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Carbolithiation of substituted stilbenes and styrenes with dithianyllithiums

Shouchu Tang [a], Junjie Han [a], Jinmei He [a], Jiyue Zheng [a], Yongping He [a], Xinfu Pan [a], Xuegong She [a,b,*]

[a] Department of Chemistry, State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou, 730000, PR China
[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences, Lanzhou 730000, PR China

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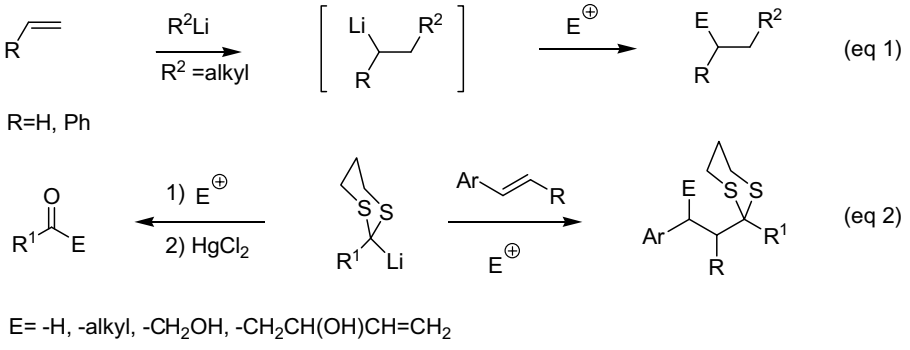
Abstract

Carbolithiation of a range of substituted stilbenes and styrenes with dithianyllithiums is described, leading to the rapid, efficient and stereocontrolled assembly of highly functionalized dithiane intermediates for acyl-equivalents synthesis.

The carbolithiation of unactivated alkenes has been widely used as a powerful tool for creating a carbon–carbon bond and a new organolithium species in a single step.[1] A range of commercial and homemade organolithium reagents to styrene derivatives have been studied extensively during the past 50 years and widely used in organic synthesis; however, the organolithium reagents are usually simple alkyl organolithium reagents such as *n*-BuLi or *t*-BuLi, leading to the further synthetic transformations limited in synthesis (Scheme 1, Eq. 1). Dithianes have evolved as invaluable tools in organic synthesis, serving primarily as acyl anion equivalents for constructing carbon–carbon bonds. In these early examples, two building blocks were joined, one a substituted lithiated 1,3-dithiane, the other an electrophile such as an iodide, epoxide, aldehyde, or ketone.[2] In contrast, the relatively unstudied carbolithiation with dithianes poses a considerable challenge. Herein, we wish to disclose the carbolithiation reaction of dithiane



Scheme 1.

* Corresponding author. Fax: +86 0 931 8912582.
E-mail address: shexg@lzu.edu.cn (X. She).

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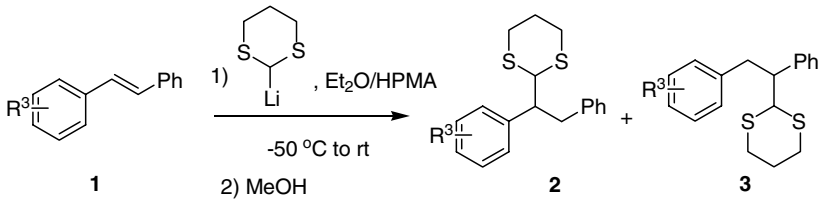
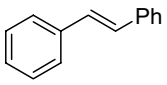
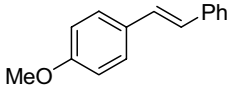
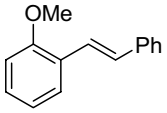
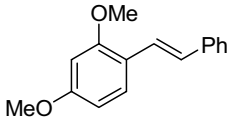
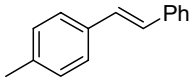
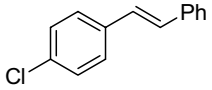
Table 1
Carbolithiation of substituted stilbene derivatives with lithiated 2-*H*-1,3-dithiane



Entry[a]	1	Substrate	Products[b]	Ratio 2:3	Yield (%)
1	**1a**		**2a**	—	82
2	**1b**		**2b**, **3b**	98:2	71
3	**1c**		**2c**, **3c**	85:15	76
4	**1d**		**2d**, **3d**	90:10	78
5	**1e**		**2e**, **3e**	96:4	69
6	**1f**		**2f**, **3f**	5:95	54[c]

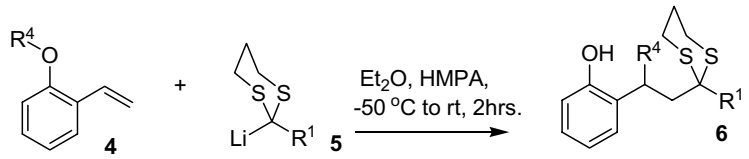
[a] Reaction conditions: (1) 1 mmol of substrate, 2.5 mmol of lithiated carbonanion, 1–3 mmol of HMPA, 20 mL of anhydrous Et_2O, −50 °C to rt, 3 h; (2) 1 mL MeOH, 1 h.
[b] The products were identified by ^1H NMR, ^{13}C NMR, HRMS and ratios determined by ^1H NMR.
[c] Recovered 20% starting material.

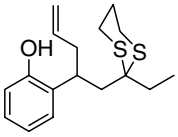
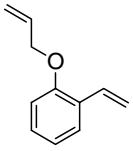
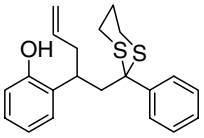
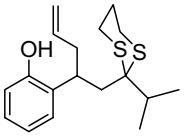
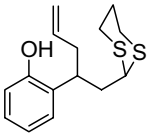
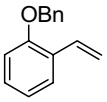
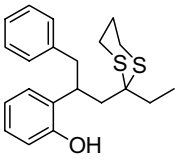
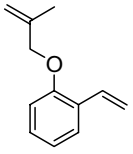
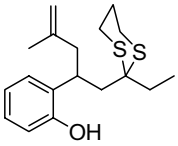
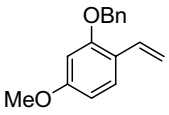
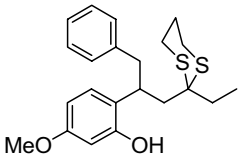
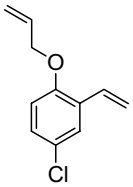
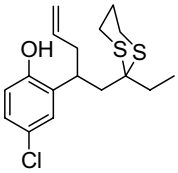
anions for the preparation of advanced fragments[3] (Scheme 1, Eq. 2).

Recently, regioselective carbolithiation of unactivated alkenes has been expanded by O'Shea.[4] Our current goal is to advance this methodology with lithiated dithiane anions. Initially, (*E*)-stilbene **1a** was first examined with lithiated 2-*H*-1,3-dithiane. After many trials, we found that the carbolithiation reaction proceeded smoothly from −50 °C to room temperature in the presence of HMPA[5] in anhydrous Et_2O (82%, Table 1). With optimal reaction condition in hand, several substituted stilbenes were prepared[6] and the reaction results are summarized in Table 1. The carbolithiation selectivity was determined by reacting the lithiated intermediates with methanol and the crude reaction products were analyzed by NMR. The reactions of the three methoxy substituted stilbenes and methyl substituted stilbene (Table 1, entries 2–5) gave the corresponding protonation in good yields (69–78%) and high regioselectivity (85:15–98:2). For example, the reaction of **1b** with lithiated 2-*H*-1,3-dithiane provided a mixture of **2b**/**3b** in 98:2 ratio (Table 1, entry 2). We became aware of a similar finding in which carbolithiation of *ortho*-substituted stilbenes with *n*-BuLi gave the major isomers having the butyl group substituted at the carbon to the ortho functionalized benzene ring.[4e] The reaction of the Cl-substituted stilbene was slower and provided a mixture of **2f**/**3f** in a ratio of 5:95 (Table 1, entry 6). The regioselective carbolithiation was presumably due to the electron donating effect and the ortho effect of unsymmetrical stilbenes.

Having established the protocol of a regioselective carbolithiation reaction with dithiane, our next aim was to demonstrate the utility of lithiated compounds in cascade reaction sequences, to provide a new entry to the complicated substituted dithiane analogues, which could be introduced invaluable tools in acyl-equivalents synthesis. According to the work of Taylor,[7] we demonstrated that the reaction was applicable to 2-substituted oxystyrene with a variety of dithianyllithiums and the reaction results are summarized in Table 2. Because of the difficulty in purifying the immediates of carbolithiation, the reaction was performed directly from −50 °C to room temperature before work-up. 2-Allyl-oxystyrene underwent

Table 2
Intramolecular alkylation processes of 2-substituted oxystyrene with dithianyllithiums



Entry[a]	4	Substrate[b]	R^1	Product	Yield[c] (%)
1	**4a**		Et		80
2	**4a**		Ph		76
3	**4a**		*i*-Pr		67
4	**4a**		H		—
5	**4b**		Et		75
6	**4c**		Et		73
7	**4d**		Et		69
8	**4e**		Et		72

[a] Reaction conditions: 0.5 mmol of substrate, 1.2 mmol of lithiated carbonanions, 3 mmol of HMPA, 15 mL of anhydrous Et_2O, −50 °C to rt, 2 h.
[b] The substrates were prepared by Wittig reaction of the corresponding benzaldehydes.
[c] Isolated yield.

carbolithiation-allyl transfer with a variety of 1,3-dithianyllithiums in good yields of 67–80% (Table 2, entries 1–3). We found that the steric hindrance of the dithianes did not affect product outcome, whereas for lithiated 2-*H*-1,3-dithiane, the expected product was obtained in a minor amount, the intermediate organolithium may be unstable

(Table 2, entry 4). Related substrates 2-benzyloxystyrene and 2-allyloxystyrene were examined under similar reaction conditions, the steric factor (Table 2, entries 5 and 6) and the electronic factor of substitution group whatever with electron-donating (Table 2, entry 7) or withdrawing groups (Table 2, entry 8) did not obviously affect the transfer reaction. This process probably involves a tandem carbolithiation addition of dithiane anions and intramolecular alkylation sequences. Further exploration of dithiane carbolithiation in conjunction with the anion relay chemistry (ARC) tactic[8] is currently in progress.

In summary, we have established that application over the more conventional stepwise addition reactions of dithiane anions to a range of substituted stilbenes and styrenes leading to the rapid, efficient and stereocontrolled assembly of highly functionalized dithiane intermediates[9] for acyl-equivalents synthesis.

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8. Reaction of dithiane anions in anion relay chemistry, see: (a) Smith, A. B.; Pitram, S. M.; Xian, M.; Kim, W. S.; Kim, D. S. *J. Am. Chem. Soc.* **2006**, *128*, 12368; (b) Smith, A. B., III; Xian, M. *J. Am. Chem. Soc.* **2006**, *128*, 66.
9. The spectral data of some products (Table 1, product **2b**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, $J = 5.7$ Hz, 2H), 7.11–7.15 (dd, $J = 8.7$, 2.1 Hz, 3H), 7.06 (d, $J = 5.7$ Hz, 2H), 6.82 (dd, $J = 8.4$, 2.1 Hz, 2H), 4.28 (d, $J =$ 5.4 Hz, 1H), 3.77 (s, 3H), 3.45 (dd, $J = 10.2$, 5.4 Hz, 1H), 3.16–3.20 (m, 1H), 2.93–2.98 (dd, $J = 10.2$, 6.6 Hz, 1H), 2.79–2.84 (m, 4H), 2.03–2.08 (m, 1H), 1.78–1.84 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.5, 139.7, 132.0, 129.6, 129.1, 128.1, 125.9, 113.3, 55.0, 53.5, 51.8, 38.8, 30.9, 30.8, 25.8. Ms *m*/*z* 330, 239, 211, 135, 119, 84. HRMS (ESI) calcd for $C_{19}H_{26}OS_2N$ $(M+NH_4)^+$: 348.1450. Found: 348.1451 (Table 2, product **6a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.17 (d, $J = 7.2$ Hz, 1H), 7.07 (t, $J = 7.5$, 6.6 Hz, 1H), 6.91 (t, $J = 7.2$, 7.2 Hz, 1H), 6.82 (d, $J = 7.8$ Hz, 1H), 5.99 (s, 1H), 5.62–5.71 (m, 1H), 4.98 (t, $J = 12.1$, 19.2 Hz, 2H), 3.22–3.26 (m, 1H), 2.75–2.78 (m, 2H), 2.66–2.69 (m, 2H), 2.40–2.44 (m, 2H), 2.31 (d, $J = 7.5$ Hz, 2H), 1.81–1.88 (m, 2H), 1.70–1.78 (m, 2H), 0.84 (t, $J = 7.5$, 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.0, 136.7, 132.3, 127.8, 127.1, 121.2, 116.9, 116.7, 54.7, 42.9, 42.2, 34.5, 31.7, 26.0, 25.9, 25.0, 8.6. Ms *m*/*z* 308, 279, 233, 201, 161, 147, 107, 84. HRMS (ESI) calcd for $C_{17}H_{24}OS_2Na$ $(M+Na)^+$: 331.1161. Found: 331.1160.