# Olefin Synthesis by Reaction of Stabilized Carbanions with Carbene Equivalents. 2.[1] Use of (Iodomethyl)tributylstannane for Methylenation of Nitriles

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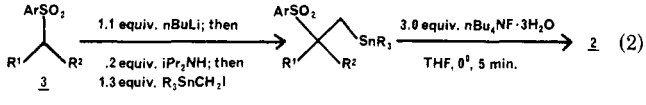
Excellent methods for elaboration of nitriles into various types of olefins are available.[2,3,4] However, none of them is effective for elaboration of nitriles into methylene compounds (**1** → **2**). In order to effect this transformation, synthetic chemists must resort to some indirect, multistep sequence of reactions.[5]


(1)

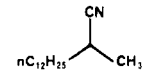
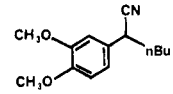
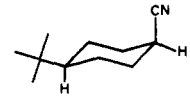
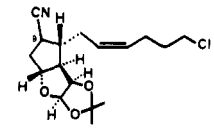
Recently, we developed a two-step, one-pot method for transformation of *sec*-alkyl aryl sulfones (**3**) into the corresponding methylene compounds (**2**), consisting of alkylation with *n*-$Bu_3SnCH_2I$[6] followed by *n*-$Bu_4NF{\cdot}3H_2O$-induced fragmentation (eq 2). The characteristic of the




(2)

arylsulfonyl group that makes this method possible is its ability to undergo β-elimination. Since the cyano group also can undergo β-elimination (although less readily[7,8]), in principle the eq 2 method should be applicable also to the problem of methylenation of nitriles. The purpose of this paper is to report that, indeed, many nitriles can be methylenated in excellent yield by a slight variant of the eq 2 method.

**Table I**[a]

| nitrile | | $LiNR_2$, R | % yield (1 → 4) | % yield (4 → 2) |
|---|---|---|---|---|
| **1a** |  | $C_6H_{11}$ | 93.4 | 89.4 |
| **1b** |  | *i*-Pr | 90.9 | 97.7 |
| **1c** |  | $C_6H_{11}$ | 82.5[14] | 78.1 |
| **1d**[15] |  | *i*-Pr | (≥99.2)[16] | 99.2 |

[a] Refer to eq 3.

The first step (alkylation with *n*-$Bu_3SnCH_2I$) is carried out according to the standard procedure for alkylation of nitriles with alkyl halides[9] (i.e., addition of the nitrile to a solution of a lithium dialkyl amide in THF at −78 °C, followed by addition of the tin–iodide reagent, followed by stirring until alkylation is complete). Yields[10] of stannylmethylated nitriles **4** are excellent (see Table I). Even hindered (**1d**) and acidic (**1b**) nitriles undergo alkylation in high yield. Compared with nitriles, sulfones undergo alkylation by *n*-$Bu_3SnCH_2I$ slowly. For example, whereas alkylation of **1d** by *n*-$Bu_3SnCH_2I$ is complete in less than 15 min at −78 °C,[12] alkylation of the *p*-tolyl sulfone corresponding to **1d** requires stirring at −30 °C for 2 h.[1] Thus, a greater variety of nitriles than sulfones undergo alkylation by *n*-$Bu_3SnCH_2I$ in high yield.

The second step (decyanostannylation) is effected by treatment with MeLi (THF, −20 °C,[13] 20 min). Less nucleophilic reagents such as *n*-$Bu_4NF{\cdot}3H_2O$ (THF, Δ, 2.5 h), MeMgCl (THF, 0 °C, 30 min), and NaCN (DMF, 80 °C, 10 h) are completely ineffective (for the case of **4a**). By contrast, stannylmethylated sulfones fragment readily upon treatment with *n*-$Bu_4NF{\cdot}3H_2O$ (THF, 0 °C, 5 min).[1] Thus, stannylmethylated nitriles fragment much less readily than do stannylmethylated sulfones. This is consistent with the conclusion of several previous studies that cyanide is a much poorer leaving group than sulfinate[7] (the rate of base-induced dehydrosulfonylation of sulfones is ~$10^8$ times greater than that of dehydrocyanation, according to one study[8]).

The fact that as harsh a reagent as MeLi is required to induce the fragmentation obviously means that the scope of the method is limited to substrates that lack sensitive functionality. Nevertheless, if no incompatible functional

(1) Part 1 of this series: Pearlman, B. A.; Putt, S. R.; Fleming, J. A. *J. Org. Chem.*, preceding paper in this issue.

(2) 1,2-Disubstituted and trisubstituted olefins (by treatment with LDA followed by the lithium salt of the tosylhydrazone of an aldehyde): Vedejs, E.; Dolphin, J. M.; Stolle, W. T. *J. Am. Chem. Soc.* **1979**, *101*, 249.

(3) Silyl enol ethers (by treatment with LDA followed by an acyl silane): (a) Reich, H. J.; Rusek, J. J.; Olson, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 2225. (b) Reich, H. J.; Kelly, M. J.; Olson, R. E.; Holtan, R. C. *Tetrahedron* **1983**, *39*, 949.

(4) Trisubstituted and tetrasubstituted olefins (by treatment of suitably protected β-hydroxy nitriles with strong reducing agents such as $Li/NH_3$): (a) Marshall, J. A.; Karas, L. J. *Synth. Commun.* **1978**, *8*, 65. (b) Marshall, J. A.; Karas, L. J. *J. Am. Chem. Soc.* **1978**, *100*, 3615. (c) Marshall, J. A.; Karas, L. J.; Royce, R. D., Jr. *J. Org. Chem.* **1979**, *44*, 2994.

(5) For example, reduction to the primary amine with LAH followed by dimethylation with formaldehyde/formic acid followed by oxidation to the amine oxide with $H_2O_2$ followed by thermolysis, see: Cope, A. C.; Ross, D. L. *J. Am. Chem. Soc.* **1961**, *83*, 3854.

(6) Prepared by addition of ordinary quality *n*-$Bu_3SnCl$ (>95%, Alfa) to a solution of $ICH_2ZnI$ in THF (Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481) followed by flash chromatography[11] (eluant, hexane) to remove small amounts of *n*-$Bu_2Sn(CH_2I)_2$ (2.6%) and *n*-$Bu_3SnI$ (6.5%). Attempts to purify the crude product by distillation [129–130 °C/2.0 mm] resulted in enhancement of the level of *n*-$Bu_3SnI$ (identified by GC–MS); no *n*-$Bu_2$(*n*-Am)SnI could be detected, although the possibility that some might have been present cannot be rigorously excluded.

(7) (a) Wallace, T. J.; Hofmann, J. E.; Schriesheim, A. *J. Am. Chem. Soc.* **1963**, *85*, 2739. (b) Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1130. (c) Stirling, C. J. M. *Acc. Chem. Res.* **1979**, *12*, 198. (d) Britten-Kelly, M. R.; Willis, B. J.; Barton, D. H. R. *J. Org. Chem.* **1981**, *46*, 5027.

(8) Marshall, D. R.; Thomas, P. J.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, *1898*.

(9) (a) House, H. O.; Bare, T. M. *J. Org. Chem.* **1968**, *33*, 943. (b) Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* **1971**, *93*, 5286. (c) Cuvigny, T.; Normant, H. *Organomet. Chem. Synth.* **1971**, *1*, 237. (d) Watt, D. S. *Tetrahedron Lett.* **1974**, 707.

(10) Each product **2** and **4** was purified to a state of chromatographic and spectroscopic ($^1H$ NMR and $^{13}C$ NMR) homogeneity by flash chromatography[11] followed by efficient evaporation of the solvent; all are oils. The weights of the products after purification were used to calculate the yields listed in Table I.

(11) (a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. (b) Still, W. C. U.S. Patent 4 293 422, Oct 6, 1981.

(12) Alkylation of **1a** and **1c** are complete in less than 15 min at −78 °C; alkylation of **1b** requires stirring at 0 °C for 3 h.

(13) Somewhat longer reaction periods are required at lower temperatures. For example, at −78 °C, fragmentation of **4a** to **2a** (with 5.8 equiv of MeLi·LiBr) is only ~90% complete after 15 min.

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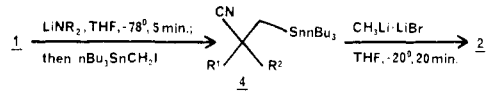
groups are present, fragmentation occurs in essentially quantitative yield.[10] Although in some cases minor amounts of some byproducts are formed, they are either much faster or slower eluting on silica gel. Thus, in all cases the methylene compounds can be isolated in homogeneous form by simple flash chromatography.[11]

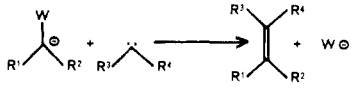
Isolation and purification of the intermediate β-tributylstannyl nitriles **4** can be omitted without sacrificing either yield or purity. For example, treatment of nitrile **1a** with 1.2 equiv of $LiN(C_6H_{11})_2$ (THF, −78 °C, 5 min)




(3)

followed by 1.00 equiv of $n$-$Bu_3SnCH_2I$ (−30 °C, 10 min) followed by 2.00 equiv of MeLi (−30 °C, 5 min) resulted in formation of olefin **4a** in 82.3% yield. This one-pot variant of the method is, therefore, recommended for preparative purposes.

In summary, it has been shown in this paper and in the first paper in this series[1] that $n$-$Bu_3SnCH_2I$ can be used for conversion of both nitriles and sulfones into methylene compounds. In subsequent papers in this series, other reagents for methylenation of these substrates and reagents for conversion of these substrates into more highly substituted types of olefins will be described. Thereby, it will be established that reaction of nitriles and sulfones with reagents that possess latent carbene character (eq 4) constitutes a general, useful method for synthesis of olefins.




(4)

## Experimental Section

**Alkylation of 1b by $n$-$Bu_3SnCH_2I$.** A solution of diisopropyl amine (0.10 mL, 0.715 mmol) in 1.0 mL of THF was cooled to 0 °C, treated with $n$-BuLi/hexane (0.39 mL of 1.55 M solution, 0.60 mmol), and then, after being stirred for 10 min, cooled to −78 °C. A solution of nitrile **1b** (99.3 mg, 0.426 mmol) in 1.3 mL of THF was then added dropwise over a period of 2 min and the reaction mixture stirred at −78 °C for 5 min. A solution of $n$-$Bu_3SnCH_2I$ (238.1 mg, 0.553 mmol) in 1.4 mL of THF was then added and the reaction mixture allowed to warm to 0 °C. The reaction mixture was then stirred at 0 °C for 3 h, poured into 40 mL of 3% NaOH, extracted with methylene chloride (2 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo to leave a light yellow oil (weight, 281.6 mg), consisting of a mixture of starting material ($R_f$ 0.18), β-tributylstannyl nitrile **4b** ($R_f$ 0.55), and $n$-$Bu_3SnCH_2I$ ($R_f$ 0.79) by TLC (silica gel; eluant, 15% EtOAc/cyclohexane). The mixture was then purified by flash chromatography[11] (eluant, 5% EtOAc/cyclohexane) to afford **4b** as a colorless oil. Yield: 207.5 mg (0.387 mmol, 90.9%).

**Fragmentation of 4b.** A solution of β-tributylstannyl nitrile **4b** (207.0 mg, 0.386 mmol) in 1.0 mL of THF was cooled to −20 °C and then treated with MeLi·LiBr/$Et_2O$ (0.60 mL of 1.4 M solution, 0.84 mmol). The reaction mixture was stirred at −20 °C for 20 min, then poured into 40 mL of 3% NaOH, extracted with methylene chloride (2 × 40 mL), dried ($MgSO_4$), and concentrated in vacuo to leave a light golden oil (weight, 195.5 mg), consisting of a mixture of **2b** ($R_f$ 0.37) and tin-containing byproducts by TLC (eluant, 10% EtOAc/cyclohexane). β-Tributylstannyl nitrile **4b** ($R_f$ 0.51) was absent. The mixture was then purified by flash chromatography (gradient elution, cyclohexane to 8% EtOAc/cyclohexane) to afford **2b** in pure form as a light yellow oil. Yield: 83.0 mg (0.377 mmol, 97.7%).

**Spectral and Analytical Data. Compound 4a:** $^1H$ NMR ($CDCl_3$) δ 0.8–1.0 (18 H, m), 1.0–1.8 (39 H, m); $^{13}C$ NMR ($CDCl_3$) δ 10.16 (t) , 13.63 (q), 14.11, (q), 22.72 (t), 23.35 (t), 25.60 (t), 27.38 (t), 28.22 (q), 29.13 (t), 29.51 (t), 29.68 (t), 31.96 (t), 35.97 (s), 43.34 (t), 126.04 (s); MS (CI), $m/e$ 526/528 (P + 1, 6.8%), 468/470 (27%), 289/291 (100%). Anal. Calcd for $C_{28}H_{57}N^{120}Sn$: $m/e$ 527.3512. Found: $m/e$ 527.3499.

**Compound 2a.** $^1H$ NMR ($CD_2Cl_2$) δ 0.88 (3 H, t, $J$ = 6.4 Hz), 1.28 (20 H, s), 1.69 (3 H, s), 2.00 (2 H, t, $J$ = 7.5 Hz), 4.65 (2 H, apparent br d, $J$ = 4.1 Hz); $^{13}C$ NMR ($CD_2Cl_2$) δ 14.49 (q), 22.68 (q), 23.34 (t), 28.34 (t), 30.01 (t), 30.04 (t), 30.22 (t), 30.33 (t), 30.36 (t), 32.61 (t), 38.47 (t), 109.91 (t), 146.78 (s); MS (EI), $m/e$ 210 (P, 33.3%), 56 (100%). Anal. Calcd for $C_{15}H_{30}$: $m/e$ 210.2347. Found: $m/e$ 210.2359.

**Compound 4b.** $^1H$ NMR ($CDCl_3$) δ 0.7–1.0 (18 H, m), 1.0–2.0 (20 H, m), 3.87 (3 H, s), 3.91 (3 H, s), 6.8–7.1 (3 H, m); $^{13}C$ NMR ($CDCl_3$) δ 9.72 (t), 13.62 (q), 13.79 (q), 22.58 (t), 24.66 (t), 27.35 (t), 28.13 (t), 29.02 (t), 45.64 (t), 46.04 (s), 56.00 (q) 109.26 (d), 111.39 (d), 117.85 (d), 124.28 (s), 134.10 (s), 148.50 (s), 149.17 (s); MS (EI), $m/e$ 536/538 (P + 1, 0.4%), 509/511 (9.0%), 478/480 (40%), 289/291 (58%), 221 (100%). Anal. Calcd for $C_{23}H_{28}NO_2{}^{120}Sn$ (P − $n$-Bu): $m/e$ 480.1923. Found: $m/e$ 480.1951.

**Compound 2b.** $^1H$ NMR ($CDCl_3$) δ 0.90 (3 H, t, $J$ = 7 Hz), 1.2–1.6 (6 H, m), 2.47 (2 H, t, $J$ = 7 Hz), 3.87 (3 H, s), 3.90 (3 H, s), 4.97 (1 H, d, $J$ = 1.5 Hz), 5.19 (1 H, d, $J$ = 1.5 Hz), 6.7–7.0 (3 H, m); $^{13}C$ NMR ($CDCl_3$) δ 13.91 (q), 22.46 (t), 30.63 (t), 35.21 (t), 55.91 (q), 109.82 (d), 110.76 (t), 111.07 (d), 118.53 (d), 134.51 (s), 148.37 (s), 148.67 (s), 148.79 (s); MS (EI), $m/e$ 220 (P, 56.9%), 178 (100%). Anal. Calcd for $C_{14}H_{20}O_2$: $m/e$ 220.1463. Found: $m/e$ 220.1469.

**Compound 4c.** $^1H$ NMR ($CDCl_3$) δ 0.90 (9 H, s), 0.8–2.1 (38 H, m); $^{13}C$ NMR ($CDCl_3$) δ 10.13 (t), 13.66 (q), 23.74 (t), 24.91 (t), 27.35 (t), 27.52 (q), 29.14 (t), 32.38 (s), 38.08 (s), 40.28 (t), 47.36 (d), 125.00 (s); MS (CI), $m/e$ 468/470 (P + 1, 100%), 410/412 (34%), 289/291 (75%), 139 (87%). Anal. Calcd for $C_{24}H_{47}N^{120}Sn$: $m/e$ 469.2729. Found: $m/e$ 469.2737.

**Compound 2c.** $^1H$ NMR ($CDCl_3$) δ 0.87 (9 H, s), 1.0–1.3 (4 H, m), 1.7–2.5 (5 H, m), 4.57 (2 H, t, $J$ = 1.5 Hz); $^{13}C$ NMR ($CD_2Cl_2$) δ 27.77 (q); 29.42 (t), 32.65 (s), 35.70 (t), 48.35 (d), 106.19 (t), 150.63 (s); MS (EI), $m/e$ 152 (P, 38.6%), 96 (96.5%), 57 (100%). Anal. Calcd for $C_{11}H_{20}$: $m/e$ 152.1565. Found: $m/e$ 152.1558.

**Compound 4d.** $^1H$ NMR ($CD_2Cl_2$) δ 0.90 (9 H, t, $J$ = 7.2 Hz), 1.0–2.5 (30 H, m), 1.30 (3 H, s), 1.50 (3 H, s), 3.57 (2 H, t, $J$ = 6.6 Hz), 4.13 (1 H, dt, $J$ = 7.0, 10.8 Hz), 4.46 (1 H, t, $J$ = 3.2 Hz), 5.48 (2 H, sym. m), 5.99 (1 H, d, $J$ = 3.3 Hz); $^{13}C$ NMR ($CD_2Cl_2$) δ 10.32 (t), 13.82 (q), 24.03 (t), 25.14 (t), 26.09 (q), 26.31 (q), 27.77 (t), 29.29 (t), 29.46 (t), 32.74 (t), 41.99 (t), 44.97 (t), 46.75 (d), 50.14 (s), 60.06 (d), 76.60 (d), 80.08 (d), 112.47 (s), 113.42 (d), 124.82 (s), 128.42 (d), 130.24 (d); MS (EI), $m/e$ 627/629 (P, 1.3%), 570/572 (100%), 289/291 (28.6%), 175/177 (66.6%). Anal. Calcd for $C_{30}H_{52}{}^{35}ClNO_3{}^{120}Sn$: $m/e$ 629.2656. Found: $m/e$ 629.2642.

**Compound 2d.** $^1H$ NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.52 (3 H, s), 1.6–2.6 (10 H, m), 3.53 (2 H, t, $J$ = 6 Hz), 4.06 (1 H, dt, $J$ = 6, 11 Hz), 4.48 (1 H, t, $J$ = 4 Hz), 5.03 (2 H, narrow m), 5.49 (2 H, m), 6.02 (1 H, d, $J$ = 3 Hz); $^{13}C$ NMR ($CD_2Cl_2$) δ 24.90 (t), 26.20 (q), 30.76 (t), 32.77 (t), 35.45 (t), 37.96 (d), 44.85 (t), 59.93 (d), 76.78 (d), 80.62 (d), 110.09 (t), 112.05 (s), 113.03 (d), 129.09 (d), 129.51 (d), 155.32 (s); MS (EI), $m/e$ 312/314 (P, 2.2%), 297/299 (100%) 195/197 (70.0%), 81 (74.7%). Anal. Calcd for $C_{17}H_{25}ClO_3$: $m/e$ 312.1492. Found: $m/e$ 312.1495.

**Registry No.** **1a**, 97415-95-7; **1b**, 97415-96-8; **1c**, 15619-19-9; **1d** (isomer 1), 97466-29-0; **1d** (isomer 2), 97466-30-3; **2a**, 52254-38-3; **2b**, 97415-97-9; **2c**, 13294-73-0; **2d**, 97466-31-4; **4a**, 97415-98-0; **4b**, 97415-99-1; **4c**, 97416-00-7; **4d** (isomer 1), 97430-84-7; **4d** (isomer 2), 97548-98-6; $Bu_3SnCH_2I$, 66222-29-5.

(14) This material is >95% isomerically homogeneous by $^{13}C$ NMR. We tentatively assign the stereochemistry to be 4β-*tert*-butyl-1α-[(tributylstannyl)methyl]-1β-cyano because **1c** undergoes alkylation with MeI to afford predominantly 4β-*tert*-butyl-1α-methyl-1β-cyanocyclohexane.[9a]

(15) The method of preparation of this compound will be described in a subsequent paper. The compound is a 83/17 mixture of C-9 epimers, both of which undergo the methylenation reaction. We tentatively assign the 9β stereochemistry to the major isomer on the basis of the fact that it is slower eluting on silica gel.

(16) In this run, the intermediate stannylmethylated nitrile **4d** was fragmented in situ. A sample isolated from another run was found to be >85.% isomerically homogeneous by $^{13}C$ NMR. We tentatively assign the stereochemistry at C-9 to be α-cyano-β-[(tributylstannyl)methyl] because 1-cyano-2-methylcyclohexane undergoes alkylation with MeI to afford predominantly 1β-cyano-1α,2β-dimethylcyclohexane, see: Ziegler, F. E.; Wender, P. A. *J. Am. Chem. Soc.* **1971**, *93*, 4318; *J. Org. Chem.* **1977**, *42*, 2001.