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EFFECT OF AMINES ON THE SELECTIVE BROMINATION OF SOME β-SUBSTITUTED-2-BUTENOIC ESTERS.

Masahisa Nakada*[a], Ei-ichi Kojima, and Hidehiro Ichinose

Department of Chemistry, Graduate School of Science and Engineering, Waseda University, [a]Materials Research Laboratory for Biosciences and Photonics, 3-4-1 Ohkubo, Shinjuku-ku, 169-8555, Tokyo, Japan

Abstract: The effect of amines on the selective bromination of some β–substituted-2-butenoic esters is described. The bromination of methyl (*Z*)-4-*t*-butyldiphenylsilyloxy-3-methylbutenoate **2** in the presence of DIPEA (*N*, *N*-diisopropylethylamine) and the successive treatment of the obtained dibromide with potassium *t*-butoxide afford the desired *Z* bromide selectively. But the corresponding *E* bromide forms exclusively when 2, 6-di-*t*-butyl-4-methylpyridine is used in the bromination.

We present here a short report on an interesting result obtained when we prepared methyl (*Z*)-2-bromo-4-*t*-butyldiphenylsilyloxy-3-methylbutenoate **1**, which is the starting material in our taxol™ synthesis[1].

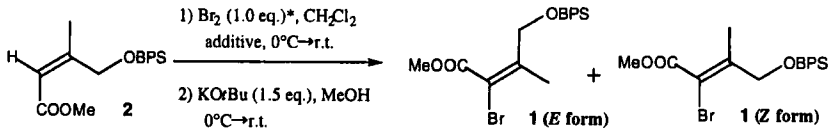
The selective preparation of the bromide **1(Z form)** was examined starting from methyl (*Z*)-4-*t*-butyldiphenylsilyloxy-3-methyl-2-butenoate **2**[2] by the standard bromination and dehydrobromination procedure. In the early stage of the conversion of **2** to **1**, the alkene **2** was simply brominated and the resulting

* To whom correspondence should be addressed.

dibromide was treated with potassium *t*-butoxide in MeOH[4]. Under these conditions, however, the yield of the bromoalkene **1** was low and a considerable amount of the *E* isomer formed[5]. This result was assumed to arise from *Z* to *E* isomerization of the alkene **2** by H^+ in the bromination step because the dehydrobromination with potassium *t*-butoxide must proceed by the well-known anti-elimination mechanism.

Hence, the bromination condition was screened, focusing on the buffer to keep the reaction medium nonacidic. Thus, the bromination of **2** was carried out in the presence of various bases to scavenge H^+, which was assumed to exist in the used bromine. The results are summarized in **Table 1**.

Table 1. Effect of Amines on the Selective Bromination of 2



Additive (eq.)*	Time(h)**	Yield of **1** (%)	*E* / *Z*
NON	36	45	33 / 67
2, 4, 6-trimetylpyridine (2.0)	36	62	50 / 50
2, 6-di-*t*-butyl-4-methylpyridine (2.0)	36	56	94 / 6
N, *N*-diisopropylethylamine (2.0)	48	94	0 / 100

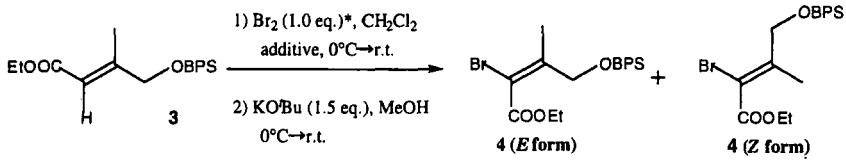
*The amount of bromine and additive indicated is the initially added amount.
**Time for bromination.

The bromination was very sluggish in the presence of a base[6], whereas bromination of **2** proceeded immediately without a base. Therefore, an additional amount of the base and then bromine (the mole ratio = 2 : 1) was added to complete the bromination. When insoluble salts, such as $CaCO_3$, NaOAc, were used, the reaction proceeded but also formed many byproducts that caused difficulty in the isolation of the final product. The yield of the 2-step reaction was good to excellent when a bulky base was used. It is interesting that the *E* / *Z* ratio of the final product varied with the base used. Thus, *E* / *Z* = 1 / 1 mixture of the final product was obtained in the case of 2, 4, 6-trimethylpyridine, but predominant formation of the *E* isomer (*E* / *Z* = 94 / 6)was

observed when 2, 6-di-*t*-butyl-4-methylpyridine was used. Finally, the bromination was controlled as expected using DIPEA (*N*, *N*-diisopropylethylamine) as the additive, and only the desired *Z* isomer was obtained in excellent overall yield.

In the case of *E* alkene **3** DIPEA was also effective for the selective bromination (**Table 2**). The formation of the undesired *Z* isomer was perfectly suppressed in the presence of DIPEA comparing with the case of using no base.

Table 2. Effect of Amines on the Selective Bromination of 3



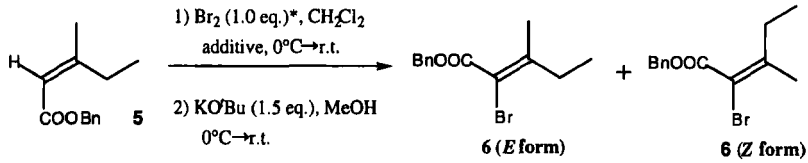
Additive (eq.)*	Time(h)**	Yield of **4** (%)	*E* / *Z*
NON	36	48	68 / 32
N, *N*-diisopropylethylamine (2.0)	48	94	100 / 0

*The amount of bromine and additive indicated is the initially added amount.
**Time for bromination.

The bromination condition has been successfully optimized. However, it is difficult to explain why the *E* isomer formed predominantly with the use of 2, 6-di-*t*-butyl-4-methylpyridine. One rational explanation is to assume the formation of the pyridinium ion intermediate. That is, 2, 6-di-t-butyl-4-methylpyridine attacked the initially formed bromonium ion to afford the pyridinium ion, which was then attacked by the bromide ion to give the formal *syn* bromine adduct, and which was finally converted to the *E* bromide[7] by potassium *t*-butoxide. If this mechanism worked, 2, 4, 6-trimethylpyridine would also exhibit the same effect. However, the result is inconsistent with this explanation and further study of the mechanism is needed.

It is expected that the selective bromination of other alkenes will be also achieved by the use of amine as the additive. For an example, alkene **5** was selectively brominated in the presence of DIPEA and successfully converted to the *Z* bromide (**Table 3**).

Table 3. Effect of Amines on the Selective Bromination of 5



Additive(eq.)	Time(h)**	Yield of **6** (%)	*E* / Z
NON	5	43	37 / 63
N, *N*-diisopropylethylamine (2.0)	48	91	0 / 100

*The amount of bromine and additive indicated is the initially added amount.
**Time for bromination.

In conclusion, the selective brominations of some butenoic esters are achieved by the use of amine as the additive. The bromoalkenes reported here and another ones that could be prepared by the method described here will be good starting materials for the isomerically pure tetrasubstituted alkenes.

Hence, the effect of amines on the selective bromination of some alkenes is now being studied and the results will be reported in due course.

Experimental

All reactions were carried out with continuous stirring under an atmosphere of dry argon. All ^1H NMR spectra were recorded on a JEOL AL 300 and EX 270, using $CDCl_3$ as the solvent. ^1H chemical shifts (δ) are given in ppm relative to tetramethylsilane as the internal standard. All IR spectra were recorded on a Perkin-Elmer 1640 FT-IR. All HRMS were run by the Materials Characterization Central Laboratory, Waseda University.

Methyl (*Z*)-2-bromo-4-t-butyldiphenylsilyloxy-3-methyl-2-butenoate (1). To a solution of **2** (15.5 mg, 0.042 mmol) in CH_2Cl_2 (1.0 ml) was added DIPEA (0.022 ml, 0.13 mmol) under Ar, and the solution was cooled by an ice bath. Bromine (0.022 ml, 0.042 mmol) was added dropwise to this stirred solution under Ar and the ice bath was removed. The reaction mixture was stirred at room temperature for 24h, and DIPEA (0.022 ml, 0.042 mmol), then bromine(0.022 ml, 0.13 mmol) was added at 0°C because the starting material remained. After 48h the starting material disappeared, and then the reaction mixture was poured into a sat.$NaHCO_3$ aq. solution containing $Na_2S_2O_3$. The

organic layer was separated and the aqueous layer was extracted twice with Et_2O. The combined organic layer was washed with brine, dried with anhydrous Na_2SO_4, evaporated, dried further under vacuum. The crude dibromide obtained was dissolved in dry MeOH (2.0 ml) under Ar, cooled with an ice bath, and to this solution was added KO*t*-Bu (7.1 mg, 0.063 mmol) portionwise with stirring. After stirring the reaction mixture at r.t. for 10min., sat.NH_4Cl aq. was added and MeOH was evaporated. The residue was extracted with Et_2O, and the separated aqueous layer was extracted with CH_2Cl_2. The organic layer was combined and washed with brine, dried with anhydrous Na_2SO_4, evaporated, dried further under vacuum. The crude **1(*Z* form)** obtained was purified by silica gel column chromatography (hexane : EtOAc = 20 : 1) to afford pure **1(*Z* form)** (17.7 mg, 0.040 mmol, y.94%) as a colorless oil: ^{1}H NMR δ 7.64-7.74 (m, 4H), 7.35-7.44 (m, 6H), 4.42 (s, 2H), 3.81 (s, 3H), 2.26 (s, 3H), 1.08 (s, 9H); IR (neat, cm^{-1}) 3072, 2960, 2860, 1722, 1428, 1250, 1114, 1066, 824, 740, 702; HRMS(FAB+; Matrix: Diethanolamine) m/z (M^+-H) calcd 445.0835, obsd 445.0840.

Methyl (*E*)-2-bromo-4-t-butyldiphenylsilyloxy-3-methyl-2-butenoate (1).

1(*E* form) : ^{1}H NMR δ 7.64-7.61 (m, 4H), 7.35-7.43 (m, 6H), 4.56 (s, 2H), 3.61 (s, 3H), 2.17 (s, 3H), 1.06 (s, 9H); IR (neat, cm^{-1}) 3076, 2960, 2860, 1724, 1430, 1250, 1114, 822, 740, 702; HRMS(FAB+; Matrix: Diethanolamine) m/z (M^+-H) calcd 445.0835, obsd 445.0840.

Ethyl (*E*)-2-bromo-4-t-butyldiphenylsilyloxy-3-methyl-2-butenoate (4).

4(*E* form) : ^{1}H NMR δ 7.66-7.55 (m, 4H), 7.35-7.43 (m, 6H), 4.55 (s, 2H), 4.06 (q, 2H, J = 7.3Hz), 2.17 (s, 3H), 1.15 (t, 3H, J = 7.3Hz), 1.06 (s, 9H); IR (neat, cm^{-1}) 3076, 2964, 2936, 2900, 2860, 1728, 1474, 1446, 1428, 1392, 1368, 1250, 1216, 1114, 1064, 824, 808, 740, 702; HRMS(FAB+; Matrix: Diethanolamine) m/z (M^+-H) calcd 459.0991, obsd 459.0973.

Phenylmethyl (*E*)-2-bromo-3-methyl-2-pentenoate (6).

6(*E* form) : ^{1}H NMR δ 7.60-7.20 (m, 5H), 7.35-7.43 (m, 6H), 5.23 (s, 2H), 2.41 (q, 2H, J = 7.3Hz), 2.10 (s, 3H), 1.07 (t, 3H, J = 7.3Hz); IR (neat, cm^{-1}) 2967, 1714, 1456, 1276, 1232, 1208, 1108, 1014, 756, 698; HRMS(FAB+; Matrix: NBA) m/z (M^++H) calcd 283.0334, obsd 283.0321.

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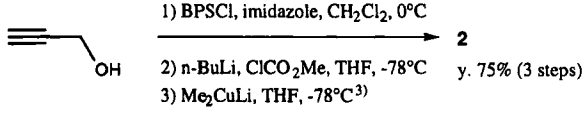
References and Notes

1. Nakada, M.; Kojima, E. *Tetrahedron Lett.* **1998**, *39*, 313.
2. (Z)-4-t-butyldimethylsilyloxy-3-methyl-2-butenoate 2 was prepared as follows.



2 : ^{1}H NMR δ 7.64-7.66 (m, 4H), 7.37-7.39 (m, 6H), 5.64 (s, 3H), 4.86 (s, 2H), 3.56 (s, 3H), 2.07 (s, 3H), 1.07 (s, 9H); IR (neat, cm^{-1}) 3072, 2956, 2860, 1720, 1430, 1230, 1152, 1112, 1060, 822, 742, 702; HRMS m/z (M^+-H) calcd 367.1729, obsd 3671723.
3. Corey, E.J.; Katzenellenbogen, J.A. *J. Am. Chem. Soc.* **1969**, *91*, 1851.
4. The dibromide was immediately used for the next step after workup without purification.
5. The stereochemistry of the tetrasubstituted alkenes was determined by 1H-NMR techniques (nOe measurement) and comparison with authentic samples prepared by another procedure.
6. Other bases were also examined. But the bromination was very slow in the case of pyridine, *N*, *N*-dimethylaniline and a considerable amount of the starting material remained even after the addition of excess base and bromine.
7. It has been reported that the stereospecificity of bromine addition to alkenes is disturbed when solvents of high electronic constant are used.

   See Buckless, R.E.; Bader, J.; Thurmaier, R.J. *J. Org. Chem.* **1962**, *27*, 4523.; Heublein, G. *J. Prakt. Chem.* **1966**, [4]*31*, 84.; Buckless, R.E.; Bader, J.; Miller, J.L.; Thurmaier, R.J. *J. Org. Chem.* **1967**, *32*, 888.; Heublein, G.; Lauterbach, H. *J. Prakt. Chem.* **1969**, *311*, 91.; Ruasse, M.; Dubois, J. E. *J. Am. Chem. Soc.* **1975**, *97*, 1977.

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