Titanium(IV) Bromide and Boron(III) Tribromide Promoted *Baylis-Hillman* Reactions of Arylaldehydes with But-3-yn-2-one

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The reaction of arylaldehydes with but-3-yn-2-one in the presence of the *Lewis* acids titanium(IV) bromide ($TiBr_4$) or boron(III) tribromide (BBr_3) (1.4 equiv.) can be drastically affected by the reaction temperature. When the reaction was carried out at $\leq -20°$, the brominated compound **1** was obtained as the major product. However, when the reaction was carried out at room temperature (20°), both the brominated compound **1** and dibrominated compound **2** were formed as major products. The substituent on the phenyl ring can affect the (*E*)/(*Z*) ratio. Moreover, with **2** as the substrate, the Pd-catalyzed allylic substitution and *Suzuki*-type coupling reaction have been examined.

Introduction. – The *Baylis-Hillman* reaction has become a topic of intense interest for synthetic chemists because the resulting adducts may have several functional groups available for numerous further transformations [1][2]. In this area, we have reported that the combination of *Lewis* bases such as chalcogenides, amines, or quaternary ammonium halides with the *Lewis* acid $TiCl_4$ can significantly increase the rate of this reaction and give the corresponding chlorinated products and the elimination products (*Z*)-olefins at different reaction temperatures [3][4]. More recently, the reaction of aldehydes with but-3-yn-2-one in the presence of $TiCl_4$ has been reported by *Li* and *Kataoka* [5][6]. This new process could afford an efficient approach to β-chloro *Baylis-Hillman* adducts. From the point of view of synthetic chemistry, the α-bromomethylene aldols **1** are more useful than the corresponding α-chloromethylene aldols because they can be more easily subjected to the transition-metal-catalyzed reactions such as allylic substitution and *Suzuki* coupling reactions. However, only one example in which $TiBr_4$ was used as the *Lewis* acid for this reaction has been examined at room temperature in these reports [5][6]. Thus, we more carefully examined the reaction of arylaldehydes with but-3-yn-2-one in the presence of the *Lewis* acids $TiBr_4$ or BBr_3 (1.4 equiv.) at different temperatures. We found that *Lewis* bases such as SMe_2, amines, and quaternary ammonium halides did not affect this reaction at all, but that the reaction temperature strongly influenced both the reaction products and stereoselectivity ((*E*)/(*Z*) ratio) of this reaction.

Results and Discussion. – At low temperature ($\leq -20°$), only α-bromomethylene aldols **1** were obtained in moderate to high yields in the presence of $TiBr_4$ or BBr_3 (1.4 equiv.) (*Scheme 1*); $TiBr_4$ was more effective than BBr_3 in this reaction (*Table 1*, *Entries 1–2*). For arylaldehydes having a strong electron-withdrawing group on the phenyl ring, the reaction proceeded quickly at $-78°$ to give **1** in high yields (*Table 1*,

Entries 2–4). However, other arylaldehydes needed higher temperature and longer time to complete the reaction (*Table 1*, *Entries 5–8*). The geometry of the major isomer was determined by ^{1}H-NMR NOESY spectroscopic data and comparison of the spectral data with those of the corresponding α-chloromethylene aldols [5][6].

Scheme 1

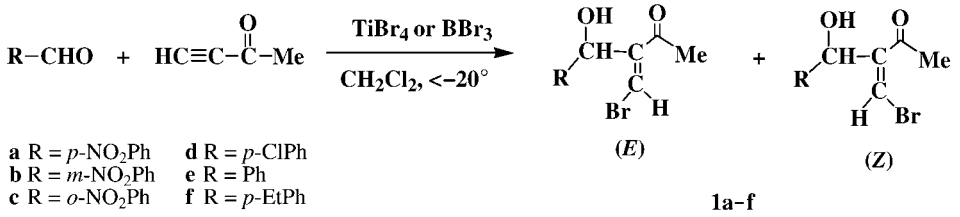


Table 1. *Low-Temperature Reaction of Arylaldehydes with But-3-yn-2-one in the presence of $TiBr_4$ or BBr_3*[a])

Entry	R	*Lewis* acid	Temp. [°]	Time [h]	Yield[b]) [%]	(*E*)/(*Z*)
1	*p*-NO_2Ph	BBr_3	–78	40	54	19:1
2	*p*-NO_2Ph	$TiBr_4$	–78	40	90	19:1
3	*m*-NO_2Ph	$TiBr_4$	–78	40	61	1:1.3
4	*o*-NO_2Ph	$TiBr_4$	–78	40	76	1:6.6
5	*p*-ClPh	$TiBr_4$	–78	72	40	19:1
6	*p*-ClPh	$TiBr_4$	–20	72	80	19:1
7	Ph	$TiBr_4$	–20	72	79	19:1
8	*p*-EtPh	$TiBr_4$	–20	72	81	19:1

[a]) Aldehyde/$TiBr_4$ or BBr_3/but-3-yn-2-one 1:1.4:2. [b]) Isolated yields.

At room temperature (20°), we found that, besides α-bromomethylene aldols **1**, dibrominated compounds **2** could be obtained at the same time when 1.4 equiv. of $TiBr_4$ or BBr_3 was used as the *Lewis* acid (*Scheme 2*). As can be seen from *Table 2*, **1** and **2** were obtained in the same (*E*)/(*Z*) ratios and similar yield in the presence of 1.4 equiv.

Scheme 2

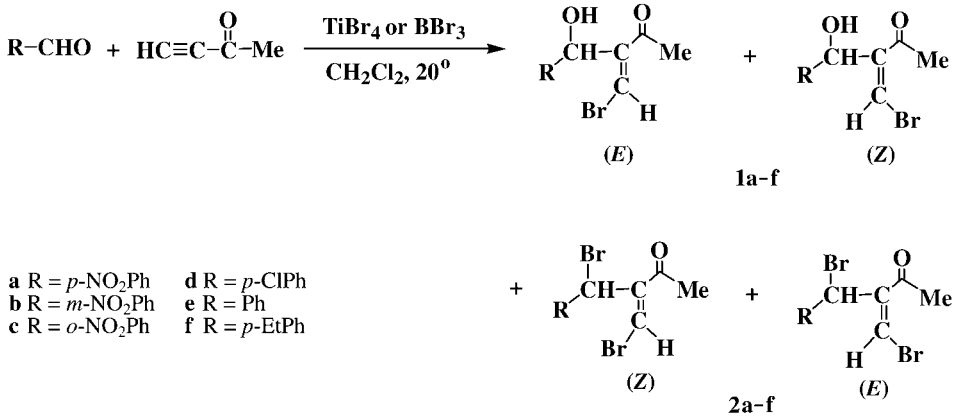


Table 2. *Room-Temperature Reaction of Arylaldehydes with But-3-yn-2-one in the Presence of $TiBr_4$ and BBr_3*[a])

Entry	R	*Lewis* acid	Time [h]	Yield[b]) **1** [%]	(*E*)/(*Z*)	Yield[b]) **2** [%]	(*E*)/(*Z*)
1	*p*-NO_2Ph	BBr_3	24	5	19:1	20	1:19
2	*p*-NO_2Ph	$TiBr_4$	24	43	19:1	20	1:19
3	*m*-NO_2Ph	$TiBr_4$	24	41	19:1	20	1:19
4	*o*-NO_2Ph	$TiBr_4$	24	36	8:1	32	1:8
5	*p*-ClPh	$TiBr_4$	30	16	19:1	28	1:19
6	Ph	$TiBr_4$	40	17	3:1	20	1:3
7	*p*-EtPh	$TiBr_4$	40	29	1:1	22	1:1

[a]) Aldehyde/$TiCl_4$/but-3-yn-2-one 1:1.4:2. [b]) Isolated yields.

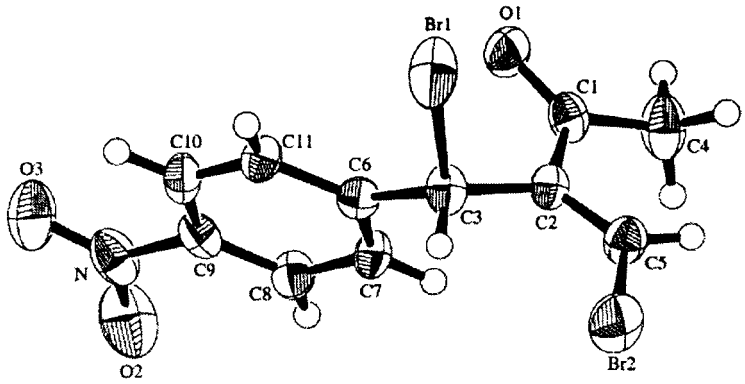
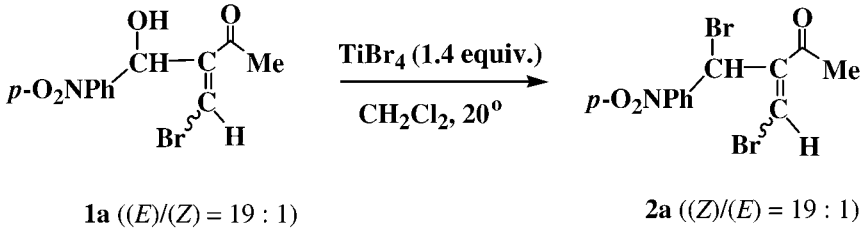


Figure. *X-Ray crystal structure of* (Z)-**2a**

of $TiBr_4$ at 20°. In general, the α-bromomethylene aldols **1** were obtained preferentially as the (*E*)-isomers and dibrominated compounds **2** as the (*Z*)-isomers. The X-ray crystal structure of **2a** was determined (*Fig.*). For benzaldehyde or *p*-ethylbenzaldehyde, the (*E*)/(*Z*) selectivity is low (*Table 2*, *Entries 6*, *7*). The substituents on the Ph ring can affect the (*E*)/(*Z*) selectivity.

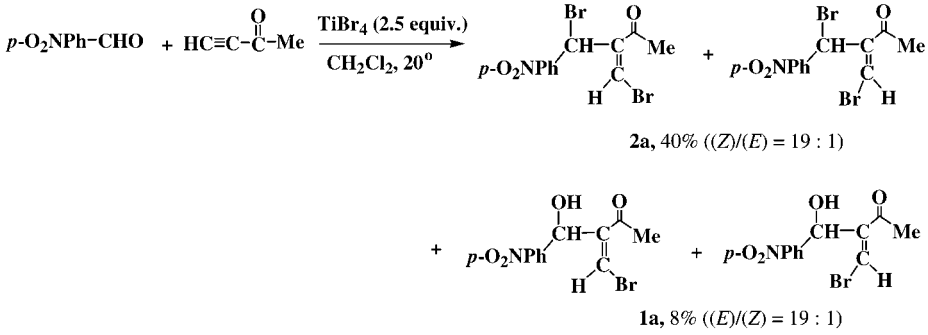
To clarify the mechanism of formation of **2**, we carried out the direct reaction of **1a** ((*E*)/(*Z*) = 19:1) with 1.4 equiv. of $TiBr_4$ at room temperature (*Scheme 3*). We found that the corresponding **2a** was exclusively obtained in the same (*E*)/(*Z*) ratio in 10 h. Based on this result, it is clear that product **2** is derived from **1** by the further reaction of

Scheme 3



1a ((*E*)/(*Z*) = 19 : 1) **2a** ((*Z*)/(*E*) = 19 : 1)

Scheme 4

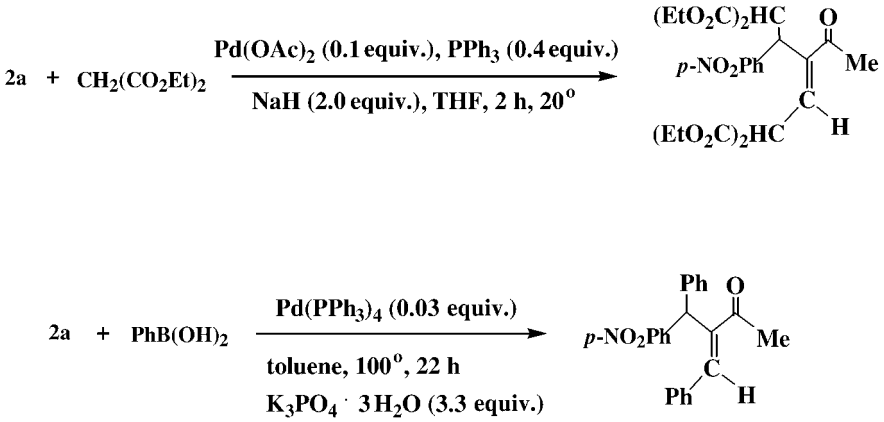


1 with $TiBr_4$ at room temperature (*Scheme 3*). We also confirmed by using 2.5 equiv. of $TiBr_4$ at room temperature that the dibrominated compound **2** could be obtained as the major product (*Scheme 4*), but, in the reaction of arylaldehydes with but-3-yn-2-one in the presence of excess $TiCl_4$ at 20°, the corresponding dichlorinated products could not be produced at all. Thus, for the formation of **2**, we believe that, at room temperature, the bromide at Ti can directly attack the C-atom bearing the OH group to give the dibrominated compound **2**, because Br^- is usually more nucleophilic than Cl^-.

The Pd-catalyzed allylic substitution and *Suzuki*-type coupling reaction were examined with **2a** (*Scheme 5*). It is very interesting to find the benzylic bromide and vinylic bromide replaced by nucleophiles (the *Suzuki*-type coupling reaction of boronic acids with benzyl bromide has been reported before [7]). We are currently optimizing the reaction conditions and examining the scope and limitations of these novel Pd-catalyzed reactions.

Conclusions. – We found that the $TiBr_4$ or BBr_3 promoted *Baylis-Hillman* reaction is not as simple as has been suggested in earlier reports. The reaction temperature and amount of the *Lewis* acid employed can drastically affect the reaction products. We first

Scheme 5



disclosed that, at room temperature, both the α-bromomethylene aldols **1** and dibrominated products **2** were formed as the reaction products and the dibrominated products **2** could be obtained as the major product with a large excess of $TiBr_4$. Efforts are underway to elucidate the mechanistic details of this reaction and to discover its scope and limitations.

Experimental Part

General. Commercially obtained reagents were used without further purification. Org. solvents were dried by standard methods when necessary. All reactions were monitored by TLC with *Huanghai* GF_{254} silica-gel-coated plates. Flash column chromatography (FC) was carried out with 200–300-mesh silica gel. M.p.: *Yanagimoto* micro-melting-point apparatus; uncorrected. IR Spectra: in $CHCl_3$; ν in cm^{-1}. ^{1}H-NMR Spectra: *Bruker AM-300* spectrometer; 300 MHz in $CDCl_3$ with Me_4Si as internal standard; δ in ppm, J in Hz. MS: *Hewlett-Packard HP-5989*; (*m*/*z* (rel.%)). HR-MS: *Finnigan MA* + mass spectrometer. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a *Carlo-Erba 1106* analyzer.

Typical Procedure for Low-Temperature Reaction: Preparation of **1a**. To a soln. of $TiBr_4$ (257 mg, 0.70 mmol) in CH_2Cl_2 (1.0 ml) was added a soln. of *p*-nitrobenzaldehyde (76 mg, 0.5 mmol) in CH_2Cl_2 (1.0 ml), and, then, but-3-yn-2-one (78 µl, 1.0 mmol) was added at $-78°$. The mixture was kept for 48 h at $-78°$. The reaction was quenched by addition of sat. aq. $NaHCO_3$ (1.0 ml) and filtered. The filtrate was extracted 2 × with CH_2Cl_2 (5.0 ml) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by FC (AcOEt/petroleum ether 1:5) to give (*E*)-**1a** (135 mg, 90%); a small amount of (*Z*)-**1a** was also formed but could not be isolated. Colorless solid. (*E*)-**1a**: M.p. 120–122°. IR: 1666 (C=O). ^{1}H-NMR: 2.35 (*s*, Me); 6.01 (*s*, 1 H); 7.56 (*d*, J = 8.7, 2 arom. H); 7.85 (*s*, 1 H); 8.20 (*d*, J = 8.7, 2 arom. H). EI-MS: 298 (0.51, $[M-1]^+$), 220 ($[M-79]^+$), 43 (100, $[M-256]^+$). Anal. calc. for $C_{11}H_{10}BrNO_4$: C 44.00, H 3.33, N 4.62; found: C 44.28, H 3.43, N 4.62.

Typical Procedure for the Room-Temperature Reaction: Preparation of **1a** *and* **2a**. As described for **1a** above, except reaction performed at 20° to give **1a** (36 mg, 20%) as a colorless solid and **2a** (64 mg, 43%) as a yellowish solid.

Data of (Z)-**2a**: M.p. 121–124°. IR: 1682 (C=O). ^{1}H-NMR: 2.35 (*s*, Me); 6.50 (*s*, 1 H); 7.66 (*d*, J = 8.7, 2 arom. H); 7.79 (*s*, 1 H); 8.16 (*d*, J = 8.7, 2 arom. H). EI-MS: 362 (4.90, $[M+1]^+$), 282 (40, $[M-79]^+$), 43 (100, $[M-318]$). Anal. calc. for $C_{11}H_9Br_2NO_3$: C 36.36, H 2.48, N 3.86, found: C 36.72, H 2.61, N 3.96.

Data of (E)-**2a**: M.p. 121–124°. IR: 1682 (C=O). ^{1}H-NMR: 2.68 (*s*, Me); 6.67 (*s*, 1 H); 7.43 (*s*, 1 H); 7.68 (*d*, J = 8.5, 2 arom. H); 8.37 (*d*, J = 8.5, 2 arom. H). EI-MS: 362 (1.44, $[M+1]^+$), 282 (3.76, $[M-79]^+$), 43 (100, $[M-318]^+$). Anal. calc. for $C_{11}H_9Br_2NO_3$: C 36.36, H 2.48, N 3.86; found: C 36.72, H 2.61, N 3.96.

Crystal-Structure Data of **2a**: empirical formula, $C_{11}H_9O_3NBr_2$; formula weight, 386.29; crystal color, colorless; habit, prismatic; dimensions, 0.20 × 0.20 × 0.30 mm; crystal system, orthorhombic; lattice type, primitive; lattice parameters, a = 13.988(4) Å, b = 17.119(6) Å, c = 10.524(4) Å, V = 2520(1) Å^3; space group: *Pbca*(#61); Z = 8; D_{calc} = 1.018 g/cm^3; F_{000} = 792.00; µ(MoKα) = 16.44 cm^{-1}; residuals: R; Rw = 0.045; 0.046.

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