



Substituent-dependent reactivity in aldehyde transformations: 4-(phenylethynyl)benzaldehydes versus simple benzaldehydes



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ABSTRACT

Effects of substituents on transformations of 4-(phenylethynyl)benzaldehydes and related benzaldehydes were analyzed in aldol and thiazolidine formation reactions. The aldol reaction of 4-cyanobenzaldehyde was 54-fold faster than that of 4-methoxybenzaldehyde. In contrast, the aldol reaction of 4-(4-cyanophenylethynyl)benzaldehyde was only 1.4-fold faster than that of 4-(4-methoxyphenylethynyl)benzaldehyde. Electronic features of substituents are significantly less influential in a diphenylacetylene system than in a simple benzene system.

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1. Introduction

Electron-withdrawing and electron-donating functional groups often determine the reactivity of molecules.^{1,2} Understanding the nature of the substituent effect is important to the design and synthesis of functionalized molecules. Although it is often considered that π -systems efficiently transmit the substituent effect through resonance,^{1,2} with the exceptions of effects on simple benzene derivatives, there is not much information regarding to what extent electronic features of substituents alter the reactivity of molecules. Here we report effects of substituents in nucleophilic addition reactions on aldehyde groups attached to diphenylacetylene derivatives.

Diphenylacetylene derivatives and related compounds containing a π -conjugated C–C triple bond are important as synthons, probes, and other functional molecules.^{3,4} In reported crystal structures of diphenylacetylene derivatives, two phenyl groups connected to the ethynylene group are located in a single plane (i.e., the coplanar conformation).⁵ This indicates that the phenyl groups are conjugated.^{3,5} Previously reported fluorescence data of diarylacetylene derivatives also suggest that the two aryl groups of the

diarylacetylene moiety are π -conjugated.^{3,4a–c} These reported results suggest that electronic features of substituents attached to one end of a diarylacetylene π -system are likely to significantly influence the reactivity of groups attached at the other end of the π -system. On the other hand, the degree of the substituent effect may vary depending on factors other than π -conjugation. In this study, to provide information useful for the design, synthesis, and use of diphenylacetylene derivatives, reactivities on 4-(phenylethynyl)benzaldehyde with various substituents and on simple benzaldehyde with the same substituents were analyzed in aldol and thiazolidine formation reactions and changes in the reactivities were compared.

2. Results and discussion

2.1. Substituent effect in aldol reactions

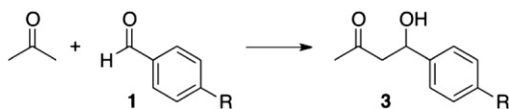
First, effect of substituents was analyzed in aldol reactions. Aldol reactions are important C–C bond forming reactions. One of potential uses of the substituted 4-(phenylethynyl)benzaldehydes is as fluorogenic probes to monitor the progress of aldol reactions.^{4d} Effects of substituents have previously been observed in enamine-based aldol reactions of benzaldehydes.^{2c}

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Aldol reactions of acetone with a series of substituted benzaldehydes (**1**) and of substituted 4-(phenylethynyl)benzaldehydes (**2**) were performed using proline as the catalyst^{4d,6} in DMSO-*d*₆. Formation of aldol products (**3** and **4**) was monitored by ¹H NMR. To provide information useful for the design and synthesis of diphenylacetylene derivatives, reaction conditions that were similar to those used actual syntheses were used. To quickly analyze the reactivity differences between the simple benzaldehyde series and the 4-(phenylethynyl)benzaldehyde series under these conditions, initial reaction rates and the ratios of the rates were determined and compared.

For both the simple benzaldehydes (Table 1) and the 4-(phenylethynyl)benzaldehydes (Table 2), reactions of aldehydes bearing the electron-withdrawing cyano substituent were faster than those of aldehydes bearing the electron-donating methoxy group (entries 2 vs entries 4). The degree of contribution of the substituents on 4-(phenylethynyl)benzaldehyde to reaction velocities was very different from that of the substituents on the simple benzaldehyde (Fig. 1). For the aldol reaction of benzaldehydes **1**, initial rates ranged 0.3–15 mM/h (Table 1). Formation of **3b** from **1b** was 54-fold faster than the formation of **3d** from **1d** (Fig. 1 and Table 1 entries 2 and 4). In contrast, for 4-(phenylethynyl)benzaldehydes **2**, the range of initial rates was 2.6–3.6 mM/h (Table 2). Formation of **4b** from **2b** was only 1.4-fold faster than the formation of **4d** from

Table 1
Comparison of initial rates of aldol reactions of acetone with benzaldehyde derivatives^a



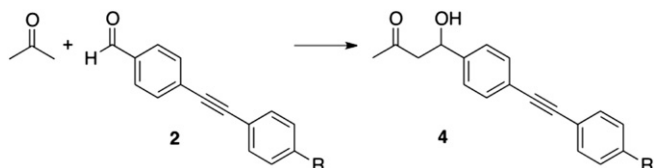
Entry	R	1	3	V_1 (mM/h) ^b	V_1/V_{1a} ^c
1	H	1a	3a	1.7	1.0
2	CN	1b	3b	15	8.6
3	Me	1c	3c	1.2	0.7
4	OMe	1d	3d	2.8×10^{-1}	0.2
5	Ethynyl	1e	3e	2.1	1.2
6	CF ₃	1f	3f	6.6	3.8

^a Reaction conditions: [acetone] 666 mM, [**1**] 44.4 mM, and [L-proline] 6.7 mM in DMSO-*d*₆ at 21 °C.

^b Initial rate of the formation of **3**.

^c Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **3a**.

Table 2
Comparison of initial rates of aldol reactions of acetone with 4-(phenylethynyl)benzaldehyde derivatives^a



Entry	R	2	4	V_2 (mM/h) ^b	V_2/V_{2a} ^c	V_2/V_{1a} ^d
1	H	2a	4a	2.7	1.0	1.6
2	CN	2b	4b	3.6	1.3	2.1
3	Me	2c	4c	3.2	1.2	1.8
4	OMe	2d	4d	2.6	1.0	1.5
5	CF ₃	2f	4f	2.8	1.0	1.6

^a Reaction conditions: [acetone] 666 mM, [**2**] 44.4 mM, and [L-proline] 6.7 mM in DMSO-*d*₆ at 21 °C.

^b Initial rate of the formation of **4**.

^c Relative initial rate determined by comparing with the initial rate of the reaction of **2a** to afford **4a**.

^d Relative initial rate determined by comparing with the initial rate of the reaction of **1a** to afford **3a** (Table 1).

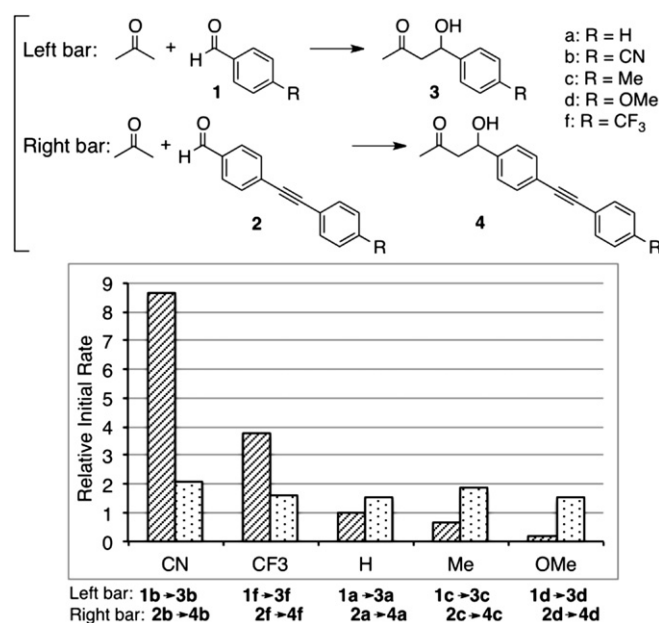
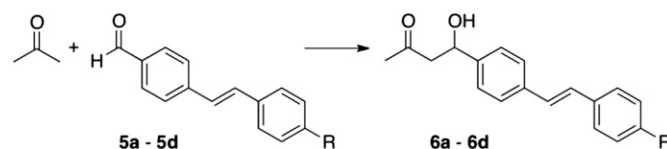


Fig. 1. Relative initial rates (V_1/V_{1a} and V_2/V_{1a}) of proline-catalyzed aldol reactions of **2** determined by comparing with the initial rate of the reaction of **1a**.

2d (Fig. 1 and Table 2 entries 2 and 4). Effect of substituents was significantly reduced through the (phenylethynyl)phenyl moiety compared to effects through the single phenyl group.

To estimate the contribution of the C–C triple bond within the (phenylethynyl)benzaldehyde derivatives in transmitting electronic features of substituents, the aldol reactions of styrylbenzaldehydes **5**, which had a C–C double bond instead of the C–C triple bond of **2**, were analyzed (Scheme 1). Reactions of **5** were performed under the same conditions used for the aldol reactions shown in Tables 1 and 2. Initial rates of the formation of **6a** and **6b** were 2.0 and 2.2 mM/h, respectively. The rate of the formation of **6b** was only 1.1-fold of that of the formation of **6a** and was slower than that of the formation of **4b** (Note that formation of **4b** was 1.3-fold faster than the formation of **4a**). These results indicated that the C–C triple bond between two phenyl groups better transmitted the electronic features of substituents than did the C–C double bond. Both **2** and **5** have π -conjugated systems; the phenylethynylphenyl moiety of **2** and the *trans*-stilbene moiety of **5** are coplanar in the most stable conformation.^{3,5,7} The C–C triple bond is shorter than the C–C double bond. In addition, the C–C triple bond provides stronger π -conjugation than the C–C double bond by bridging two benzene rings in linear structure. These features may underline the reactivity differences between **2** and **5** (i.e., influence of substituents on reactivities: **1** >> **2** > **5**).



Scheme 1. Aldol reactions of styrylbenzaldehydes.

2.2. Substituent effect in thiazolidine formation reactions

Next, effect of substituents was analyzed in the thiazolidine formation⁸ reactions. Aldehydes were mixed with cysteine and the formation of thiazolidine was monitored by ¹H NMR. Initial rates were determined and compared (Tables 3 and 4). Initial rates

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