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FULL PAPER

Cyanide Free One-pot Synthesis of Methacrylic Esters from Acetone

Minoru Koyama,[a] Takafumi Kawakami,[a] Takashi Okazoe,*[a,b] and Kyoko Nozaki*[a]

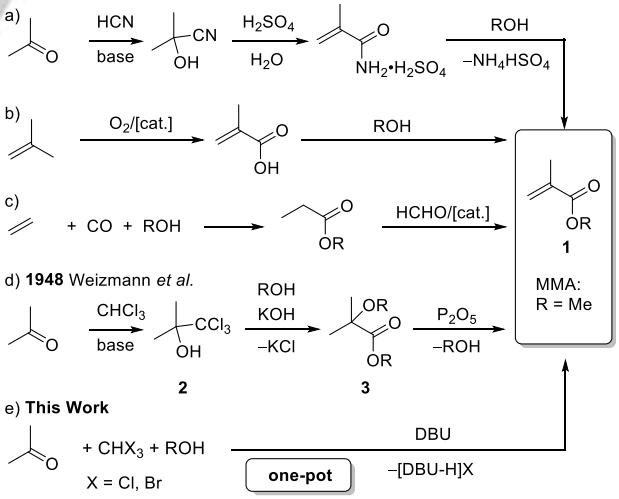
Dedication ((optional))

Abstract: Methacrylic esters, represented by methyl methacrylate (MMA), are widely used as commodity chemicals. Here we present the one-pot synthesis of methacrylic esters from acetone, haloroform and alcohols in the presence of an organic base. Employing DBU as the organic base for the reaction of acetone, chloroform and methanol in acetonitrile afforded MMA in 66% yield. When the solvent was replaced by benzonitrile, the product MMA was successfully purified by distillation. Applicability of this process to various alcohols was also investigated to show ethyl, phenyl, CF_3CH_2, and n-$C_6F_{13}CH_2CH_2$ esters were obtained in moderate yields. The use of bromoform instead of chloroform resulted in the improvement of the yield, e.g. methyl and n-$C_6F_{13}CH_2CH_2$ esters up to 81 and 70%, respectively. The reaction with deuterated starting materials, acetone-d_6 and methanol-d_4, with DBU in benzonitrile afforded deuterated MMA (MMA-d_8) in 70% yield.

Introduction

Methacrylic esters are widely used as monomers for the synthesis of variety of polymeric materials. Among them, methyl methacrylate (MMA) is used for producing acrylic plastics poly(methyl methacrylate) (PMMA), whose world production reaches about 2.5 million metric tons,[1,2] and its demand continues to increase year by year. Three representative industrial synthetic processes of MMA are summarized in Scheme 1a–c.[3] A process shown in Scheme 1a is the C3 process, by which, currently 60% of MMA is industrially produced.[2] In the first step, acetone and hydrogen cyanide are converted to acetone cyanohydrin in the presence of a base. Secondly, methacryl amide is formed in the presence of sulfuric acid. Addition of methanol completes the process for the MMA synthesis. The major drawbacks of this process could be the formation of stoichiometric amount of ammonium bisulfate as a waste. In order to avoid this problem, two new routes have been developed. In the C4 process (Scheme 1b), oxidation of isobutylene via methacrolein provides methacrylic acid. MMA is produced by the subsequent esterification with methanol. The third process is the C2 process (Scheme 1c): First, methyl propionate is made from ethylene, carbon monoxide, and methanol. Subsequently, methyl propionate reacts with formaldehyde and then dehydration results in the formation of MMA.[4] As an alternative route to methacrylate esters, here we propose the use of chloroform in place of hydrogen cyanide in Scheme 1a as a C1 source. In 1948, Weizmann *et al.* reported the reaction of 1,1,1-trichloro-2-methyl-propan-2-ol(acetonechloroform, **2**) with potassium hydroxide in alcohol to form α-alkoxypropanoic acid **3** (Scheme 1d). Isolation of **3** followed by treatment with phosphorus pentoxide resulted in the formation of methacrylic esters.[5] As shown above, all pathways require multi-step operations.

Here we report, a one-pot synthesis of methacrylic esters **1** from acetone, haloroform, and alcohols (Scheme 1e). The use of an organic base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was the key for our success. Given that haloform is easily available in laboratory scale, this provides an effective synthetic pathway for various methacrylate esters.



Scheme 1. Synthetic methods of methacrylates: Current industrial processes for MMA synthesis (a–c) versus the route from acetone, chloroform, and alcohols (d and e).

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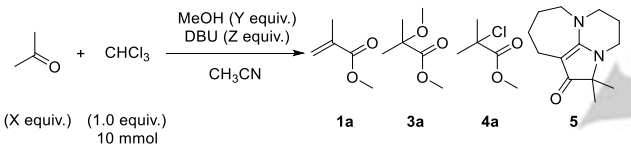
Results and Discussion

First, equimolar amount of acetone and chloroform were mixed with 3.0 equiv. of DBU in methanol (10 equiv.). After 96 h at 50°C, chloroform was consumed in 82% conversion. The products were analyzed by ^{1}H NMR spectroscopy to show, while α-methoxyester **3a** and the α-chloroester **4a** were the major products (35% and 24% yield, respectively), the desired methacrylate ester **1a** was obtained in 5.4%(Table1, entry1). By optimizing the feed ratio (entries 1–5), the yield of **1a** was improved to 40% but α-chloroester **4a** remained as the major side product (entry 4). The use of acetonitrile under reflux condition improved the conversion of **4a** to **1a** albeit undesired side product **5**[8] generated (entry 6). By lowering the reaction temperature to 50 °C, we confirmed the consumption of acetone in 18 h (entry 7). Accordingly, we carried out the reaction first at 50 °C for 18 h and then heated additional 24 h under reflux to obtain **1a** in 66% (Table 1, entry 8). Among the examined solvents, acetonitrile and benzonitrile afforded 1a in the higher yields (entries 8–12).

Table1. Optimization of the reaction condition for the synthesis of methyl methacrylate (**1a**) from acetone, chloroform, and methanol in the presence of DBU as base. [a]

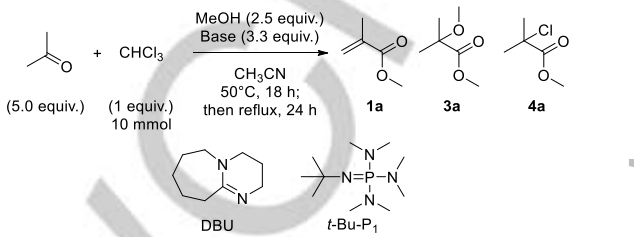


Entry	X	Y	Z	CH_3CN (mL)	$CHCl_3$ Conv. (%)	**1a** (%)	**3a** (%)	**4a** (%)	**10** (%)
1[a]	1.0	10	3.0		82	5.4	35	24	0.0
2[a]	1.0	3.5	3.0		87	37	16	14	0.3
3[a]	5.0	3.5	3.0		100	39	13	36	1.4
4[a]	5.0	2.5	3.0		100	40	8.3	37	1.3
5[a]	5.0	2.0	3.0		100	36	5.3	40	2.6
6[b]	5.0	2.5	3.3	5	98	48	2.9	17	11
7[c]	5.0	2.5	3.3	5	89	16	5.7	59	2.5
8[d]	5.0	2.5	3.3	5	100	66	6.5	14	5.3
9[d,e]	5.0	2.5	3.3	8	88	29	2.7	19	7.2
10[f,g]	5.0	2.5	3.0	8	76	18	0.9	32	13
11[f,h]	5.0	2.5	3.0	8	87	25	1.3	13	14
12[f,i]	5.0	2.5	3.3	5	100	55	6.5	9.4	6.2

[a] 50°C, 96 h. [b] reflux 24 h. [c] 50°C, 18 h. [d] 50°C, 18 h; then reflux, 24 h. [e] $CHCl_3$, 2.5 mmol. [f] 50°C, 18 h; then 80°C, 24 h. [g] 1,4-dioxane as a solvent. [h] diglyme as a solvent. [i] PhCN as a solvent.

Among the organic bases examined in this study, the highest yield was detected with DBU. With triethylamine, no reaction was observed (Table 2, entry 2). On the other hand, with phosphazene *t*-Bu-P_1, the yield of **1a** was lower (21%), and a significant amount of α-chloroester **4a** (74% yield) was produced (Table 2, entry 3). By the sequential addition of *t*-Bu-P_1 and then DBU, the yield of **1a** was elevated up to 78% (Table 2, entry 4). Purification of the product MMA was accomplished by distillation by using benzonitrile as the solvent (64% NMR yield, 35% isolated yield, Table 2, entry 5), showing its potential application to a larger scale synthesis.

Table 2. Optimization of the reaction condition for the synthesis of methyl methacrylate (**1a**) from acetone, chloroform, and methanol. [a]



Entry	Base	Conv (%)	**1a** (%)	**3a** (%)	**4a** (%)
1	DBU	100	66	6.5	14
2	Et_3N	0.0	0.0	0.0	0.0
3[b]	*t*-Bu-P_1	100	21	5.6	74
4[c],[d]	DBU, *t*-Bu-P_1	100	78	1.3	2.9
5[e]	DBU	100	64 (35)[f]	6.6	14

[a] The yields of the products were determined by ^{1}H NMR using 1,4-dibromobenzene as an internal standard. [b] 5.0 mmol of chloroform was used. [c] 2.5 mmol of chloroform was used. [d] First *t*-Bu-P_1 (3.3 equiv.) 50 °C, 18 h and then DBU (2.0 equiv.) reflux, 24 h. [e] 300 mmol of chloroform was used and PhCN was in place of CH_3CN as a solvent. [f] Isolated yield.

The possible reaction mechanism shown in Scheme 2 nicely explains the base effect. In 2000, Aggarwal *et al.* reported the formation of acetonechloroform **2** from acetone and chloroform in the presence of DBU.[9] It is likely that the same reaction took place as the first step in our system. While subsequent elimination of hydrogen chloride from **2** to form dichloroepoxide **6** was proposed in literature,[10] direct formation of **6** by the reaction of acetone with dichlorocarbene ($:CCl_2$) might be another possibility. Since triethylamine is a weaker base (pK_{BH} = 18.63 in MeCN) than DBU (pK_{BH} = 24.16 in MeCN),[11] the deprotonation of chloroform seems insufficient with triethylamine to retard the reaction (Table 1, entry 2). Subsequently, the reaction of **6** with methanol would generate α-chloroester **4**. In fact, Stick reported the reaction of dialkyl(trichloromethyl)methanol $R_2C(CCl_3)OH$ can be converted to α-chloroesters in the presence of DBU and alcohols.[12] A proposed reaction mechanism in literature for the conversion of **6** to **4** is drawn as **A** in Scheme 2: addition and elimination of chloride take place spontaneously accompanied by the ring opening of epoxide. α-Alkoxyester **3**, which was the exclusive product by using potassium hydroxide as a base (Scheme 1d), was a minor product in all entries in Table 1. With an organic base, DBU for example, the chloride anion of the neutralized HCl remains in solution, unlike the inorganic base form insoluble salts such as KCl. Assuming that the selectivity to α-chloroester **4** over α-alkoxyester **3** originates from the nucleophilic species, either chloride or alkoxide in mechanism **A**, the higher concentration of the chloride anion with organic base could be the origin of the selective formation of **4** in this study. For the last step, the

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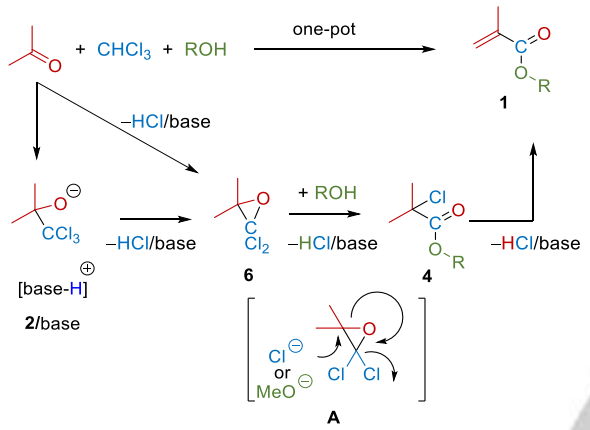
dehydrochlorination of α-chloroester **4** was successfully mediated by a base, especially by DBU.[13] This is contrastive to the reaction in Scheme 1d, which required the use of acidic conditions to eliminate methanol from α-alkoxyester **3**. Notably, DBU is known to be a uniquely efficient base for the elimination of hydrogen chloride.[14] Although phosphazene *t*-Bu-P_1 is a stronger base (pK_{BH} = 26.88 in MeCN)[11] than DBU, DBU shows higher activity for the dehydrochlorination of **4** to form methacrylate **1**. In fact, dehydrochlorination of **4** to **1** proceeded in a quantitative conversion with DBU. The reaction resulted in a low conversion with *t*-Bu-P_1 under the same conditions (see Supporting Information).

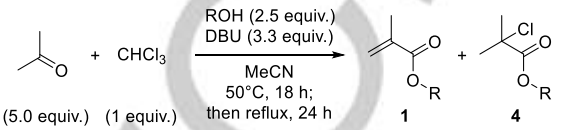


Scheme 2. Possible reaction mechanism for the one-pot formation of methacylic ester in this study.

In addition to methanol, the reaction was applicable to other alcohols. Under the same conditions as MMA was obtained in 66% (entry 1 in Table 2), the reaction was examined with several alcohols, and the results are summarized in Table 3. From ethanol, ethyl methacrylate **1b** was obtained in 46% yield along with 25% of α-chloroester **4b** (entry 1). The reaction was susceptible to steric repulsions thus the conversion stayed low for *i*-PrOH (entry 2). With PhOH, the major product was α-chloroester **4d** (58% yield) (entry 3). The lower conversion from **4d** to **1d** may be attributed to the higher acidity of PhOH (pK_a 9.95), which would have humpered the deprotonation of **4d** by DBU.[15a] With 2,2,2-trifluoroethanol (pK_a 12.4), the corresponding methacrylate **1e** was given in a comparable yield (50%) to that of ethanol (pK_a 15.9) (entry 4).[15b] The much lower yield of **1f** starting from ethanol bearing a perfluoroalkyl group at the 2-position of alcohol (entry 5) may be attributed to the undesirable elimination of methacrylic acid from **1f** because the formation of terminal alkene *n*-$C_6F_{13}CH{=}CH_2$ was confirmed in 38% yield.

For small scale synthesis, the use of bromoform in place of chloroform was proven to be far more effective. From bromoform, methyl methacrylate (**1a**) was obtained in 81% yield at 25 °C in 5 h (Figure 1), the value being superior to 66% yield from chloroform at 50°C for 18 h and then reflux for 24 h (entry 1 in Table 2). The higher activity of bromoform may be attributed to its higher acidity (pK_a of chloroform 15.5, bromoform 13.7).[16] Facile deprotonation accelerates the formation of dibromoepoxide, **6**-**Br** (analogous to **6** in Scheme 2). Bromide is also a better leaving group than chloride in acetonitrile so that the isomerization from **6**-**Br** to **4a**-**Br** can be accelerated. More importantly, it is advantageous for the dehydrohalogenation form **4a**-**Br** compared to **4a**. This shows good consistency with the absence of α-bromoester **4a**-**Br** in the crude mixture (see Supporting Information). The use of iodoform resulted in lower conversion due to the lower solubility in acetonitrile.

Table 3. Synthesis of methacrylic esters (**1a**–**f**) from various alcohols.[a]



entry	R	Conv. (%)	**1** (%)	**4** (%)
1	Et	97	46	25
2	*i*-Pr	94	8.6	10
3	Ph	97	31	58
4	CF_3CH_2	100	50	8.6
5	*n*-C_6F_{13} $(CH_2)_2$	79	8.8	[b]

[a] The reaction was carried out under the same conditions as entry 2 in Table 1 by varying the alcohol. [b] Not identified.

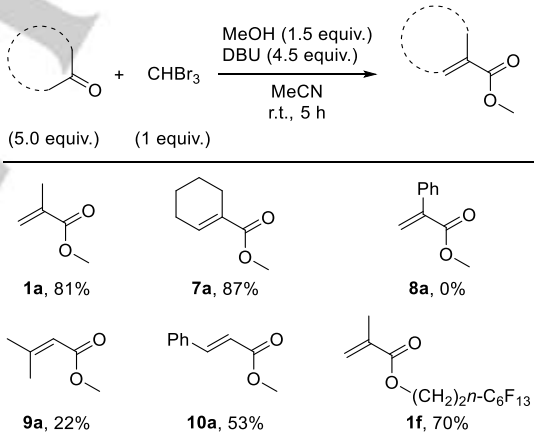


Figure 1. The use of bromoform and its application to other carbonyl compounds.

The reactant carbonyl compound was not limited to acetone (Figure 1). Cyclohexanone was successfully converted to cyclohexenecarboxylic ester **7a** in 87% yield.[17] Regarding to acetophenone, the product was a complex mixture, and the desired α-phenyl acrylate **8a** was not obtained. Aldehydes, such as isobutyraldehyde and benzaldehyde were converted to the corresponding α,β-unsaturated esters **9a** and **10a** in 22% and 53% yields, respectively. Notably, by using bromoform, perfluoroalkyl-group was successfully incorporated to form methacrylate **1f** in 70% yield, which is contrastive to the low yield with chloroform (entry 5 in Table 2). The higher yield may be attributed to the much lower reaction temperature in case for bromoform compared to that for chloroform, that suppressed the undesired elimination of methacrylic acid.

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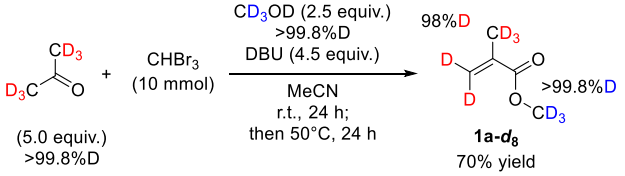
The reaction was successfully applied to the synthesis of deuterated methyl methacrylate (MMA-d_8). As shown in Scheme 3, the reaction of acetone-d_6, bromoform, and methanol-d_4 afforded MMA-d_8 (**1a**-d_8) in 70% yield (analyzed by GC).[18] In this cases, the yield of **1a**-d_8 was lower compared to the non-deuterated MMA (**1a**). In the reactions (Scheme 3), longer reaction time and heating was needed for full conversion of α-bromoester **4a-Br-*d*$_9$** (See Supporting information for details). This may correspond that the elimination of hydrogen bromide from **4a-Br-*d*$_9$** was slower than that from **4a-Br** because a C–D bond is stronger than a C–H bond. The polymer of deuterated MMA is known to be a promising material for optical waveguide owing to its transparency in the region of absorption due to C–H bonds. [19]



Scheme 3. Synthesis of deuterated MMA (**1a**-d_8)

Conclusions

In conclusion, methacrylic esters were synthesized in one-pot from acetone, chloroform, and various alcohols using acetonitrile or benzonitrile as a solvent. The reaction is also applicable to bromoform and other carbonyl compounds. Deuterated methyl methacrylate (MMA-d_8) was easily produced. We believe, the reaction described here provides a new synthetic route for MMA production from easily available starting materials.

Experimental Section

General: All manipulations were carried out using standard Schlenk techniques under N_2 purified by passing through a hot column packed with BASF catalyst R3-11.NMR spectra were recorded on JEOL JNM-ECS400 (^{1}H: 400 MHz, ^{13}C: 101 MHz), Bruker Ascend 500 (^{1}H: 500 MHz, ^{13}C: 126 MHz) NMR spectrometers, or JEOL ECZ-400 (^{1}H: 400 MHz). ^{1}H NMR analyses were performed in dimethylsulfoxide-d_6 with the number of FID's collected per sample of 16–128. Chemical shift values for protons are referenced to the residual proton resonance of dimethylsulfoxide-d_6 (δ 2.49). ^{13}C NMR analyses were performed in dimethylsulfoxide-d_6 with the number of FID's collected per sample of 1024–2048. Chemical shift values for carbons are referenced to the carbon resonance of dimethylsulfoxide-d6 (δ 39.52). High-resolution mass (HRMS) spectra were taken on a JEOL JMS-T100LP mass spectrometer with the electron spray ionization time-of-flight (ESI-TOF) method. GC analysis was performed by Agilent Technologies 7890B equipped with DB-1301 capillary column (0.250 ID, 1.00 μm df, 30 m). Karl Fischer titration was performed by Mitsubishi Chemical Analytech CA-21 equipped with AQUAMICRON AX/CXU.Distillation of 1a (MMA) was performed with Kiriyama Glass Works Co. FR 64-4-C. Benzonitrile was purchased from TCI and dried with $MgSO_4$, filtered, and purified by distillation. Bromoform was purchased from Kanto Chemical Co., Inc. (Kanto) and washed with H_2O, and purified by distillation over CaH_2. Chloroform, which is stabilized by amylene, was purchased from Kanto and used as received. 4a was recieved from AGC Inc. and used as recieved. All other materials were purchased from Kanto, Wako Pure Chemical Industries, Ltd., TCI, Aldrich and used as received.

Representative procedure for the one-pot synthesis of MMA (**1a**) (Table 1, entry 7): To a solution of acetone (2.90 g, 50 mmol), DBU (5.02 g, 33 mmol) and methanol (0.801 g, 25 mmol) in acetonitrile (5.0 mL) and 1,4-dibromobenzene (internal standard, 0.150 g, 0.64 mmol) was slowly added chloroform (1.19 g, 10 mmol) at 0 °C and the mixture was stirred for 18 hours at 50 °C. Then the mixture was warmed to the reflux condition and kept stirred for further 24 hours. After cooling to ambient temperature, the yield of 1a was determined by 1H NMR using 1,4-dibromobenzene as internal standard (6.6 mmol, 66%).

Optimization of the reaction conditions was carried out as shown below by varying the reaction temperature and time, concentration, and the equivalence of acetone, methanol, and DBU to chloroform. In some entries, the DBU adduct 10 was produced as a side product.

5: ^{1}H NMR (500 MHz, DMSO-d_6) δ; 3.29–3.26 (m, 2H), 3.24–3.21 (t, J = 5.5 Hz, 2H), 3.10–3.07 (t, J = 5.5 Hz, 2H); 2.18–2.16 (m, 2H), 1.97–1.92 (quin, J = 6.0 Hz, 2H), 1.78–1.73 (m, 2H), 1.58–1.51 (quin, J = 6.0 Hz, 2H), 1.01 (s, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ; 193.3, 165.9, 89.1, 63.4, 52.6, 48.3, 35.9, 28.4, 26.0, 22.0, 21.8, 20.7; HRMS(ESI) $[M + Cs]^+$ Calcd for $C_{13}H_{20}CsN_2O$ 353.0625. Found 353.0640.

Large scale synthesis and isolation of MMA (**1a**) (Table 2, entry 5): To a solution of acetone (110 mL, 1.5 mol), DBU (145 mL, 0.99 mol) and methanol (30 mL, 0.75 mol) in benzonitrile (150 mL) and 1,4-dibromobenzene (0.979 g, 4.15 mmol), was slowly added chloroform (35.80 g, 0.30 mol) at 0 °C and the mixture was stirred for 18 hours at 50 °C. Then the mixture was warmed to 80°C and keep stirred for further 24 hours. After cooling to ambient temperature, the yield of methyl methacrylate was determined by ^{1}H NMR using 1,4-dibromobenzene as internal standard (0.19 mmol, 64%). After three distillations (first: simple distillation to separate DBU and its salt, second and third: precise distillation with fractionating column), 1a was isolated (10.4 g, 35% yield, >99% pure by GC).

One-pot synthesis of α,β-unsaturated esters from bromoform: To a solution of carbonyl compound (5.0 equiv.), DBU (4.5 equiv.), and methanol (1.5 equiv.) in acetonitrile (1.3 mL) and 1,4-dibromobenzene, was slowly added bromoform (2.5 mmol, 1.0 equiv.) at 0 °C and the mixture was stirred for ambient temperature (*Warning*: This reaction is exothermic; water bath is necessary to control the reaction) at 5 hours. The yield of the corresponding methacrylate was determined by ^{1}H NMR analysis using 1,4-dibromobenzene as internal standard.

One-pot synthesis of deuterated MMA (**1a-*d*$_8$**): To a solution of acetone-d_6 (5.0 equiv.), DBU (3.3 equiv.) and methanol-d_4 (2.5 equiv.) in benzonitrile was slowly added bromoform (10 mmol = 1.0 equiv.) at 0 °C and the mixture was stirred for 24 hours at ambient temperature and then at 50°C for 24 h. After cooling to ambient temperature, the yield of the corresponding methacrylate was determined by GC analysis using benzene as an internal standard (70% yield).

Determination of the deuterated ratio: The measurement was carried using a reference solution prepared from 111.8 mg of C_6H_6 in 2.9285 g of DMSO-d_6. To a portion of transferred mixture containing **1a-*d*$_8$** (214 mg, containing 5.5 mg of **1a-*d*$_8$** based on GC analysis), was added the solution of benzene in DMSO-d_6 (667.1 mg, containing 24.5 mg of benzene). By ^{1}H NMR analysis, the deuterated ratio was determined comparing the integration of each peak of **1a-*d*$_8$** with that of C_6H_6.

Acknowledgments

We are grateful to Prof. Takanori Iwasaki (University of Tokyo) for helpful discussions.

Keywords: Methacrylic ester • Acetone • Chloroform • DBU • one-pot synthesis

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[8] See supporting information for details for the formation of **5**.

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