A New and Facile Method for Stereoselective Synthesis of (*E*)-Styryl Bromides by the Reduction of 1,1-Dibromoalkenes Using $LiAlH_4$–EtOAc (1:1)

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Abstract: A facile method for stereoselective synthesis of (*E*)-styryl bromides by the reduction of 1,1-dibromoalkenes using $LiAlH_4$–EtOAc (1:1) is described. We believe that the present procedure is a good alternative to the Tokuda's microwave method with good stereoselectivity.

Key words: 1,1-dibromoalkenes, $LiAlH_4$–EtOAc, styryl bromides

(*E*)- and (*Z*)-Vinyl bromides are very useful intermediates in organic synthesis and the development of methods for their stereoselective synthesis is of considerable importance. Their use as precursors to vinyl anion such as vinyl lithium[1a] and as coupling partners in a wide range of transition metal-catalyzed coupling reactions[1b] has stimulated a great deal of interest in their synthesis. A number of one- or two-step procedures exist for stereoselective synthesis of (*Z*)-vinyl bromide.[2] However, efficient synthesis of (*E*)-vinyl bromides seems to be somewhat underdeveloped, although Takai's $CHBr_3$–$CrCl_2$ method,[3] the hydrometalation-bromination methods[4] and the decarboxylation methods of cinnamic acid derivatives,[5] perform this transformation well in a number of favorable cases.[6] Reduction of 1,1-dibromoalkenes, readily available from a simple reaction of an aldehyde with CBr_4 and PPh_3,[7] represents a practical alternative to the stereoselective synthesis of (*E*)-vinyl bromide. Several procedures for the reduction of 1,1-dibromoalkenes to the corresponding vinyl bromides have been reported, which is induced by various reagents, such as alkyl metal reagents,[8] In,[9] Sm,[10] Bu_3SnH–Et_3B,[11] and $(RO)_2POH$[12]. However, these synthetic methods have some drawbacks, including very low reaction temperature[8] (–94 °C to –110 °C), limitation of substrates and/or unfavorable ratios of the *E*/*Z* isomers. In 2002, Tokuda et al. reported a good stereoselective synthesis of (*E*)-styryl bromides by microwave-induced reduction using a $(EtO)_2POH$–EtONa–EtOH system (*E*/*Z* = >20–16:1; various 1,1-dibromo-2-arylethenes as substrates).[13] Herein, we would like to report a facile method for stereoselective synthesis of (*E*)-styryl bromides by the reduction of 1,1-dibromoalkenes using $LiAlH_4$–EtOAc (1: 1) in THF.

We chose $LiAlH_4$ as a simple reducing reagent,[14] and began with optimization of reaction conditions using 1,1-dibromo-2-(4-methoxyphenyl)ethene as a substrate. The selected results are shown in entries 1-4, Table 1. As shown in entry 1, when using 2 mol equivalents of $LiAlH_4$ (THF, –40 °C), the desired (*E*)-bromostyrene was obtained in low yield with poor selectivity in a ratio of 2 (*E*-isomer):1 (*Z*-isomer):3 (styrene). After intensive screening of reaction conditions such as solvents and additives, the addition of EtOAc ($LiAlH_4$–EtOAc = 1:1) as an additive was found to improve significantly the yield and the stereoselectivity (*E*/*Z*/styrene = >20:1:2, entry 2).[15] We assume that the effective reducing agent is $Li(EtO)_2AlH_2$, although further investigation to clarify the detailed role of EtOAc is needed. On the other hand, the addition of EtOH gave less satisfactory results (entries 3 and 4). The addition of stoichiometric quantities of EtOH (2–3 equiv) with $LiAlH_4$, leads to $Li(EtO)_2AlH_2$ or $Li(EtO)_3AlH$, but the alkoxides rapidly undergo disproportionation.[16] This disproportionation may cause lower selectivity than the $LiAlH_4$–EtOAc (1:1) system.

Having optimized the reaction conditions, substrate generality was investigated. The results are shown in entries 5–11. A variety of aryl-substituted dibromoalkenes with electron-donating or withdrawing groups were converted to the corresponding styryl bromide in good yields with *E*/*Z* = >20–18:1 selectivities (entries 5–10). This procedure allows for the presence of bromo, chloro and fluoro groups on the benzene ring (entries 5 and 10). The 5 mmol scale reaction (entry 9) also gave the same selectivity, compared with the ca. 0.3 mmol scale reaction (entry 8). Unfortunately, the stereoselectivity of the alkyl-substituted dibromoalkene was low (entry 11). In most cases, the stereoselectivity is comparable to that of Tokuda's microwave-induced $(EtO)_2POH$–EtONa–EtOH system.[13]

The present procedure a provides new and facile two-step method for stereoselective synthesis of (*E*)-styryl bromides from aryl aldehydes, and is a good alternative to the Tokuda's microwave method.[13]

IR spectra were measured on a JASCO IR Report-100 diffraction grating IR spectrophotometer. ^1H (270 MHz) and ^{13}C NMR (68 MHz) spectra were measured on a JEOL JNM-EX-270 NMR spectrometer. EI and FAB MS spectra were measured on a JEOL JMS-SX-102A instrument. Commercially available $LiAlH_4$ was used without any further purification. THF was distilled from Na/benzophenone ketyl under a nitrogen atmosphere. EtOAc was dis-

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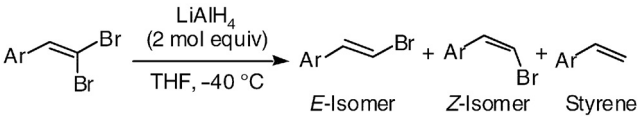
Table 1 Optimized Conditions and Substrate Generality[a]



Entry	Substrate Ar =	Additive (mol equiv)	Time (h)	Yield (%)[b]	Ratio (*E*/*Z*:styrene)[c]
1	4-$MeOC_6H_4$	none	7	31	2:1:3
2	4-$MeOC_6H_4$	EtOAc (2)[d]	6	76	>20:1:2
3	4-$MeOC_6H_4$	EtOH (4)	10	70	18:1:2
4	4-$MeOC_6H_4$	EtOH (6)	13	12[e]	13:1:2
5	4-ClC_6H_4	EtOAc (2)	3	86	>20:1:1
6[f]	4-$MeO_2CC_6H_4$	EtOAc (3)	12	75[g]	19:1:1
7	4-MeC_6H_4	EtOAc (2)	6	82	19:1:2
8	4-*i*-PrC_6H_4	EtOAc (2)	4	69	19:1:3
9[h]	4-*i*-PrC_6H_4	EtOAc (2)	5	74	19:1:3
10	2-F-4-BrC_6H_4	EtOAc (2)	2	83	18:1:<1
11	$PhCH_2CH_2$	EtOAc (2)	13	60	3:2:<1

[a] Reaction conditions: Substrate (ca. 0.3 mmol), $LiAlH_4$ (ca. 0.6 mmol), additive, THF at –40 °C.
[b] Combined yield (*E* + *Z*).
[c] Determined by ^1H NMR analysis of the crude product.
[d] 1 Mol equiv of EtOAc gave less satisfactory results. 3 Mol equiv of EtOAc resulted in no reaction.
[e] The starting substrate was recovered in 61% yield.
[f] 3 Mol equiv of $LiAlH_4$ was used.
[g] The CO_2Me group was also reduced to the CH_2OH group.
[h] Run with 5 mmol substrate.

tilled after drying with CaH_2. Silica gel column chromatography was performed on Fuji silysia PSQ 60B.

The known dibromoalkenes shown below were prepared according to the published procedure.[7] Their physical data were comparable to those of the corresponding literature: 1,1-dibromo-2-(4-chlorophenyl)ethane,[17] 1,1-dibromo-2-(4-methoxycarbonylphenyl)ethane,[17] 1,1-dibromo-2-(4-methoxyphenyl)ethane,[17] 1,1-dibromo-4-phenyl-1-butene,[8d] 1,1-dibromo-2-(4-tolyl)ethene.[17]

The physical data of the new dibromoalkenes are shown below.

1,1-Dibromo-2-(4-bromo-2-fluorophenyl)ethane

The published procedure[7] was used to afford the title dibromoalkene as a colorless oil; yield: 90%.

IR ($CHCl_3$): 1600, 1485, 864 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.26 (br d, *J* = 9.9 Hz, 1 H), 7.30 (br d, *J* = 9.9 Hz, 1 H), 7.46 (s, 1 H), 7.65 (t, *J* = 8.1 Hz, 1 H).

^{13}C NMR ($CDCl_3$): δ = 92.95 (d, *J* = 2.2 Hz), 119.21 (d, *J* = 24.6 Hz), 122.39 (d, *J* = 13.4 Hz), 122.76 (d, *J* = 9.5 Hz), 127.20 (d, *J* = 3.9 Hz), 128.82 (d, *J* = 4.5 Hz), 130.30 (d, *J* = 2.8 Hz), 158.98 (d, *J* = 254.3 Hz).

EIMS: *m*/*z* = 362 [M^+], 360 [M^+], 358 [M^+], 356 [M^+], 83 [bp].

Anal. Calcd for $C_8H_4Br_3F$: C, 26.78; H, 1.12. Found: C, 26.85; H, 1.16.

1,1-Dibromo-2-(4-isopropylphenyl)ethene

The published procedure[7] was used to afford the title dibromoalkene as a colorless oil; yield: (89%).

IR (neat): 1610, 1510, 880 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.25 (d, *J* = 6.9 Hz, 6 H), 2.90 (sept, *J* = 6.9 Hz, 1 H), 7.23 (d, *J* = 8.2 Hz, 2 H), 7.45 (s, 1 H), 7.48 (d, *J* = 8.2 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 23.86, 34.05, 88.43, 126.37, 128.31, 132.65, 136.63, 149.38.

EIMS: *m*/*z* = 306 [M^+], 304 [M^+], 302 [M^+], 128 [bp].

Anal. Calcd for $C_{11}H_{12}Br_2$: C, 43.46; H, 3.98. Found: C, 43.22; H, 3.99.

Stereoselective Synthesis of (*E*)-1-Bromo-2-(4-methoxyphenyl)ethene by the Reduction of 1,1-Dibromo-2-(4-methoxyphenyl)ethane; Typical Procedure

To a stirred solution of 1,1-dibromo-2-(4-methoxyphenyl)ethene (91.7 mg, 0.314 mmol) and EtOAc (55.0 mg, 0.620 mmol) in THF (1.0 mL) was gradually added $LiAlH_4$ (23.8 mg, 0.627 mmol) at –40 °C. The mixture was stirred for 6 h at the same temperature and quenched with a small amount of acetone. To the mixture was then added $Na_2SO_4 \cdot 10H_2O$. The whole mixture was stirred for 1 h at r.t. and filtered through Celite to remove white precipitates. After concentration, the ratio of the (*E*)- and (*Z*)-1-bromo-2-(4-methoxyphenyl)ethene, and 4-methoxystyrene was determined by ^1H NMR analysis of the crude product. Purification by silica gel column (hexane) gave 1-bromo-2-(4-methoxyphenyl)ethene (50.8 mg, 76%) as a >20:1 mixture of *E*- and *Z*-isomers. The physical data were comparable to those reported in literature.[13]

The physical data of the other known monobromoalkenes shown below were comparable to those of the corresponding literature: (*E*)-1-bromo-2-(4-chlorophenyl)ethane,[13] (*E*)-1-bromo-4-phenyl-1-butene,[18] (*E*)-1-bromo-2-(4-tolyl)ethene.[13]

The physical data of the new monobromoalkenes are shown below.

(*E*)-1-Bromo-2-(4-bromo-2-fluorophenyl)ethene
Colorless viscous oil.

IR ($CHCl_3$): 1598, 1482, 938 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.94 (d, *J* = 14.0 Hz, 1 H), 7.12 (d, *J* = 14.0 Hz, 1 H), 7.18–7.33 (m, 3 H).

^{13}C NMR ($CDCl_3$): δ = 110.39 (d, *J* = 8.4 Hz), 119.60 (d, *J* = 25.1 Hz), 121.83 (d, *J* = 9.5 Hz), 122.69 (d, *J* = 12.9 Hz), 127.64 (d, *J* = 3.9 Hz), 128.68 (d, *J* = 4.5 Hz), 129.43 (d, *J* = 1.7 Hz), 159.22 (d, *J* = 254.3 Hz).

EIMS: *m*/*z* = 282 [M^+], 280 [M^+], 278 [M^+], 120 [bp].

Anal. Calcd for $C_8H_5Br_2F$: C, 34.32; H, 1.80. Found: C, 34.58; H, 2.08.

(*E*)-1-Bromo-2-(4-hydroxymethylphenyl)ethane
Colorless plates; mp 71 °C (EtOAc–hexane).

IR (nujol): 3320, 1610, 1515, 938 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.92 (br s, 1 H), 4.66 (s, 2 H), 6.76 (d, *J* = 14.0 Hz, 1 H), 7.09 (d, *J* = 14.0 Hz, 1 H), 7.24–7.34 (m, 4 H).

^{13}C NMR ($CDCl_3$): δ = 64.87, 106.49, 126.13, 127.22, 135.11, 136.63, 140.77.

EIMS: *m*/*z* = 214 [M^+], 212 [M^+], 133, 105 [bp], 103.

Anal. Calcd for C_9H_9BrO: C, 50.73; H, 4.26. Found: C, 50.51; H, 4.34.

(*E*)-1-Bromo-2-(4-isopropylphenyl)ethane
Colorless oil.

IR (neat): 1608, 1515, 938 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.24 (d, *J* = 6.9 Hz, 6 H), 2.88 (sept, *J* = 6.9 Hz, 1 H), 6.70 (d, *J* = 14.0 Hz, 1 H), 7.07 (d, *J* = 14.0 Hz, 1 H), 7.18 (d, *J* = 8.4 Hz, 2 H), 7.23 (d, *J* = 8.4 Hz, 2 H).

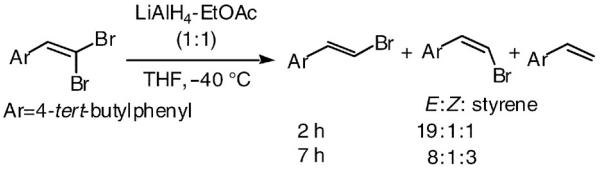
^{13}C NMR ($CDCl_3$): δ = 23.91, 33.97, 105.43, 125.99, 126.74, 133.43, 136.89, 149.06.

FABMS: *m*/*z* = 225 [M^+ + 1], 223 [M^+ + 1].

Anal. Calcd for $C_{11}H_{13}Br$: C, 58.69; H, 5.82. Found: C, 58.30; H, 5.72.

References

(1) (a) Knight, D. W. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, 241–292. (b) Tamao, K.; Knight, D. W.; Sonogashira, K. In *Comprehensive Organic Synthesis*, Vol. 3; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: New York, **1991**, 435–561.
(2) Uenishi, J.; Kawahama, R.; Yonemitsu, O.; Tsuji, J. *J. Org. Chem.* **1996**, *61*, 5716; and references cited therein.
(3) Takai, K.; Nitta, K.; Utimoto, K. *J. Am. Chem. Soc.* **1986**, *108*, 7408.
(4) (a) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753. (b) Brown, H. C.; Bhat, N. G.; Rajagopalan, S. *Synthesis* **1986**, 480. (c) Masuda, Y.; Hoshi, M.; Arase, A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2725. (d) Petasis, N. A.; Zavialov, I. A. *Tetrahedron Lett.* **1996**, *37*, 567. (e) Hoshi, M.; Tanaka, H.; Shirakawa, K.; Arase, A. *Chem. Commun.* **1999**, 627. (f) Miller, R. B.; McGarvey, G. *J. Org. Chem.* **1978**, *43*, 4424. (g) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257. (h) Lipshutz, B. H.; Lindsley, C.; Bhandari, A. *Tetrahedron Lett.* **1994**, *35*, 4669. (i) Huang, X.; Wang, J.-H.; Yang, D.-Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 673.
(5) (a) Barton, D. H. R.; Lacher, B.; Zard, S. Z. *Tetrahedron Lett.* **1985**, *26*, 5939. (b) Graven, A.; Jørgensen, K. A.; Dahl, S.; Stanczak, A. *J. Org. Chem.* **1994**, *59*, 3543. (c) Chowdhury, S.; Roy, S. *Tetrahedron Lett.* **1996**, *37*, 2623. (d) Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* **2000**, 1439. (e) Naskar, D.; Roy, S. *Tetrahedron* **2000**, *56*, 1369. (f) You, H.-W.; Lee, K.-J. *Synlett* **2001**, 105. (g) Sinha, J.; Layek, S.; Mandal, G. C.; Bhattacharjee, M. *Chem. Commun.* **2001**, 1916.
(6) Another method: Haack, R. A.; Penning, T. D.; Djurić, S. W.; Dziuba, J. A. *Tetrahedron Lett.* **1988**, *29*, 2783.
(7) Ramirez, F.; Desai, N. B.; McKelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.
(8) (a) Charreau, P.; Julia, M.; Verpeaux, J.-N. *J. Organomet. Chem.* **1989**, *379*, 201. (b) Harada, T.; Katsuhira, T.; Oku, A. *J. Org. Chem.* **1992**, *57*, 5805. (c) Grandjean, D.; Pale, P. *Tetrahedron Lett.* **1993**, *34*, 1155. (d) Harada, T.; Katsuhira, T.; Hara, D.; Kotani, Y.; Maejima, K.; Kaji, R.; Oku, A. *J. Org. Chem.* **1993**, *58*, 4897. (e) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadére, B. *J. Organomet. Chem.* **2001**, *624*, 131.
(9) Ranu, B. C.; Samanta, S.; Guchhait, S. K. *J. Org. Chem.* **2001**, *66*, 4102.
(10) Wang, L.; Li, P.; Xie, Y.; Ding, Y. *Synlett* **2003**, 1137.
(11) Miura, K.; Ichinose, Y.; Nozaki, K.; Fugami, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 143.
(12) (a) Hirao, T.; Masunaga, T.; Ohshiro, Y.; Agawa, T. *J. Org. Chem.* **1981**, *46*, 3745. (b) Abbas, S.; Hayes, C. J.; Worden, S. *Tetrahedron Lett.* **2000**, *41*, 3215.
(13) Kuang, C.; Senboku, H.; Tokuda, M. *Tetrahedron* **2002**, *58*, 1491.
(14) The use of other reagents, such as Li(*i*-Bu)$_2$BuAlH, LiEt$_3$BH and Li(*s*-Bu)$_3$BH, gave less satisfactory results. In the case of $NaBH_4$, no reaction occurred.
(15) When the reaction time was made longer from 2 h to 7 h, an increase in the ratio of the styrene was observed as shown below (Scheme 1).



Scheme 1

(16) In *Reduction by the Alumino- and Borohydrides in Organic Synthesis*; Seyden-Penne, J., Ed.; VCH Publishers: New York, **1991**, 4–5.
(17) Huh, D. H.; Jeong, J. S.; Lee, H. B.; Ryu, H.; Kim, Y. G. *Tetrahedron* **2002**, *58*, 9925.
(18) Pinhey, J. T.; Stoermer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2455.