## 132. Efficient Synthesis of Methyl 2-(tert-Butyl)acrylate and Analogous Esters

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The title products are prepared via an efficient three-step synthesis which involves hydroalumination of methyl propiolate and *Lewis*-acid-promoted reaction with acetone in the presence of BF<sub>3</sub> followed by two highly selective  $S_N2'$  reactions. The key step is the reaction of 2-(chloromethyl)acrylates with  $R_2CuLi/ZnCl_2$  reagents which takes place with complete allylic rearrangement.

Unlike less sterically hindered acrylates, methyl 2-(*tert*-butyl)acrylate (2a) does not polymerize when treated with radical initiators [1]. This property makes 2a a useful radical trapping agent in mechanistic studies [2]. Acrylate 2a has been synthesized from isopropylidenemalonate in four steps but with a poor overall yield of < 10% due to one inefficient step in the sequence [1b]. To our knowledge, only one other synthesis of 2a was reported: acrylate 2a was formed unexpectedly *via* the reaction of a ketene acetal with CHBr<sub>3</sub> and Et<sub>2</sub>Zn [3].

We describe here a new and concise three step synthesis of 2a and analogous compounds. The key step of the reaction sequence is an  $S_N2'$  allylation of  $R_2CuLi/ZnCl_2$  reagents.

We based our approach on the reports by *Nakamura* and coworkers of highly selective  $S_N2'$  allylation reactions of organocopper or organozinc reagents with allylic chlorides [4]. It was shown that quaternary C-centers can be readily generated by this method. The exact nature of the reagent is not known, and we note that alkylzinc halides, derived from *Grignard* reagents, ZnCl<sub>2</sub>, and LiCl react with allylic halides and sulfonates to give highly selectively the  $S_N2'$  allylation products [5].

New in the  $S_N 2'$  allylation procedure reported here is its application to the generation of a quaternary C-center attached to C(2) of an acrylate.

The R<sub>2</sub>CuLi/ZnCl<sub>2</sub> reagents were prepared by the literature procedure from the appropriate alkyllithium reagent, CuBr · Me<sub>2</sub>S, and ZnCl<sub>2</sub> [4a]. Reaction of a slight excess of the nucleophile with 2-(chloromethyl)acrylates 1 in THF gave products 2 (*Scheme 1*) in the yields shown in the *Table*. Both GLC and <sup>1</sup>H-NMR analysis of the crude product resulting from the reaction of the Me<sub>2</sub>CuLi/ZnCl<sub>2</sub> reagent with **5a** showed the  $S_N 2'$  product methyl 2-(*tert*-butyl)acrylate (**2a**) to be the only product formed. GLC Analysis indicated a close to quantitative yield. Purification by chromatography (hexane/Et<sub>2</sub>O) on silica gel and careful removal of the solvent afforded the volatile product **2a** in 86% yield (*Entry 1*). To establish that the product is not consumed *via Michael* addition of the alkyl nucleophile, it was subjected to the reaction conditions detailed above. Acrylate **2a** was recovered quantitatively from the reaction mixture.

## Scheme 1



Table. Reaction of 2-(Chloromethyl)acrylates 1 Leading to the Products 2

Entry	Educt	$\mathbf{R}^{1}$	$\mathbb{R}^2$	R <sup>3</sup> Li	$MX_n^{a}$ )		Product Yield <sup>b</sup> ) [%]
1	1a	Me	Me	MeLi	CuBr · Me <sub>2</sub> S/ZnCl <sub>2</sub>	2a	86 <sup>c</sup> )
2	1a	Me	Me	BuLi	$CuBr \cdot Me_2S/ZnCl_2$	2b	80
3	1a	Me	Me	BuLi	CuBr Me <sub>2</sub> S	d)	
4	1a	Me	Me	BuLi	$ZnCl_2^e$	2b	91
5	1b	Pr	Pr	BuLi	CuBr · Me <sub>2</sub> S/ZnCl <sub>2</sub>	2c	93
6	1b	Pr	Pr	MeLi	CuBr Me <sub>2</sub> S/ZnCl <sub>2</sub>	2d	95
7	1c	Me	Bu	MeLi	CuBr · Me <sub>2</sub> S/ZnCl <sub>2</sub>	2b	94
8	1d	cyclohexyl		MeLi	CuBr Me <sub>2</sub> S/ZnCl <sub>2</sub>	2e	89
3) 0	cc 1		D3	T :			

a) 0.55 mol-equiv. with respect to R<sup>3</sup>Li.

<sup>b</sup>) Yield of isolated products.

c) GLC Yield 94%.

<sup>d</sup>) <sup>1</sup>H-NMR of the crude material showed the major product to be the  $S_N^2$  product Me<sub>2</sub>C=C(CO<sub>2</sub>Me)(C<sub>5</sub>H<sub>11</sub>).

<sup>e</sup>) In the presence of HMPA, 24 h, 20°.

In agreement with literature reports, it was found that  $ZnCl_2$  is crucial to the success of the alkylation with allylic inversion [4]. Product **2b** was formed efficiently with  $Bu_2Cu/$  $ZnCl_2$  (*Entry 2*). Without  $ZnCl_2$ , 'H-NMR analysis showed the  $S_N2$  substitution product to be formed. Acrylate **2b** was notably absent (*Entry 3*). Conversely, leaving out copper and using  $Bu_2Zn$  as alkylating agent gave **2b** in high yield and selectivity. Compared to the reaction with the  $R_2CuLi/ZnCl_2$  reagent, formation of **2b** was slower, however, and required HMPA as cosolvent (*Entry 4*). We, therefore, preferred to use the cuprate/ZnCl\_2 method in the reactions with **1b-d** (*Entries 5-8*). The results demonstrate that this alkylation with allylic transposition remains selective and efficient also with acrylates bearing bulkier (**1b**, c) or cyclic (**1d**) groups.

The required 2-(chloromethyl)acrylates 1 were obtained in two steps. Following the procedure reported by *Tsuda et al.*, methyl propiolate (3) was reacted with DIBAH. In situ coupling of the generated  $[\alpha$ -(methoxycarbonyl)vinyl]aluminum reagent with ketones in the presence of BF<sub>3</sub>·Et<sub>2</sub>O gave methyl 2-(1-hydroxyalkyl)acrylates 4 in good yields [6] (*Scheme 2*). We note that an alternative synthesis of 4a via the DABCO-catalyzed addition of methyl acrylate to acetone under 5-kbar pressure was reported [7]. Compounds 4 reacted with N-chlorosuccinimide/Me<sub>2</sub>S to give the desired allylic rearrangement products 1 highly selectively in high yields [8].

In conclusion, the method presented here for the preparation of 2-substituted acrylates has the merit of being short and selective. Methyl 2-(*tert*-butyl)acrylate (2a) was synthesized on a 10-g scale without loss of selectivity and with an overall yield of 55% based on 3.



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## **Experimental Part**

General. THF was distilled from sodium-benzophenone ketyl immediately prior to use. Hexamethylphosphortriamide (HMPA; *Fluka*) was stirred with CaH<sub>2</sub> for 15 h at 60° before distillation under a reduced atmosphere (10 mm Hg) of N<sub>2</sub>, MeLi, BuLi (*Fluka*) were titrated before use. Methyl propiolate (*Fluka*), ZnCl<sub>2</sub> (*Aldrich*; 1M in Et<sub>2</sub>O), Me<sub>2</sub>Zn (*Aldrich*; 2M in toluene), CuBr  $\cdot$ SMe<sub>2</sub> (*Fluka*), diisobutylaluminium hydride (DIBALH; *Aldrich*; 1M in hexane) were used as received. Anal. and prep. TLC: Merck silica gel 60 F<sub>254</sub> plates. GC: Hewlett-Packard capillary-column instrument. IR Spectra: Perkin Elmer 1660 Series FT spectrometer; NaCl soln. cells. <sup>1</sup>H- and <sup>13</sup>C-NMR Spectra: Bruker 400-MHz or a Varian-XL-200 spectrometer. Electron impact (70 eV) mass spectra (EI-MS): Varian CH 4 or SM 1 spectrometer; relative intensities are given in parentheses. High-resolution mass spectra (HR-MS): VG analytical 7070E instrument.

Methyl 3-Hydroxy-3-methyl-2-methylidenebutanoate (4a) [6]. Diisobutylaluminium hydride (DIBAH; 22 ml of 1m soln. in hexane, 22.0 mmol) was added dropwise to a soln. of HMPA (5.8 ml, 33.1 mmol) in THF (80 ml) at 0°. After 30 min, methyl propiolate (3; 1.70 ml, 20.3 mmol) was added and, after stirring for 1 h at 0°, the mixture was treated with acetone (3 ml, 40.8 mmol) and  $BF_3 \cdot Et_2O$  (11 ml, 42.0 mmol). The reaction mixture was stirred first for 1 h at 0°, then 20 h at r.t., and then diluted with  $Et_2O$  (100 ml) and washed with 3 portions of aq. HCl (1N), followed by sat. aq. NaHCO<sub>3</sub>. The org. phase was dried (MgSO<sub>4</sub>), solvent was removed at reduced pressure, and the residue was chromatographed on silica gel (hexane/Et<sub>2</sub>O) to give 2.17 g (74%) of 4a as a colorless oil. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 1.42 (*s*, 6 H); 3.75 (*s*, 3 H); 3.85 (br. *s*, OH); 5.77 (*s*, 1 H); 6.12 (*s*, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 28.9; 51.9; 71.3; 123.3; 145.7; 167.8.

Allylic alcohols 4b-d were prepared analogously and used directly in the synthesis of 1b-d.

Methyl 2-(Chloromethyl)-3-methylbut-2-enoate (1a). To a mixture of N-chlorosuccinimide (2.30 g, 17.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 ml) at 0° was added Me<sub>2</sub>S (1.45 ml, 19.8 mmol). On stirring for 10 min, a white suspension formed. The mixture was treated with a soln. of 4a (1.66 g, 11.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> and stirred for 20 h at 0°. After this time, the mixture was diluted with hexane (50 ml) and washed with brine. The aq. phase was extracted with Et<sub>2</sub>O, and the combined org. phase dried (MgSO<sub>4</sub>). Solvent removal and chromatography (hexane/Et<sub>2</sub>O) afforded 1a (1.75 g, 94%) as a colorless oil. IR (hexane): 1729s, 1636m, 1474m, 1435m, 1317m, 1268s, 1219s, 1077s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 2.00 (s, 3 H); 2.15 (s, 3 H); 3.76 (s, 3 H); 4.38 (s, 2 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 22.8; 23.6; 41.3; 51.7; 124.4; 153.8; 167.1.

Compounds 1b-d were prepared analogously.

*Methyl 2-(Chloromethyl)-3-propylhex-2-enoate* (1b). IR (hexane): 1729*s*, 1625*w*, 1434*w*, 1269*m*, 1199*s*, 1170*s*. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 0.82–0.97 (*m*, 6 H); 1.31–1.55 (*m*, 4 H); 2.10–2.40 (*m*, 4 H); 3.70 (*s*, 3 H); 4.31 (*s*, 2 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 14.3; 21.9; 22.1; 36.1; 36.4; 41.2; 51.5; 124.8; 159.9; 167.2.

*Methyl 2-(Chlormethyl)-3-methylhept-2-enoate* (1c). IR (hexane): 1728*s*, 1628*m*, 1436*w*, 1266*s*, 1196*s*, 1170*s*, 1092*m*. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 0.85–1.00 (*m*, 3 H); 1.20–1.55 (*m*, 4 H); 1.98 (*s*, 3 H); 2.40–2.55 (br. *m*, 2 H); 3.67 (*s*, 3 H); 4.37 (*s*, 2 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 13.9; 22.8; 30.3; 36.4; 41.9; 51.6; 124.4; 157.5; 167.0.

*Methyl 2-(Chloromethyl)-2-cyclohexylidenepropanoate* (1d). IR (hexane): 1728s, 1628m, 1432w, 1364w, 1274m, 1209s, 1168s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 1.50–1.80 (m, 6 H); 2.30–2.65 (m, 4 H); 3.77 (s, 3 H); 4.38 (s, 2 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 26.1; 28.3; 32.3; 32.8; 40.9; 51.7; 121.7; 159.0; 167.9.

 $S_N2^2$  Allylation of  $Me_2CuLi/ZnCl_2$ . a) Methyl 2-(tert-Butyl)prop-2-enoate (2a). To a suspension of CuBr  $Me_2S$  (438 mg, 2.13 mmol) in THF (8 ml) at  $-70^\circ$  was added MeLi (1.6M in Et<sub>2</sub>O, 2.7 ml, 4.32 mmol). The resulting mixture was warmed to 0°, stirred for 10 min, then cooled to  $-70^\circ$ , and treated with a soln. of ZnCl<sub>2</sub> (1M in Et<sub>2</sub>O, 2.2 ml, 2.2 mmol). After 10 min, 1a (326 mg, 2.0 mmol) in THF (7 ml) was added. The mixture was stirred first at  $-70^\circ$  for 1 h, then at 0° overnight. Then hexane was added, and the soln. was washed with brine and dried (MgSO<sub>4</sub>). Solvents were removed by distillation, and the crude product was purified by chromatography (5–10% Et<sub>2</sub>O/hexane) to give 2a as colorless oil (244 mg, 86%). IR (hexane): 1729s, 1615w, 1470w, 1436w, 1376w, 1311m, 1229m, 1118s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 1.19 (s, 9 H); 3.72 (s, 3 H); 5.51 (d, J = 0.9, 1 H); 5.91 (d, J = 0.9, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 29.3; 34.8; 51.4; 121.1; 150.0; 168.2. MS: 142 (24), 127 (43), 111 (32), 95 (76), 83 (91), 73 (91), 67 (100), 55 (68). HR-MS: 142.0968 (C<sub>8</sub>H<sub>14</sub>O<sub>2</sub>;  $M^+$ , calc. 142.1004).

b) Methyl 2-(1-Methyl-1-propylbutyl)prop-2-enoate (2d). IR (hexane): 2980w, 1729s, 1614m, 1456m, 1435w, 1284w, 1192m, 1121s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 0.83 (t. J = 7.1, 6 H); 0.95–1.45 (m, 6 H); 1.05 (s, 3 H); 1.60–1.80 (m, 2 H); 3.70 (s, 3 H); 5.38 (s, 1 H); 5.96 (s, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 14.7; 17.5; 23.6; 41.4; 42.3; 51.4; 123.1; 147.3; 168.4. MS: 199 (80), 198 (12), 167 (21), 155 (45), 123 (67), 95 (100), 81 (38). HR-MS: 198.1615 (C<sub>12</sub>H<sub>20</sub>O<sub>2</sub>;  $M^+$ , calc. 198.1619).

*Methyl 2-(1-Methylcyclohexyl)prop-2-enoate* (2e). IR (hexane): 1729s, 1614*m*, 1434*m*, 1306s, 1272s, 1190s, 1149s, 1114s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 1.19 (*s*, 3 H); 1.25–1.85 (*m*, 10 H); 3.71 (*s*, 3 H); 5.48 (*s*, 1 H); 5.91 (*s*, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 22.3; 26.4; 26.7; 36.4; 38.0; 51.4; 121.5; 149.8; 168.7. MS: 183 (100), 182 (37), 167 (14), 151 (37), 135 (25), 123 (38), 95 (62), 91 (23), 81 (96). HR-MS: 182.1302 (C<sub>11</sub>H<sub>18</sub>O<sub>2</sub>; *M*<sup>+</sup>, calc. 182.1306).

 $S_N2'$  Allylation of  $Bu_2CuLi/ZnCl_2$ . a) Methyl 2-(1,1-dimethylpentyl)prop-2-enoate (2b). To a suspension of CuBr · Me<sub>2</sub>S (215 mg, 1.05 mmol) in THF (3 ml) at  $-70^\circ$  was added BuLi (1.54m in hexane, 1.36 ml, 2.09 mmol). The resulting mixture was warmed to  $-40^\circ$ , stirred for 40 min, then cooled to  $-70^\circ$ , and treated with a soln. of ZnCl<sub>2</sub> (1m in Et<sub>2</sub>O, 1.06 ml, 1.05 mmol). After 10 min, 1a (163 mg, 1.0 mmol) in THF (4 ml) was added. The mixture was stirred, first at  $-70^\circ$  for 1 h, then at  $-40^\circ$  overnight. The reaction mixture was diluted with hexane, washed with sat. aq. NaCl, and dried (MgSO<sub>4</sub>). Solvents were removed by distillation, and the crude product was purified by chromatography (5–10% Et<sub>2</sub>O/hexane) to give 2b as colorless oil (148 mg, 80%). IR (hexane): 1728s, 1615m, 1436m, 1326w, 1289m, 1240m, 1195m, 1119s, 943m. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 0.84 (t, J = 7.1, 3 H); 1.00–1.35 (m, 4 H); 1.14 (s, 6 H); 1.50–1.65 (m, 2 H); 3.71 (s, 3 H); 5.45 (s, 1 H); 5.95 (s, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): (140, 23.2; 27.0; 27.6; 37.9; 40.3; 51.3; 122.2; 148.6; 168.3. MS: 185 (51), 169 (11), 153 (15), 141 (32), 128 (32), 109 (31), 95 (100), 81 (29), 67 (70), 55 (34). HR-MS: 184.1458 (C<sub>11</sub>H<sub>20</sub>O<sub>2</sub>;  $M^+$ , calc. 184.1458).

b) Methyl 2-(1,1-Dipropylpentyl)prop-2-enoate (2c). IR (hexane): 2988w, 1730s, 1614w, 1436m, 1287m, 1260m, 1196m, 1119s. <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): 0.85 (br. t, J = 6.5, 9 H); 0.95–1.37 (m, 8 H); 1.37–1.55 (m, 6 H); 3.69 (s, 3 H); 5.36 (s, 1 H); 5.92 (s, 1 H). <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): 14.1; 14.7; 16.7; 23.3; 25.7; 34.5; 37.1; 43.8; 51.4; 122.8; 147.6; 168.9. MS: 240 (5), 197 (33), 183 (18), 165 (19), 151 (20), 137 (32), 123 (34), 109 (31), 95 (62), 81 (100), 69 (56), 55 (98). HR-MS: 240.209 (C<sub>15</sub>H<sub>28</sub>O<sub>2</sub>;  $M^+$ , calc. 240.211).

 $S_N 2'$  Allylation of  $Bu_2 Zn$ . Ester 2b. To a soln. of  $ZnCl_2$  (1M in Et<sub>2</sub>O, 1.05 ml, 1.05 mmol) in THF (7 ml) at  $-70^{\circ}$  was added BuLi (1.54M in hexane, 1.36 ml, 2.09 mmol) and HMPA (0.37 ml, 2.11 mmol). After 10 min, 1a (162 mg, 1.0 mmol) was added. The mixture was stirred first at  $-70^{\circ}$  for 1 h and then at r.t. for 24 h. The reaction mixture was diluted with wet hexane and filtered through a pad of silica gel. After careful removal of the solvent, the residue was purified by chromatography (5–10% Et<sub>2</sub>O/hexane) to give 2b (168 mg, 91%).

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