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Base-Catalyzed Cascade 1,3-H Shift/Cyclization Reaction to Construct Polyaromatic Furans

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Abstract: A convenient new method was developed to prepare unfused polyaromatic furan derivatives from diynyl-1,6-diols through a novel base-catalyzed cascade 1,3-H shift/cyclization process. Deuterium experiments were performed to determine that the 1,3-H shift was the rate-determining step.

Keywords: cyclization reaction; diynyl-1,6-diols; furans; 1,3-H shift

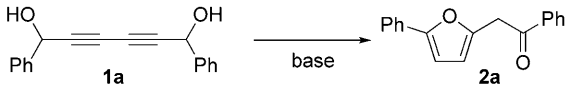
The chemistry of propargylic alcohols has been the object of many studies, but their dimeric analogues, diynyl-1,6-diol derivatives have so far received considerably less attention. This subunit can be simply prepared from the terminal propargylic alcohols through a coupling reaction. It has even been utilized to synthesize the highly reactive hexapentaenes,[1] and the compounds have been employed as the host molecules in asymmetric solid syntheses.[2] Despite these applications, examples of the use of this subunit in organic synthesis are very scarce.

Among the various classes of heterocyclic compounds, furan ring systems form an important component of pharmacologically active compounds, as they are associated with a wide spectrum of biological activities ranging from antifungal,[3] antitrypanosomal[4] and gastrointestinal motility activity[5] to farnesyl transferase[6] and phosphodiesterase inhibitory activity.[7] Because of the importance of this five-membered structural entity, the development of new strategies to construct furan derivatives has attracted much synthetic effort,[8] and is always of great interest.

In 1995, Ong's group reported the synthesis of unfused arylfurans from 1,6-dioxo-(*E,E*)-dienes *via* an acid- or base-catalyzed cyclization process.[9] However, the utility of this preparation was limited by the tedious preparation of the dienyl diketone substrates and the poor regioselectivities. In this communication, we want to report an efficient new method to construct unfused polyaromatic furan derivatives from diynyl-1,6-diols through a novel base-catalyzed cascade 1,3-H shift/Michael addition process, in which the regioselectivity was determined by the electronegativity difference of the substituents attached to the aryl groups.

As shown in Table 1, compound **1a** was chosen as the model system for our initial investigation. When **1a** was treated with NaH (1.2 equiv.) in THF (2 mL),

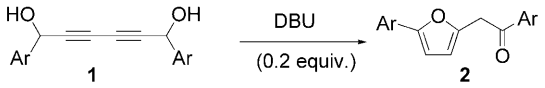
Table 1. Investigation of the reaction of compound **1a** with different catalysts.[a]



	Base (equiv.)	Solvent	*T* [°C]/Time	Yield [%][b]
1	NaH (1.2)	THF	r.t./1 h	65
2	CH_3ONa (1.2)	THF	r.t./1 h	30
3	*t*-BuOK (1.2)	THF	r.t./10 min	78
4	NaOH (1.2)	THF	r.t./10 min	40
5	NEt_3 (1.2)	THF	reflux/1 h	NR
6	DBU (1.2)	THF	r.t./7 h	56
7	DBU (1.2)	CH_3OH	r.t./1.5 h	NR
8	DBU (1.2)	toluene	r.t./1.5 h	41
9	DBU (1.2)	DCE	r.t./1.5 h	40
10	DBU (1.2)	CH_3CN	r.t./1.5 h	10
11	DBU (1.2)	THF	60/1 h	60
12	DBU (0.5)	THF	60/1 h	72
13	DBU (0.2)	THF	60/4 h	83
14	DBU (0.1)	THF	60/5 h	65

[a] Unless otherwise noted, all reactions were carried out on a 0.2 mmol scale in 2 mL solvent.
[b] Isolated yields.

Table 2. DBU-promoted the reaction of the symmetric diynyl diesters to construct polysubstituted furans.[a]



Entry	Compound **1**	Reaction time	Product **2**	Yield [%] [b]
1	**1a**, X = H	4 h		**2a**, 83
2	**1b**, X = OMe	15 h		**2b**, 86
3	**1c**, X = Me	4 h		**2c**, 76
4	**1d**, X = Br	1 h		**2d**, 80
5	**1e**, X = Cl	1 h		**2e**, 71
6	**1f**, X = F	1 h		**2f**, 31
7	**1g**, X = OMe	3 h		**2g**, 74
8	**1h**, X = Me	2 h		**2h**, 76
9	**1i**, X = Cl	1 h		**2i**, 51
10	**1j**	12 h		**2j**, 15
11	**1k**	1.5 h		**2k**, 78
12	**1m**	1 h		**2m**, 71

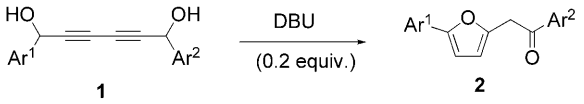
[a] Unless noted, all reactions were carried out at 0.2 mmol scale in 2 mL solvent at 60 °C with 20% mol equiv. of DBU.
[b] Isolated yields.

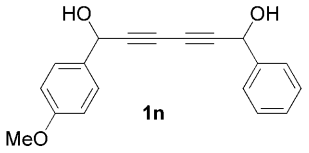
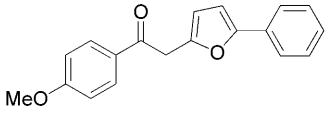
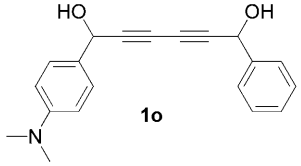
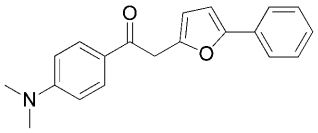
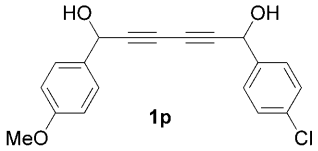
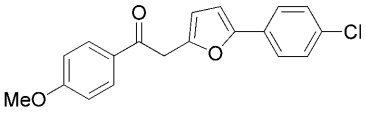
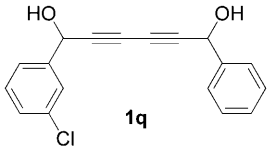
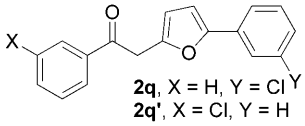
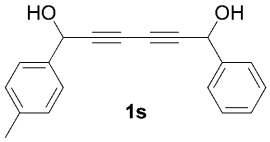
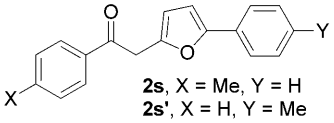
the furanyl ketone **2a** was obtained in 65% yield (Table 1, entry 1).

Various bases were then screened to improve the reaction yield. Other non-amine bases, such as CH_3ONa, *t*-BuOK and NaOH can also trigger this reaction, among which *t*-BuOK gave the highest reaction yield (Table 1, entry 3).[10] Several tertiary amine bases were then tested, among which, Et_3N and 1,4-diazabicyclo[2.2.2]octane were not effective in this reaction even at elevated temperature. When the strong base DBU (1.2 equiv.) was used as the catalyst, furanyl ketone **2a** was obtained in 56% yield (Table 1, entry 6). Solvent screening showed that THF was the best reaction medium in combination with the DBU conditions. Further optimization of the reaction temperature and the amount of DBU amount then identified a set of best conditions to give the desired furan product in 83% yield (Table 1, entry 13).

Under the conditions from entry 13 in Table 1, the scope and limitations for this reaction were explored. As shown in Table 2, a number of polysubstituted 2-furanyl ketone products **2a–m** were synthesized from the symmetrical diynyl-1,6-diol derivatives **1a–m**. The effect of different substitution patterns on the reaction yield was investigated. Both electron-rich and electron-poor substrates worked very well, affording the desired products in moderate to good yields. The reaction of electron-rich substrates took longer reac-

Table 3. DBU promoted the reaction of the asymmetric diynyl diesters to construct polysubstituted furans.[a]

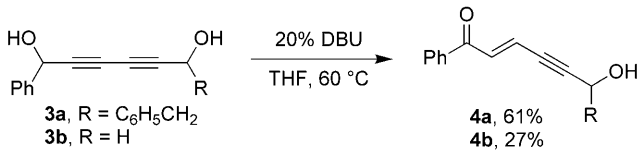


Entry	Compound **1**	Reaction time	Product **2** (major)	Yield [%][b]/ regio[c]
1	 **1n**	4 h		**2n**, 66 one isomer
2	 **1o**	4h		**2o,** 65 one isomer
3	 **1p**	3 h		**2p,** 67 one isomer
4[d]	 **1q**	2 h	 **2q**, X = H, Y = Cl **2q'**, X = Cl, Y = H	**2q,** 53 (**2q/2q'** = 10/1)
5[d]	 **1s**	1 h	 **2s**, X = Me, Y = H **2s'**, X = H, Y = Me	**2s,** 71 (**2s/2s'** = 4/1)

[a] Unless noted, all reactions were carried out at 0.2 mmol scale in 2 mL solvent at 60 °C with 20% mol equiv. of DBU.
[b] Isolated yields.
[c] The ratio of the regioisomers was determined from ^{1}H NMR spectral data.
[d] The reaction was carried out at 30 °C.

tion times, and gave higher conversions; whereby **2b** was obtained in the highest yield (Table 2, entry 2). The effects of *o*-, *m*-, *p*-substitution patterns on the reaction yield were examined (Table 2, entries 3, 8, 10). It was found that the reactivity of *p*-methyl-substituted substrate **1c** was similar to that of its *meta* analogue **1h**, while the reaction yield of the *o*-substituted substrate **1j** was very low. The heteroaromatic substituted diynyl-1,6-diol derivatives were also tested, among which **1k** and **1m** afforded the desired products **2k** and **2m** in good yields.

We then turned to investigate the reaction of unsymmetrical dialkynyl-1,6-diols. When 1-(4-methoxyphenyl)-6-phenylhexa-2,4-diyne-1,6-diol **1n** was treated with 20% mol equiv. of DBU in THF at room temperature, only product **2n** was obtained in 66% yield (Table 3, entry 1). No other regioisomer was separated in this reaction. Similarly, the reaction of **1o** and **1p** gave the corresponding products **2o** and **2p** in 65% and 67% yields, without the formation of any regioisomers. However, when compound **1q** was treated with 20% mol equiv. of DBU, a mixture of **2q** and **2q′**

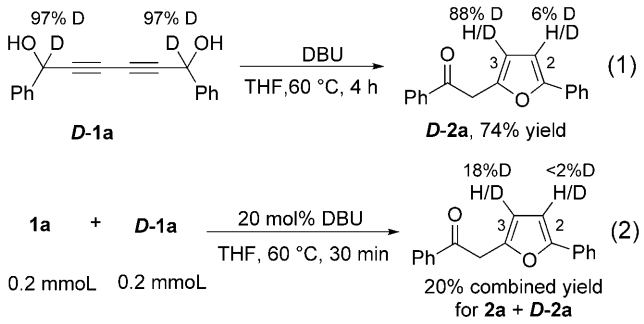


Scheme 1. Investigation of the reaction of substrates **3a** and **3b**.

was obtained 53% yield (**2q**/**2q′** = 10/1, Table 3, entry 4). As compared with substrates **1n–p**, the electronegativity difference between the two end groups in substrate **1q** was relatively small. For the same reason, the reaction of **1s** gave a mixture of **2s** and **2s′** in 71% yield (**2s**/**2s′** = 4/1, Table 3, entry 5).[11]

The reactions of substrates **3a** and **3b** were then investigated, in which the phenyl group at one end was replaced either by a benzyl group or by a hydrogen atom (Scheme 1). To our surprise, no desired furan products were obtained in these reactions. Substrate **3a** afforded enyne ketone **4a** in moderate yield, while the reaction of **3b** gave only **4b** in 27% yield. This result indicated that the isomerization reaction of the dialkynyl diols might start from a 1,3-H shift, which was facilitated by the presence of the conjugated aromatic group. Breakage of the conjugated system by the sterically neighboring methyl group in substrate **1j** led to a low reaction yield.

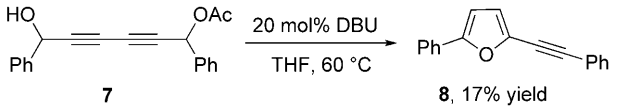
Deuteration experiments were performed to probe the reaction mechanism. As shown in Scheme 2, **D-1a** underwent isomerization in THF to give **D-2a** in 74% yield, in which 88% deuterium atom was incorporated into the C-3 position, with less than 6% deuterium in the C-2 position. This means that the 1,3-shift step primarily proceeded through a contact ion pair process.[12,13] Subsequent kinetic isotopic effect (KIE) experiments were carried out by competition experiments [Eq. (2), Scheme 2]. When a mixture of **1a** and **D-1a** (**1a**/**D-1a** = 1/1) was treated with 20% mol equiv. of DBU in THF at 60 °C for 30 min, the desired furan product was obtained in 20% yield, in which 18% deuterium atom was incorporated into the C-3 position. The calculated k_H/k_D value is about 4.36. This significant isotopic effect indicated that C–H bond cleavage is the rate-determining step of this transformation.



Scheme 2. DBU-promoted reaction of **D-1a** and the competition experiments.

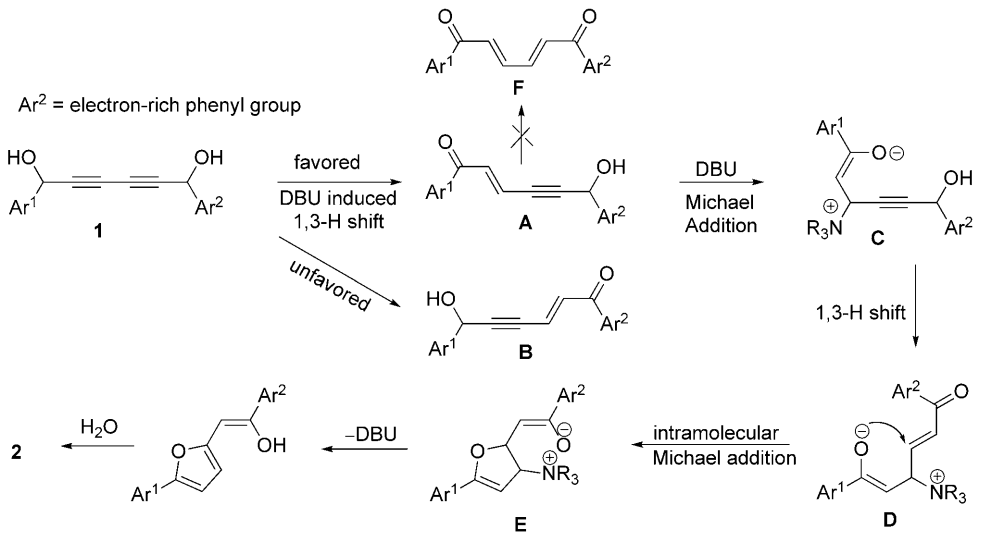
To elucidate the regioselectivity of this reaction, enyne ketone **5** was prepared and treated with 20% mol equiv. of DBU (Scheme 3). Product **2n**'s regioisomer **6** was obtained in 87% yield, without the formation of **2n**. As compared with product **2n** obtained in the reaction of **1n**, the furan ring in **6** was located near to the electron-rich *p*-methoxyphenyl group. The monoester 6-hydroxy-1, 6-diphenylhexa-2,4-diynyl acetate **7** was also tested in this reaction; it was found that furan alkyne **8** was obtained in 17% yield (Scheme 4).[14]

A plausible mechanism was then proposed (Scheme 5). The first 1,3-H shift of the unsymmetrical dialkynyl 1,6-diol substrate **1** is favored to occur at the hydroxy carbon attached to the electron-poor phenyl group, which afforded an alkynyl vinyl ketone intermediate **A**.[15] Michael addition of the amine onto intermediate **A** gave zwitterion **C**, in which the enolate unit or DBU triggered the second 1,3-shift to give intermediate **D**. Intramolecular Michael addition and the following elimination then provided the desired furanyl ketone **2**. The regioselectivity was determined by the difference of the electronegativity between the two phenyl groups in the unsymmetrical dialkynyl-1,6-diol substrate **1**. A small electronegativity difference would lead to the formation of the intermediate regioisomer **B**, and would lower the regiose-



Scheme 4. DBU-induced reaction of the monoester **7** to give furan alkyne **8**.

Scheme 3. DBU-promoted reaction of compound **5** to give the regiosiomer **6** of **2n**.



Scheme 5. A possible mechanism for the base-catalyzed cascade 1,3-H shift/cyclization reaction of diynyl diesters to provide polyaromatic furans.

lectivity. Formation of the dialkenyl diketone **F** was unlikely because no regioisomer was obtained in the reaction of compound **5**.

In conclusion, we have developed a new method to construct a series of the unfused polyaromatic furan derivatives from the base-induced reaction of the diynyl-1,6-diols through a novel cascade 1,3-H shift/Michael addition process. Deuterium experiments revealed that a 1,3-H shift was the rate-determining step, which primarily proceeded through a contact ion pair process. This is the first report, to the best of our knowledge, of a tandem process by using the base-catalyzed 1,3-H shift as the starting step.

Experimental Section

Typical Procedure for the DBU-Mediated Reaction of Diynyl Diesters

To an oven-dried Schlenk tube containing a magnetic stir bar, 0.2 mmol substrate **1a** was added under N_2, followed by 20 mol% DBU and 2 mL THF. The resulting mixture was allowed to stand at 60 °C, until complete consumption of the starting material was shown TLC monitoring. The reaction was quenched by addition of 2 mL saturated aqueous ammonium chloride solution, extracted with ethyl acetate, and the combined organic layers were then washed with brine, dried over anhydrous sodium sulfate and filtered. After removing the solvent, the residue was purified by column chromatography on silica gel to afford product **2a**; yield: 83%.

Acknowledgements

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[10] Efforts to improve the reaction yield by optimizing the amount of *t*-BuOK proved to be fruitless.

[11] Products **2q/2q′** and **2s/2s′** are inseparable mixtures.

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[14] After the formation of the alkynyl vinyl ketone intermediate in the reaction of **2**, AcO might act as the leaving group in an S_N2' type nucleophilic addition onto the propargylic acetate unit, see Scheme 5.

[15] The first 1,3-H shift could be the rate-determining step, the second 1,3-H shift might be an intramolecular process. The second reason is that no vinyl ketone intermediate was detected in the reaction mixture.

