramon, J. M. *Chem.—Eur. J.* **2005**, *11*, 5966. (c) Lopez, C. S.; Faza, O. N.; Cossio, F. P.; York, D. M.; de Lera, A. R. *Chem.—Eur. J.* **2005**, *11*, 1734. (d) Wang, F.; Tong, X.; Cheng, J.; Zhang, Z. *Chem.—Eur. J.* **2004**, *10*, 5338. (e) Rodriguez-Otero, J.; Cabaleiro-Lago, E. M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1147. (f) Myers, A. G.; Dragovicb, P. S.; Kuo, E. Y. *J. Am. Chem. Soc.* **1992**, *114*, 9369. (g) Porter, N. A.; Hogenkamp, D. J.; Khouri, F. F. *J. Am. Chem. Soc.* **1990**, *112*, 2403.

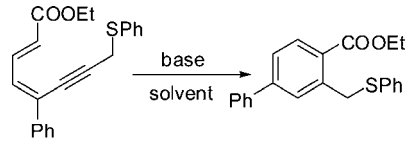
10.1021/ol101479d
Published on Web 07/16/2010

Scheme 2



On the basis of the previous investigation, we initiated our study by testing the reaction of **1a** in the presence of various bases and examining the solvent effect because the base and the reaction solvent may significantly influence the propargyl−allenyl isomerization.[2c] Triethylamine, DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), and DBN (1,5-diazabicyclo[4.3.0]non-5-ene) could trigger the expected reaction and give ethyl 3-(phenylthiomethyl)biphenyl-4-carboxylate (**2a**) as the product. Further examination showed that triethylamine and DBU could offer acceptable yields at 60 °C and room temperature, respectively, and acetonitrile was the suitable reaction medium for this reaction (entries 6 and 12, Table 1).

Table 1. Base and Solvent Effect[a]



1a **2a**

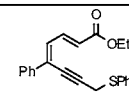
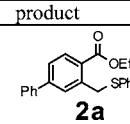
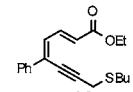
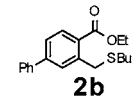
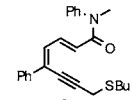
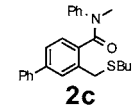
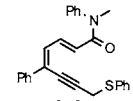
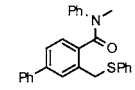
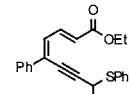
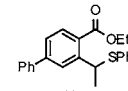
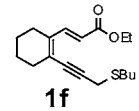
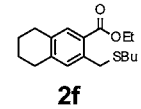
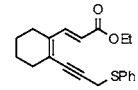
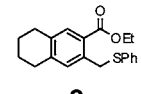
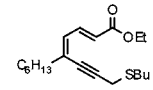
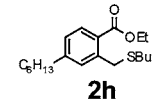
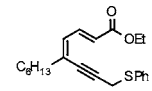
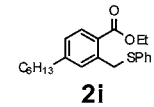
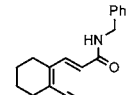
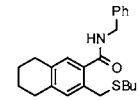
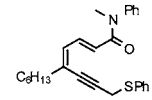
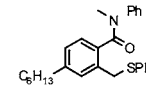
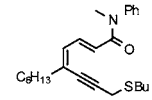
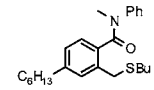
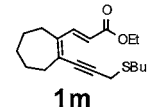
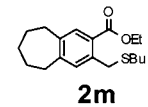
entry	base	solvent	time (h)	temp (°C)	yield of **2a** (%)
1	Et_3N	toluene	24	rt	NR
2	Et_3N	THF	24	rt	NR
3	Et_3N	MeCN	24	rt	NR
4	Et_3N	toluene	12	90	mixture
5	Et_3N	THF	12	60	55
6	Et_3N	MeCN	12	60	**80**
7	DBN	toluene	6	rt	mixture
8	DBN	THF	4	rt	38
9	DBN	MeCN	4	rt	48
10	DBU	toluene	6	rt	mixture
11	DBU	THF	4	rt	45
12	DBU	MeCN	4	rt	**75**

[a] Substrate **1a** (0.5 mmol) and base (1.0 mmol) in solvent (3 mL) under a N_2 atmosphere.

Inspired by this result, we examined the scope of the reaction and obtained polyfunctionalized benzenes in moderate to good yields under mild conditions (Table 2).

(*E*)-Ethyl 3-(2-(3-(phenylthio)prop-1-ynyl)phenyl)acrylate (**3a**), in which the *Z*-double bond of **1a** was replaced by a benzene ring, could be thought of as a promising expansion of **1a** and might be the starting material for the synthesis of ethyl 3-(phenylthiomethyl)-2-naphthoate

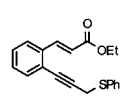
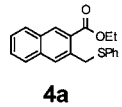
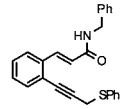
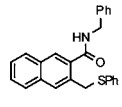
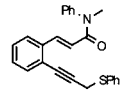
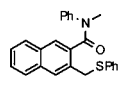
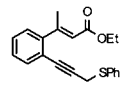
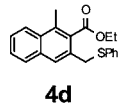
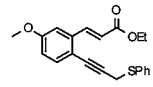
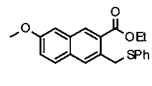
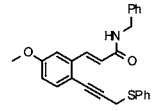
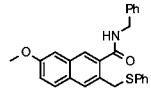
Table 2. Synthesis of Polyfunctionalized Benzenes[a]

entry	substrate	method	product	yield (%)
1	 **1a**	A	 **2a**	80
2	 **1b**	A	 **2b**	72
3	 **1c**	A	 **2c**	67
4	 **1d**	A	 **2d**	65
5	 **1e**	A	 **2e**	70
6	 **1f**	B	 **2f**	91
7	 **1g**	A	 **2g**	78
8	 **1h**	B	 **2h**	76
9	 **1i**	A	 **2i**	70
10	 **1j**	B	 **2j**	62
11	 **1k**	A	 **2k**	82
12	 **1l**	B	 **2l**	88
13	 **1m**	B	 **2m**	90

[a] Method A: **1** (0.5 mmol) and triethylamine (1.0 mmol) in acetonitrile (3 mL) under a N_2 atmosphere at 60 °C for 12 h. Method B: **1** (0.5 mmol) and DBU (1.0 mmol) in acetonitrile (3 mL) under a N_2 atmosphere at room temperature for 3 h.

(**4a**). However, we failed to obtain any product using triethylamine as the base. Luckily, DBU in acetonitrile at 60 °C gave the desired product **4a** in a yield of 72%, and a series of polysubstituted naphthalenes were prepared in satisfactory yields (Table 3).

Table 3. Synthesis of Polysubstituted Naphthalenes[a]

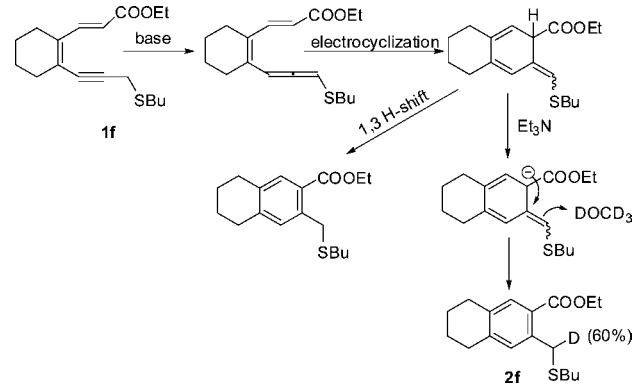
entry	substrate	time (h)	product	yield (%)
1	 **3a**	12	 **4a**	72
2	 **3b**	4	 **4b**	56
3	 **3c**	12	 **4c**	62
4	 **3d**	12	 **4d**	80
5	 **3e**	6	 **4e**	65
6	 **3f**	6	 **4f**	70

[a] Substrate **3** (0.5 mmol) and DBU (1.0 mmol) in acetonitrile (3 mL) at 60 °C under a N_2 atmosphere.

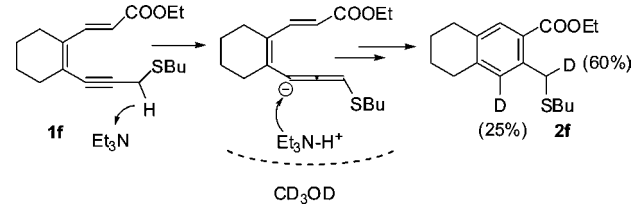
Although we did not detect the allene intermediate, we conducted control experiments which might be helpful for supporting the pathway proposed in Scheme 1. We treated (*E*)-ethyl 3-(2-(3-(butylthio)prop-1-ynyl)cyclohex-1-enyl)-acrylate (**1f**) with 20 equiv of methanol-d_4 in acetonitrile and obtained deuterated **2f**. We observed 60% deuterium on one of the protons of the methylene group adjacent to the sulfur atom, which might come from the base-assisted isomerization of the intermediate isotoluene (Scheme 3).

We had expected more deuterium on the new benzene ring before conducting this control experiment, but only 25% deuterium on the new benzene ring was observed, probably because the propargyl−allene isomerization is so fast that the protonated triethylamine does not have enough time to leave (Scheme 4).

Scheme 3



Scheme 4



Notably, the electron-withdrawing groups (ester or amide group) of **1** or **3**, which could increase the acidity of the methylene group adjacent to the sulfur atom, are essential to the propargyl−allenyl isomerization promoted by the mild bases and may improve the consequential 6 π-electrocyclization process.[2c] Importantly, the ester or amide group, which would be playing a role as a reactivity controlling element during the process, could also be used as a convenient chemical handle for preparing other useful compounds. We treated **2a** and **4b** with $LiAlH_4$ and $NaBH_4$/BF_3•Et_2O to access alcohol (**5**) and amine (**6**), respectively, in good yields (Figure 1).

On the other hand, the sulfane group, which triggered the propargyl−allenyl isomerization, might be used as a "key" for

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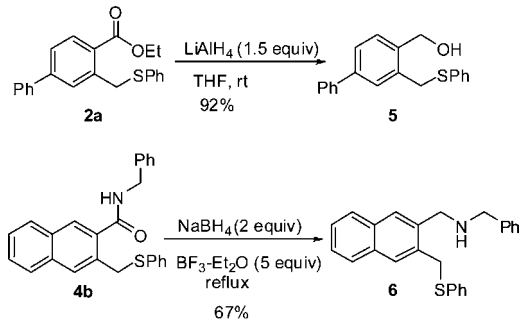

Figure 1. Reduction of **2a** and **4b**.

further generation of chemical diversity, such as oxidation to sulfoxide[5] and sulfone,[6] reduction,[7] alkylation,[8] and acylation.[9]

In summary, we developed a facile and efficient electrocyclization for the synthesis of polyfunctionalized benzene and naphthalene derivatives. As a result of the ready availability of starting materials and the simple operation, this type of reaction presented here has potential utility in organic synthesis.

Acknowledgment. Dedicated to the memory of Prof. Xian Huang. Financial support was received from the Natural Science Foundation of China (Nos. 20702046 and 20972134).

Supporting Information Available: Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL101479D

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