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

by **Long-He Xu** and **Ernst Peter Kündig***

Département de Chimie Organique, Université de Genève, CH–1211 Genève 4

(7.VII.94)

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_3 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 $CHBr_3$ and Et_2Zn [3].

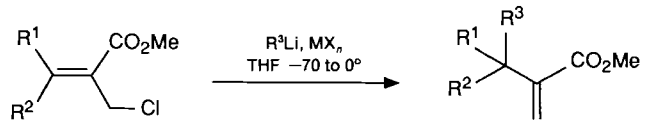
We describe here a new and concise three step synthesis of **2a** and analogous compounds. The key step of the reaction sequence is an S_N2' allylation of $R_2CuLi/ZnCl_2$ reagents.

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, $ZnCl_2$, and LiCl react with allylic halides and sulfonates to give highly selectively the S_N2' allylation products [5].

New in the S_N2' allylation procedure reported here is its application to the generation of a quaternary C-center attached to C(2) of an acrylate.

The $R_2CuLi/ZnCl_2$ reagents were prepared by the literature procedure from the appropriate alkyllithium reagent, $CuBr \cdot Me_2S$, and $ZnCl_2$ [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 ^{1}H-NMR analysis of the crude product resulting from the reaction of the $Me_2CuLi/ZnCl_2$ reagent with **5a** showed the S_N2' 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_2O) 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



1a–d **2a–e**

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

Entry	Educt	R^1	R^2	R^3Li	MX_n[a])		Product Yield[b]) [%]
1	**1a**	Me	Me	MeLi	$CuBr \cdot Me_2S/ZnCl_2$	**2a**	86[c])
2	**1a**	Me	Me	BuLi	$CuBr \cdot Me_2S/ZnCl_2$	**2b**	80
3	**1a**	Me	Me	BuLi	$CuBr \cdot Me_2S$	[d])	
4	**1a**	Me	Me	BuLi	$ZnCl_2$[e])	**2b**	91
5	**1b**	Pr	Pr	BuLi	$CuBr \cdot Me_2S/ZnCl_2$	**2c**	93
6	**1b**	Pr	Pr	MeLi	$CuBr \cdot Me_2S/ZnCl_2$	**2d**	95
7	**1c**	Me	Bu	MeLi	$CuBr \cdot Me_2S/ZnCl_2$	**2b**	94
8	**1d**	cyclohexyl		MeLi	$CuBr \cdot Me_2S/ZnCl_2$	**2e**	89

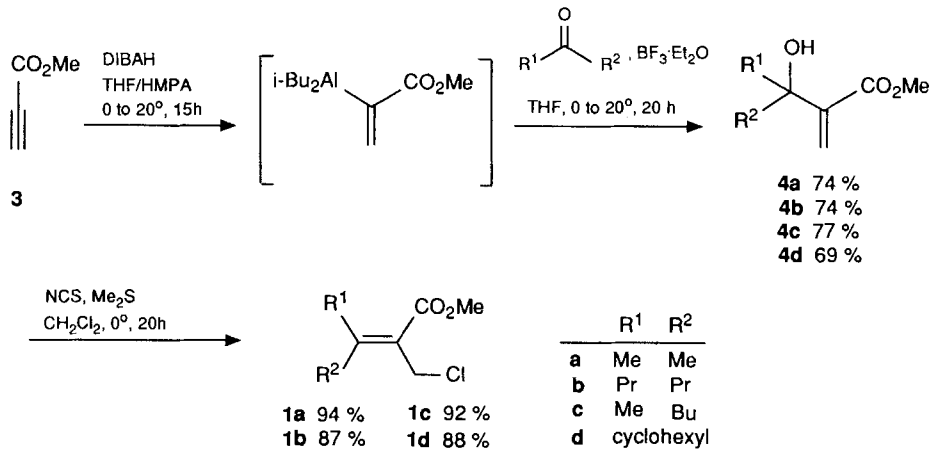
[a]) 0.55 mol-equiv. with respect to R^3Li.
[b]) Yield of isolated products.
[c]) GLC Yield 94%.
[d]) ^{1}H-NMR of the crude material showed the major product to be the S_N2 product $Me_2C{=}C(CO_2Me)(C_5H_{11})$.
[e]) In the presence of HMPA, 24 h, 20°.

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 $ZnCl_2$, ^{1}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 [α-(methoxycarbonyl)vinyl]aluminum reagent with ketones in the presence of $BF_3 \cdot Et_2O$ 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_2S 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**.

Scheme 2



We are grateful for financial support of this work by *Ciba-Geigy AG*. We also wish to thank Mr. *J. P. Saulnier*, Mr. *A. Pinto*, and Mrs. *D. Clément* for NMR and MS measurements.

Experimental Part

General. THF was distilled from sodium-benzophenone ketyl immediately prior to use. Hexamethylphosphortriamide (HMPA; *Fluka*) was stirred with CaH_2 for 15 h at 60° before distillation under a reduced atmosphere (10 mm Hg) of N_2. MeLi, BuLi (*Fluka*) were titrated before use. Methyl propiolate (*Fluka*), $ZnCl_2$ (*Aldrich*; 1M in Et_2O), Me_2Zn (*Aldrich*; 2M in toluene), $CuBr \cdot SMe_2$ (*Fluka*), diisobutylaluminium hydride (DIBALH; *Aldrich*; 1M in hexane) were used as received. Anal. and prep. TLC: *Merck* silica gel *60* F_{254} plates. GC: *Hewlett-Packard* capillary-column instrument. IR Spectra: *Perkin Elmer 1660 Series FT* spectrometer; NaCl soln. cells. ^{1}H- and ^{13}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. $NaHCO_3$. The org. phase was dried ($MgSO_4$), solvent was removed at reduced pressure, and the residue was chromatographed on silica gel (hexane/Et_2O) to give 2.17 g (74%) of **4a** as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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_2Cl_2 (20 ml) at 0° was added Me_2S (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_2Cl_2 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_2O, and the combined org. phase dried ($MgSO_4$). Solvent removal and chromatography (hexane/Et_2O) afforded **1a** (1.75 g, 94%) as a colorless oil. IR (hexane): 1729*s*, 1636*m*, 1474*m*, 1435*m*, 1317*m*, 1268*s*, 1219*s*, 1077*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 2.00 (*s*, 3 H); 2.15 (*s*, 3 H); 3.76 (*s*, 3 H); 4.38 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 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*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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): 1728*s*, 1628*m*, 1432*w*, 1364*w*, 1274*m*, 1209*s*, 1168*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.50–1.80 (*m*, 6 H); 2.30–2.65 (*m*, 4 H); 3.77 (*s*, 3 H); 4.38 (*s*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 26.1; 28.3; 32.3; 32.8; 40.9; 51.7; 121.7; 159.0; 167.9.

S_N2' *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° was added MeLi (1.6M in Et_2O, 2.7 ml, 4.32 mmol). The resulting mixture was warmed to 0°, stirred for 10 min, then cooled to −70°, and treated with a soln. of $ZnCl_2$ (1M in Et_2O, 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° for 1 h, then at 0° overnight. Then hexane was added, and the soln. was washed with brine and dried ($MgSO_4$). Solvents were removed by distillation, and the crude product was purified by chromatography (5–10% Et_2O/hexane) to give **2a** as colorless oil (244 mg, 86%). IR (hexane): 1729*s*, 1615*w*, 1470*w*, 1436*w*, 1376*w*, 1311*m*, 1229*m*, 1118*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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 ($C_8H_{14}O_2$; M^+, calc. 142.1004).

b) *Methyl 2-(1-Methyl-1-propylbutyl)prop-2-enoate* (**2d**). IR (hexane): 2980*w*, 1729*s*, 1614*m*, 1456*m*, 1435*w*, 1284*w*, 1192*m*, 1121*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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 ($C_{12}H_{20}O_2$; M^+, calc. 198.1619).

Methyl 2-(1-Methylcyclohexyl)prop-2-enoate (**2e**). IR (hexane): 1729*s*, 1614*m*, 1434*m*, 1306*s*, 1272*s*, 1190*s*, 1149*s*, 1114*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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 ($C_{11}H_{18}O_2$; M^+, 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_2S (215 mg, 1.05 mmol) in THF (3 ml) at −70° was added BuLi (1.54M in hexane, 1.36 ml, 2.09 mmol). The resulting mixture was warmed to −40°, stirred for 40 min, then cooled to −70°, and treated with a soln. of $ZnCl_2$ (1M in Et_2O, 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° for 1 h, then at −40° overnight. The reaction mixture was diluted with hexane, washed with sat. aq. NaCl, and dried ($MgSO_4$). Solvents were removed by distillation, and the crude product was purified by chromatography (5–10% Et_2O/hexane) to give **2b** as colorless oil (148 mg, 80%). IR (hexane): 1728*s*, 1615*m*, 1436*m*, 1326*w*, 1289*m*, 1240*m*, 1195*m*, 1119*s*, 943*m*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 14.0; 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 ($C_{11}H_{20}O_2$; M^+, calc. 184.1458).

b) *Methyl 2-(1,1-Dipropylpentyl)prop-2-enoate* (**2c**). IR (hexane): 2988*w*, 1730*s*, 1614*w*, 1436*m*, 1287*m*, 1260*m*, 1196*m*, 1119*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 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). ^{13}C-NMR (50 MHz, $CDCl_3$): 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 ($C_{15}H_{28}O_2$; M^+, calc. 240.211).

S_N2' *Allylation of* Bu_2Zn. *Ester* **2b**. To a soln. of $ZnCl_2$ (1M in Et_2O, 1.05 ml, 1.05 mmol) in THF (7 ml) at −70° 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° 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_2O/hexane) to give **2b** (168 mg, 91%).

REFERENCES

[1] a) J. W. C. Crawford, S. D. Swift, *J. Chem. Soc.* **1952,** 1220; b) J. W. C. Crawford, *ibid.* **1953,** 2658.

[2] a) K. Dietliker, personal communication (*Ciba-Geigy AG,* Additive Division); b) B. Giese, S. Lachhein, *Angew. Chem. Int. Ed.* **1981,** *20,* 967.

[3] G. Rousseau, N. Slougui, *J. Am. Chem. Soc.* **1984,** *106,* 7283.

[4] a) E. Nakamura, K. Sekiya, M. Arai, S. Aoki, *J. Am. Chem. Soc.* **1989,** *111,* 3091; b) M. Arai, T. Kawasuji, E. Nakamura, *J. Org. Chem.* **1993,** *58,* 5121, and ref. cit. therein. For organocopper reagents prepared from organozinc reagents, also see: c) P. Knochel, M. C. P. Yeh, M. S. Berk, J. Talbert, *J. Org. Chem.* **1988,** *53,* 2390; d) Y. Tamaru, H. Tanigawa, T. Yamamoto, Z. Yoshida, *Angew. Chem. Int. Ed.* **1989,** *28,* 351; e) P. Knochel, S. A. Rao, *J. Am. Chem. Soc.* **1990,** *112,* 6146; f) S. A. Rao, P. Knochel, *ibid.* **1991,** *113,* 5735; g) L. Zhu, R. M. Wehmeyer, R. D. Rieke, *J. Org. Chem.* **1991,** *56,* 1445; h) Y. Yamamoto, M. Tanaka, T. Ibuka, *ibid.* **1992,** *57,* 1024. For organocyanocopper·BF_3 reagents see: i) Y. Chounan, H. Nemto, Y. Yamamoto, *J. Org. Chem.* **1993,** *58,* 1207, and ref. cit. therein.

[5] a) N. Fuji, K. Nakai, H. Habashita, H. Yoshizawa, T. Ibuka, F. Garrido, A. Mann, Y. Chounan, Y. Yamamoto, *Tetrahedron Lett.* **1993,** *34,* 4227; b) K. Sekiya, E. Nakamura, *ibid.* **1988,** *29,* 5155.

[6] a) T. Tsuda, T. Yoshida, T. Kawamoto, T. Saegusa, *J. Org. Chem.* **1987,** *52,* 1624; b) T. Tsuda, T. Yoshida, T. Saegusa, *ibid.* **1988,** *53,* 1037.

[7] J. S. Hill, N. S. Isaacs, *Tetrahedron Lett.* **1986,** *27,* 5007.

[8] a) H. M. R. Hoffmann, J. Rabe, *J. Org. Chem.* **1985,** *50,* 3849; b) A. Charette, B. Côté, *Tetrahedron Lett.* **1993,** *34,* 6833; c) A. Foucaud, F. Guemmout, *Bull. Soc. Chim. Fr.* **1989,** *3,* 403.