Synthesis of 2-Alkyl-2-methyl-3-butenenitriles by Alkylation of 2-Methyl-2-butenal *N,N*-Dimethylhydrazone

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Nitriles are important compounds because the cyano group can be transformed to many other key functional groups. They are usually prepared by nucleophilic substitution of alkyl halides with cyanide by rearrangement, oxidation, or elimination. In the case of elimination, there is the conversion of aldehyde *N,N*-dimethylhydrazones to nitriles with magnesium monoperoxyphthalate (MMPP).[1] The alkylation of aldehydes or ketones as *N,N*-dimethylhydrazones have been widely used to synthesize variety of organic compounds such as terpenes[2] and pheromones.[3] We have previously reported the alkylation of *N,N*-dimethylhydrazones of various α,*β*-unsaturated aldehydes gave α-alkylated *β*,*γ*-unsaturated aldehydes *N,N*-dimethylhydrazones with double bond migration.[4] We now wish to describe a novel synthesis of 2-alkyl-2-methyl-3-butenenitriles **4**, which have a flexible quaternary carbon atom at α-position, by the foregoing reaction sequence (Scheme 1).

2-Methyl-2-butenal *N,N*-dimethylhydrazone (**2**) was conveniently prepared from 2-methyl-2-butenal (**1**) and *N,N*-dimethylhydrazine using trifluoroacetic acid as a catalyst in 86% isolated yield.[4] After deprotonation with lithium diisopropylamide (LDA) in THF, the resulting azaenolate was trapped with various alkyl halides at −5 °C. After workup and purification by flash column chromatography, the dimethylhydrazones **3**, which were substituted with two different alkyl groups and a vinyl group at α-position, were obtained in moderate yields (53−68%) (method A). When hexamethylphosphorus triamide (HMPA) was used as cosolvent (method B), the yields of **3** increased to 72−90% (Table 1).

From dimethylhydrazones **3**, 2-alkyl-2-methyl-3-butenenitriles **4** were obtained by Cope-type elimination with MMPP at −5 °C in good yields (83−94 %) except **4b** (Table 2). Nitrile **4b** was only identified by MS.[5] To our knowledge, no synthesis of these α,α-dialkyl-α-vinylcarbonitriles has been reported.

In summary, it is noted that α-quaternary nitriles **4** were obtained from 2-methyl-2-butenal *N,N*-dimethylhydrazone (**2**) in good overall yield (66−85%). We are now studying the application of this reaction to enantioselective synthesis.

Scheme 1

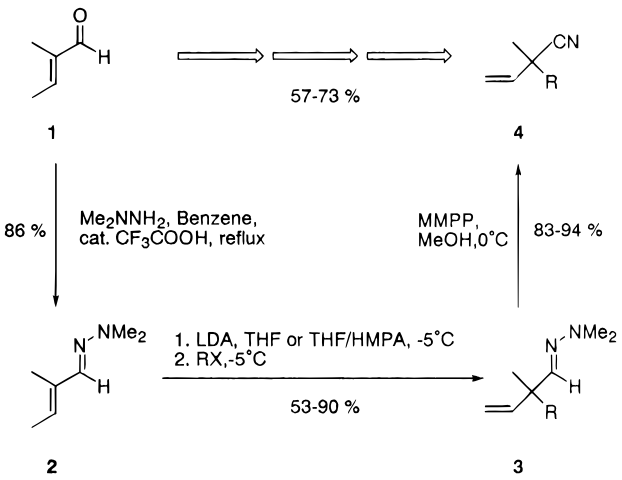
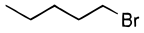
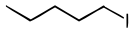
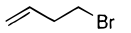
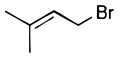
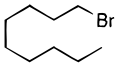
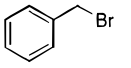


Table 1. Alkylation of 2-Methyl-2-butenal *N,N*-Dimethylhydrazone (2)

Entry	RX	Product **3**	Method	Yield / %[a]
1		**3a**	A	68
2			A	64
			B	90
3		**3b**	A	68
			B	72
4		**3c**	A	66
			B	79
5		**3d**	A	53
			B	86
6		**3e**	A	54
			B	87

[a] Isolated yields.

Experimental Section

General. ^{1}H-NMR spectra were taken (at 400 MHz) in $CDCl_3$ solvent and recorded in parts per million (ppm, *δ*) downfield from internal tetramethylsilane (Me_4Si). Column chromatography was performed using silica gel 60 (230−400 mesh) and thin-layer chromatography (TLC) was performed on silica gel 60 plate F_{254}. THF was dried and deoxygenated by distillation from potassium−benzophenone under argon atmosphere just before use. Benzene was purified by distillation over $CaCl_2$. Diisopropylamine was dried by distillation from potassium hydroxide. *n*-Butyllithium as a *ca.* 1.6 M hexane solution was titrated with *sec*-butyl alcohol using *o*-phenanthroline as an indicator just before use. The other organic compounds were commercial products of the highest available purity.

2-Methyl-2-butenal *N,N*-dimethylhydrazone (2).[4] In a flask equipped with a trap to remove water, the mixture of 2-methyl-2-butenal (100 mmol, 9.65 mL), *N,N*-dimethylhydrazine (120 mmol, 9.12 mL), trifluoroacetic acid (0.05 mL), and benzene (40 mL) was added. The mixture was heated under reflux for 5 h, and then cooled to room temperature. The reaction mixture was diluted with ether and water. The organic layer was washed with brine and dried over $MgSO_4$. The filtrate was concentrated with a rotary evaporator. The residue was purified by distillation under reduced pressure: oil (86%); bp 84 °C/40 hPa; IR (neat) 2860 (NMe_2), 1570 (C=N) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.77 (d, *J* = 6.7 Hz, 3H), 1.82 (d, *J* = 0.9 Hz, 3H), 2.80 (s, 6H), 5.64 (dd, *J* = 6.7 Hz and 13.7 Hz, 1H), 7.07 (s, 1H); MS *m*/*z* 126 (M^+, 57).

General Procedure for the Preparation of 2-Alkyl-2-methyl-3-butenal *N,N*-Dimethylhydrazone 3a−e. To a THF (20 mL) (method A) or THF/HMPA (15 mL/3.48 mL (20.0 mmol))

(1) (a) Fernández, R.; Gasch, C.; Lassaletta, J.; Llera, J.; Vázquez, J. *Tetrahedron Lett.* **1993**, *34*, 141. (b) Enders, D.; Backhaus, D.; Runsink, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2098.

(2) (a) Yamashita, M.; Matsumiya, K.; Tanabe, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 407. (b) Yamashita, M.; Matsumiya, K.; Tanji, K.; Suemitsu, R. *J. Jpn. Oil Chem. Soc.* **1986**, *35*, 1041. (c) Yamashita, M.; Matsumiya, K.; Tanabe, M.; Suemitsu, R. *J. Jpn. Oil Chem. Soc.* **1988**, *37*, 245.

(3) Yamashita, M.; Matsumiya, K.; Murakami, M.; Suemitsu, R. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3368.

(4) Yamashita, M.; Matsumiya, M.; Nakano, K. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1759.

(5) MS *m*/*z* (rel intensity): 135 (M^+, 4), 120 (3), 108 (3), 81 (22), 68 (20), 55 (100).

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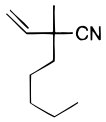
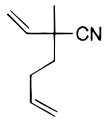
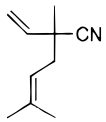
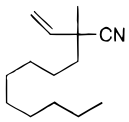
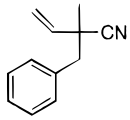
Table 2. Cope-type Elimination of *N,N*-Dimethylhydrazone 3

Entry	Hydrazone 3	Nitrile 4		Yield / %[a]
1	**3a**		**4a**	94
2	**3b**		**4b**	–
3	**3c**		**4c**	83
4	**3d**		**4d**	89
5	**3e**		**4e**	85

[a] Isolated yields.

(method B) solution of diisopropylamine (10.2 mmol, 1.40 mL) in a dried reaction flask was added dropwise with stirring *n*-butyllithium in hexane (10.3 mmol, 6.64 mL) at −5 °C under argon atmosphere. After 0.5 h, 2-methyl-2-butenal *N,N*-dimethylhydrazone (**2**) (10.0 mmol, 1.26 g) was added. After 1 h alkyl halide (10.3 mmol) was added, and stirring was continued for 20 h at room temperature. The reaction mixture was quenched with water and diluted with ether. The organic layer was washed with water and brine and dried over $MgSO_4$. The crude product **3** was purified by column chromatography.

2-Methyl-2-vinylheptanal *N,N*-dimethylhydrazone (3a): oil (68% from 1-bromopentane and 64% 1-iodopentane (method A) or 90% 1-iodopentane (method B)); IR (neat) 1630 (C=N) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.87 (t, J = 7.0 Hz, 3H), 1.15 (s, 3H), 1.24−1.34 (m, 6H), 1.46−1.50 (m, 2H), 2.72 (s, 6H), 4.97 (d, J = 17.4 Hz *trans*, 1H), 5.01 (d, J = 10.7 Hz *cis*, 1H), 5.89 (dd, J = 10.7 Hz and 17.4 Hz, 1H), 6.55 (s, 1H); MS m/z 196 (M^+, 5). Anal. Calcd for $C_{12}H_{22}N_2$: C, 73.41; H, 12.32. Found: C, 73.13; H, 12.33.

2-Methyl-2-vinyl-5-hexenal *N,N*-dimethylhydrazone 3b: oil (68% (method A) or 72% (method B)); IR (neat) 1640 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.17 (s, 3H), 1.58−1.62 (m, 2H), 1.99−2.05 (m, 2H), 2.73 (s, 6H), 4.91−5.05 (m, 4H), 5.77−5.92 (m, 2H), 6.52 (s, 1H); MS m/z 180 (M^+, 8). Anal. Calcd for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18. Found: C, 73.11; H, 11.39.

2,5-Dimethyl-2-vinyl-4-hexenal *N,N*-dimethylhydrazone (3c): oil (66% (method A) or 79% (method B)); IR (neat) (C=N) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.60 (d, J = 4.6 Hz, 3H), 1.70 (d, J = 0.9 Hz *cis*, 3H), 2.20−2.20 (m, 2H), 2.72 (s, 6H), 4.95−5.03 (m, 2H), 5.11−5.15 (m, 1H,), 5.91 (dd, J = 10.7 Hz and 17.7 Hz, 1H) and 6.55 (s, 1H); MS m/z 194 (M^+, 0.4).

2-Methyl-2-vinylundecanal *N,N*-dimethylhydrazone (3d): oil (53% (method A) or 86% (method B)); IR (neat) 1645 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.7 Hz , 3H), 1.14 (s, 3H), 1.25 (br, 14H), 1.46−1.50 (m, 2H), 2.72 (s, 6H), 4.97 (dd, J = 1.2 Hz and 17.7 Hz *trans*, 1H), 5.01 (dd, J = 1.2 Hz and 10.7 Hz *cis*, 1H), 5.88 (dd, J = 10.7 Hz and 17.7 Hz, 1H), and 6.57 (s, 1H); MS m/z 252 (M^+, 1). Anal. Calcd for $C_{16}H_{32}N_2$: C, 76.13; H, 12.78. Found: C, 76.41; H, 13.07.

2-Benzyl-2-methyl-3-butenal *N,N*-dimethylhydrazone (3e):[4] oil (54% (method A) or 87% (method B)); IR (neat) 1635 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (s, 3H), 2.73 (s, 6H), 2.84 (d, J = 5.1 Hz, 2H), 4.92 (d, J = 17.7 Hz, 1H), 5.03 (d, J = 10.7 Hz *cis*, 1H), 5.97 (dd, J = 10.7 Hz and 17.7 Hz, 1H), 6.55 (s, 1H), 7.12−7.33 (m, 5H); MS m/z 216 (M^+, 1). Anal. Calcd for $C_{14}H_{20}N_2$: C, 77.73; H, 9.32. Found: C, 78.03; H, 9.43.

General Procedure for the Preparation of 2-Alkyl-2-methyl-3-butenenitrile 4a−e. To a solution of MMPP (0.870 mmol, 0.430 g) in methanol (4.0 mL) was added a solution of dimethylhydrazone **3** (0.380 mmol) in methanol (1.0 mL) at 0 °C, and the solution was stirred for 1 h at the temperature. The reaction mixture was diluted with CH_2Cl_2 and water. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. The crude product **4** was purified by TLC.

2-Methyl-2-vinylheptanenitrile (4a): oil (94%); IR (neat) 2255 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.0 Hz, 3H), 1.26−1.67 (m, 8H), 1.42 (s, 3H), 5.21 (d, J = 10.1 Hz *cis*, 1H), 5.45 (d, J = 17.0 Hz *trans*, 1H) and 5.59 (dd, J = 10.1 Hz and 17.0 Hz, 1H); MS m/z 151 (M^+, 0.1). Anal. Calcd for $C_{10}H_{17}N$: C, 79.41; H, 11.33. Found: C, 79.19; H, 11.26.

2,5-Dimethyl-2-vinyl-4-hexenenitrile (4c): oil (83%); IR (neat) 2250 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.41 (s, 3H), 1.64 (s, 3H), 1.76 (d, J = 1.2 Hz *trans*, 3H), 2.27−2.38 (m, 2H), 5.17−5.21 (m, 1H), 5.22 (d, J = 10.4 Hz *cis*, 1H), 5.44 (d, J = 17.1 Hz *trans*, 1H), 5.65 (dd, J = 10.4 Hz and 17.1 Hz, 1H); MS m/z 149 (M^+, 0.5). Anal. Calcd for $C_{10}H_{15}N$: C, 80.48; H, 10.13. Found: C, 80.30; H, 10.21.

2-Methyl-2-vinylundecanenitrile (4d): oil (89%); IR (neat) 2265 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, J = 6.7 Hz , 3H), 1.26 (br, 14H), 1.42 (s, 3H), 1.43−1.68 (m, 2H), 5.21 (d, J = 10.4 Hz *cis*, 1H), 5.44 (d, J =17.1 Hz *trans*, 1H), 5.68 (dd, J = 10.4 Hz and 17.1 Hz, 1H); MS m/z 217 (M^+, 1). Anal. Calcd for $C_{14}H_{25}N$: C, 81.09; H, 12.15. Found: C, 80.58; H, 12.10.

2-Benzyl-2-methyl-3-butenenitrile (4e): oil (85%); IR (neat) 2255 (CN) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43 (s, 3H), 2.88 (d, J = 13.4 Hz, 1H), 2.94 (d, J = 13.4 Hz, 1H), 5.21 (d, J = 10.0 Hz *cis*, 1H), 5.38 (d, J = 17.1 Hz *trans*, 1H), 5.69 (dd, J = 10.0 Hz and 17.1 Hz, 1H), 7.24−7.33 (m, 5H); MS m/z 171 (M^+, 3). Anal. Calcd for $C_{12}H_{13}N$: C, 84.16; H, 7.66. Found: C, 84.10; H, 7.70.

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