EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

Title: One-pot Preparation of C1-Homologated Aliphatic Nitriles from Aldehydes via Wittig Reaction under Metal Cyanide-free Conditions

Authors: Hideo Togo and Masatoshi Ezawa

To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201700277

Link to VoR: http://dx.doi.org/10.1002/ejoc.201700277

Supported by
ACES Asian Chemical Editorial Society

WILEY-VCH

FULL PAPER

DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

One-pot Preparation of C_1-Homologated Aliphatic Nitriles from Aldehydes via Wittig Reaction under Metal Cyanide-free Conditions

Masatoshi Ezawa [a] and Hideo Togo[a] *

Keywords: Aldehyde / Molecular Iodine / Wittig reaction / Nitrile / C_1-Homologation

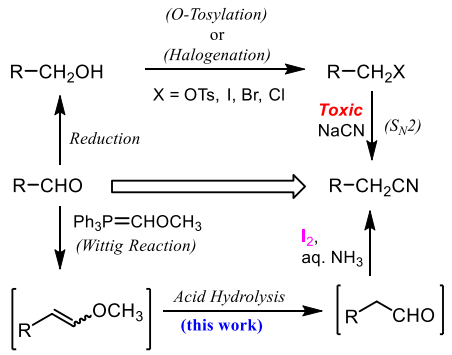
C_1-Homologated aliphatic nitriles could be obtained smoothly in one pot by the treatment of aromatic and aliphatic aldehydes with (methoxymethyl)triphenylphosphonium ylide and then hydrolysis of the formed methyl vinyl ether with *p*-TsOH, followed by the reaction with molecular iodine and aq. ammonia under metal cyanide-free conditions. Neopentyl-type nitriles, which could not be obtained by the conventional method using neopentyl-type alcohol *O*-Ts and metal cyanide, could be obtained smoothly by the treatment of neopentyl-type aldehydes using the present method.

[a] Graduate School of Science, Chiba University, Yayoi-cho 1-33, Inage-ku, Chiba 263-8522 Japan
Fax: 81-43-290-2792
E-mail: togo@faculty.chiba-u.jp
Homepage: http://reaction-2.chem.chiba-u.jp/index.html
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.xxxxxxxxx.

Introduction

Nitriles are one of the most important functional groups because they can be smoothly transformed to amides, carboxylic acids, amines, aldehydes, ketones, and nitrogen-containing heteroaromatics, such as tetrazoles and oxazoles, which have generally potent biological activity.[1] In this regard, nitriles have been used as synthetic precursors for agrochemicals, pharmaceuticals, and functional materials. The most typical procedure for the preparation of aliphatic nitriles is the dehydration of primary aliphatic amides with $SOCl_2$, TsCl/Py, P_2O_5, $POCl_3$, $COCl_2$, $(EtO)_3P/I_2$, or Ph_3P/CCl_4 *etc.*, (while retaining the number of carbon atoms) and the reaction of alkyl *O*-tosylates or halides with metal cyanides (C_1 homologation).[2] However, in the latter method, highly toxic metal cyanides are required (Scheme 1). Here, as part of our studies of molecular iodine for organic

Scheme 1. Preparation of C_1-Homologated Nitriles

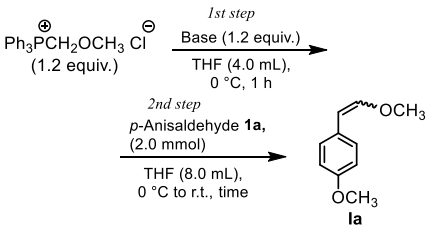


synthesis,[3] we would like to report the one-pot preparation of C_1-homologated aliphatic nitriles from aldehydes through the Wittig reaction with (methoxymethyl)triphenylphosphonium chloride and NaHMDS, the subsequent hydrolysis of the formed methyl vinyl ether with *p*-TsOH, and the final treatment of the formed aldehydes with molecular iodine and aq. ammonia.

Results and Discussion

First, the screening of the best reaction conditions for the Wittig reaction with (methoxymethyl)triphenylphosphonium chloride and bases, such as *t*BuOK, *t*BuONa, *t*BuOLi, $NaNH_2$, NaH, *n*BuLi, and NaHMDS (sodium bis(trimethylsilyl)amide), at 0 °C in THF, followed by the reaction with *p*-anisaldehyde **1a** at 0 °C was carried out, as shown in Table 1. NaHMDS showed the best reactivity to give methyl 2-(*p*-methoxyphenyl)vinyl ether **Ia** in 92% yield (entries 8 and 9). Then, the screening of the best reaction conditions for the hydrolysis of methyl

Table 1. Wittig Reaction of *p*-Anisaldehyde **1a**

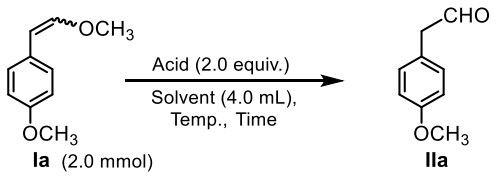


Entry	Base	Time	Yield (%)
1	*t*BuOK	3	48
2	*t*BuOK	24	14
3	*t*BuONa	3	22
4	*t*BuOLi	3	46
5	$NaNH_2$	3	0
6	NaH	3	<1
7	*n*BuLi	3	50
8[a]	NaHMDS	2	92
9[a,b]	NaHMDS	2	92

[a] Reaction time was 0.5 h at 1st step.
[b] Reaction was carried out at -78 °C at 1st step and -78 °C to r.t. at 2nd step.

2-(*p*-methoxyphenyl)vinyl ether **Ia** with acids, such as 18% aq. HCl, 2% aq. H_2SO_4, *p*-TsOH•H_2O, and TMSCl / NaI, at room temperature, 40 °C, and 0 °C was performed, as shown in Table 2. It was found that the treatment of **Ia** with *p*-TsOH•H_2O and TMSCl / NaI gave *p*-methoxyphenylacetaldehyde **IIa** in 78% and

Table 2. Hydrolysis of Methyl 2-(*p*-Methoxyphenyl)vinyl Ether **Ia**



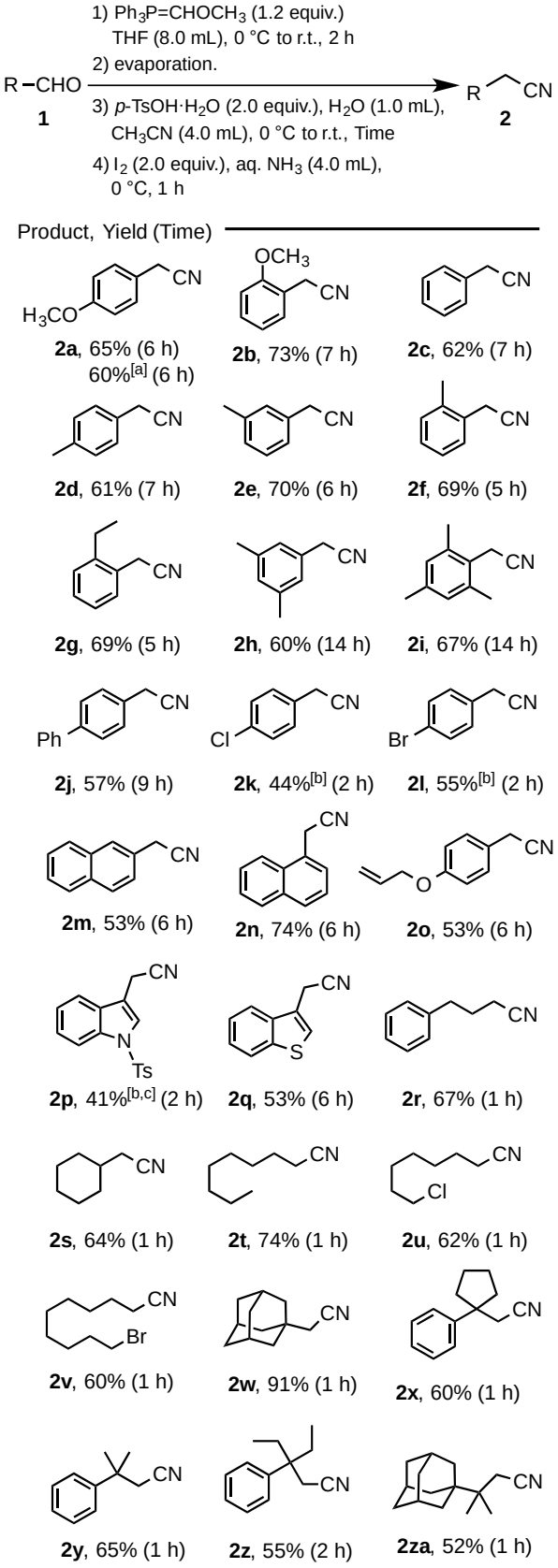
Entry	Acid	Solvent	Temp. (°C)	Time (h)	yield (%)
1[a]	18% HCl	THF	r.t.	24	27
2[a]	2% H_2SO_4	THF	40	24	6
3[b]	*p*-TsOH•H_2O	THF	40	24	25
4[b,c]	*p*-TsOH•H_2O	CH_3CN	r.t.	20	43
5[b,c]	*p*-TsOH•H_2O	CH_2Cl_2	r.t.	20	6
6[c]	*p*-TsOH•H_2O	H_2O	r.t.	20	19
7[b,c]	*p*-TsOH•H_2O	CH_3CN	0	20	15
8[b,c]	*p*-TsOH•H_2O	CH_3CN	r.t.	6	78
9[b,c]	NaI + TMSCl	CH_3CN	r.t.	2	75

[a] Acid (1.0 mL) was used. [b] H_2O (1.0 mL) was used.
[c] Solvent (8.0 mL) was used.

75% yields, respectively, (entries 8, 9). It is known that once aldehydes are formed, they react smoothly with molecular iodine in aq. ammonia at room temperature to form the corresponding nitriles in good yields.[3,4]

Based on those results, the one-pot preparation of C_1-homologated nitriles **2** from aromatic aldehydes **1** was carried out, which involved the treatment with (methoxymethyl)triphenylphosphonium ylide at 0 °C to room temperature, subsequent hydrolysis of the formed methyl vinyl ether with *p*-TsOH•H_2O at 0 °C to room temperature, and a final treatment with molecular iodine and aq. ammonia at 0 °C for one hour, as shown in Table 3. *p*-Methoxybenzaldehyde **1a**, *o*-methoxybenzaldehyde **1b**, benzaldehyde **1c**, *p*-tolualdehyde **1d**, *m*-tolualdehyde **1e**, *o*-tolualdehyde **1f**, *o*-ethylbenzaldehyde **1g**, 3,5-dimethylbenzaldehyde **1h**, 2,4,6-trimethylbenzaldehyde **1i**, *p*-phenylbenzaldehyde **1j**, *p*-chlorobenzaldehyde **1k**, *p*-bromobenzaldehyde **1l**, β-naphthaldehyde **1p**, and α-naphthaldehyde **1n** were smoothly converted into the C_1-homologated nitriles **2a**~**2n** in good to moderate yields, respectively. When the reaction was carried out using 10 mmol of *p*-anisaldehyde **1a** under the same procedure and conditions, *p*-methoxyphenylacetonitrile **2a** was obtained in 60% yield, as shown in Table 3. The same successive treatment of *p*-allyloxybenzaldehyde **1o** bearing an olefinic group under the same procedure and conditions provided the corresponding nitrile **2o** while retaining the olefinic group in moderate yield. Similarly, the same successive treatment of *N*-tosylindole-3-carboxaldehyde **1p** and benzothiophene-3-carboxaldehyde **1q** under the same procedure and conditions gave the corresponding nitriles **2p** and **2q** in moderate yields, respectively. Then, aliphatic aldehydes, such as 3-phenylpropionaldehyde **1r**, cyclohexanecarboxaldehyde **1s**, octanal **1t**, 8-chlorooctanal **1u**, and 10-bromodecanal **1v**, were also treated with (methoxymethyl)triphenylphosphonium ylide, and

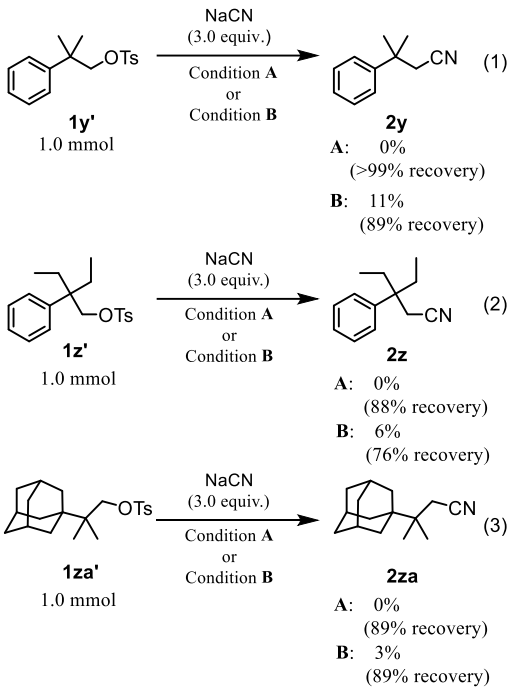
Table 3. Preparation of C_1-Homologated Nitriles



[a] Compound **1a** (10 mmol) was used.
[b] TMSCl (2.0 equiv.) and NaI (2.0 equiv.) were used instead of *p*-TsOH·H_2O.
[c] CH_3CN (8.0 mL) was used.

this was followed by the hydrolysis of the formed methyl vinyl ethers with *p*-TsOH•H_2O and the final treatment with molecular iodine and aq. ammonia to give the corresponding aldehydes **2r**~**2v** in good to moderate yields, respectively. Moreover, neopentyl-type nitriles, such as **2w**, **2x**, **2y**, **2z**, and **2za**, were also obtained in moderate to good yields, respectively, by the same successive treatment of 1-adamantanecarboxaldehyde **1w**, α-phenyl-α,α-tetramethyleneacetaldehyde **1x**, α-phenyl-α,α-dimethylacetaldehyde **1y**, α-phenyl-α,α-diethylacetaldehyde **1z**, and α-(1-adamantyl)-α,α-dimethylacetaldehyde **1za**. Generally,

Scheme 2. Cyanation of Neopentyl-typed *O*-Tosylates with NaCN



Condition **A**: CH_3CN (3.0 mL), reflux, 20 h
Condition **B**: DMF (3.0 mL), 80 °C, 20 h

the S_N2 reaction of neopentyl-type *O*-tosylates and halides with metal cyanide does not occur smoothly (Scheme 1). Practically, the nucleophilic cyanation of 2-phenyl-2,2-(dimethyl)ethyl *O*-tosylate **1y'**, 2-phenyl-2,2-(diethyl)ethyl *O*-tosylate **1z'**, and 2-(1'-adamantyl)-2,2-(dimethyl)ethyl *O*-tosylate **1za'** with NaCN in refluxing acetonitrile for 20 h did not generate the corresponding C_1-homologated nitriles **2y**, **2z**, and **2za** at all, respectively, as shown in Scheme 2 (Condition **A**).

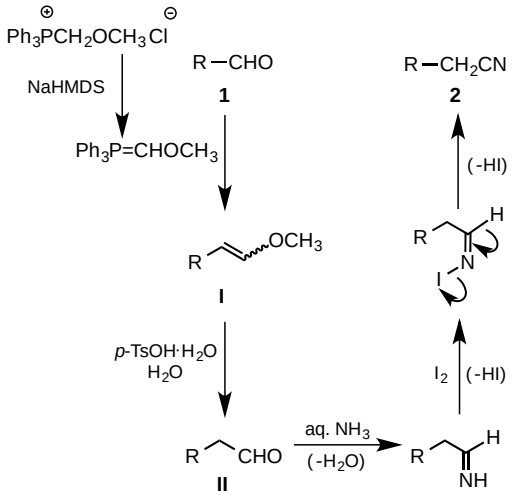
Even if the nucleophilic cyanation of the *O*-tosylates **1y'**, **1z'**, and **1za'** with NaCN was carried out in DMF, an excellent aprotic polar solvent, at 80 °C for 20 h, the corresponding nitriles **2y**, **2z**, and **2za** were obtained in only 11%, 6%, and 3% yields, respectively, together with the recovery of the starting *O*-tosylates (Condition **B**).

The reaction pathway of the present one-pot transformation of aldehydes to the corresponding C_1-homologated nitriles is shown in Scheme 3. Thus, aldehyde reacts with (methoxymethyl)triphenylphosphonium ylide to form methyl vinyl ether **I** which is further hydrolyzed to C_1-homologated aldehyde **II**. Once aldehyde **II** is formed, it smoothly reacts with ammonia to form imine. Imine smoothly reacts with molecular iodine to form *N*-iodoimine and smooth HI elimination occurs to give C_1-homologated nitrile **2**.

Conclusions

The treatment of aromatic aldehydes and aliphatic aldehydes with (methoxymethyl)triphenylphosphonium ylide, followed by the hydrolysis of the formed methyl vinyl ethers with *p*-TsOH•H_2O and finally the reaction with molecular iodine and aq. ammonia gave the corresponding C_1-homologated nitriles smoothly. The present reaction is useful method for the preparation of C_1-homologated nitriles without using metal cyanides, and is effective for the preparation of neopentyl-type nitriles.

Scheme 3. Reaction Pathway for One-pot Transformation of Aldehydes to C_1-Homologated Nitriles



Experimental Section

General. ^1H NMR and ^{13}C NMR spectra were obtained with JEOL-JNM-ECX400, JEOL-JNM-ECS400, and JEOL-JNM-ECA500 spectrometers. Chemical shifts are expressed in ppm downfield from TMS in δ units. Mass spectra were recorded on Thermo LTQ Orbitrap XL spectrometers. IR spectra were measured with a JASCO FT/IR-4100 spectrometer. Melting points were determined with a Yamato Melting Point Apparatus Model MP-21. Silica gel 60F_{254} (Merck) was used for TLC and Silica gel 60 (Kanto Kagaku Co.) was used for short column chromatography.

Typical Procedure for Preparation of C_1-Homologated Nitriles from Aldehydes: A solution of sodium bis(trimethylsilyl)amide (1.12 M in THF, 2.143 mL, 2.4 mmol) was added dropwise to (methoxymethyl)triphenylphosphonium chloride (848.2 mg, 2.4 mmol) in THF (4 mL) at 0 °C, and the mixture was stirred at 0 °C for 0.5 h. A solution of *p*-anisaldehyde **1a** (272.3 mg, 2.0 mmol) in THF (4 mL) was added at 0 °C, and the obtained mixture was stirred at room temperature for 2 h. The solvent was removed, and H_2O (1 mL) and CH_3CN (4 mL) were added. Then, *p*-TsOH•H_2O (760.9 mg, 4.0 mmol) was added at 0 °C, and the obtained mixture was stirred at room temperature for 6 h. This was followed by the addition of aq. ammonia (concentration: 28.0-30.0%, 4 mL) and I_2 (4.0 mmol, 1015.2 mg) at 0 °C, and the mixture was stirred for 1 h at 0 °C. The reaction mixture was quenched by adding sat. aq. Na_2SO_3 (10 mL) and extracted with AcOEt (20 mL × 3). Then, the organic layer was washed with brine (20 mL) and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by short column chromatography on silica gel (hexane: AcOEt = 9:1) to afford 4-methoxyphenylacetonitrile **2a** in 65% yield (191.3 mg).

***p*-Methoxyphenylacetonitrile (2a)**: (commercially available): Yield: 191.3 mg (65%); colorless oil; IR (neat): $\tilde{\nu}$ = 1248, 2250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.69 (s, 2H), 3.81 (s, 3H), 6.90 (d, *J* = 8.8 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.8, 55.3, 114.5, 118.2, 121.7, 129.0, 159.3 ppm.

***o*-Methoxyphenylacetonitrile (2b)**: (commercially available): Yield: 214.4 mg (73%); white sold: Mp 68 °C; IR (neat): $\tilde{\nu}$ = 1248, 2251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.69 (s, 2H), 3.87 (s, 3H), 6.89 (d, *J* = 8.4 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 7.30-7.37 (m, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.6, 55.4, 110.4, 118.0, 118.5, 120.7, 129.1, 129.5, 156.7 ppm.

Phenylacetonitrile (2c): (commercially available): Yield: 144.1 mg (62%); colorless oil; IR (neat): $\tilde{\nu}$ = 2251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.76 (s, 2H), 7.32-7.41 (m, 5H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.5, 117.8, 127.8, 127.9, 129.0, 129.8 ppm.

***p*-Methylphenylacetonitrile (2d)**: (commercially available): Yield: 160.6 mg (61%); colorless oil; IR (neat): $\tilde{\nu}$ = 2250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 2H), 3.71 (s, 2H), 7.17-7.22 (m, 4H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.0, 23.1, 118.0, 126.7, 127.7, 129.7, 137.7 ppm.

***m*-Methylphenylacetonitrile (2e)**: (commercially available): Yield: 184.4 mg (70%); colorless oil; IR (neat): $\tilde{\nu}$ = 2250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.71 (s, 2H), 7.11-7.15 (m, 3H), 7.26 (t, *J* = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.3, 23.5, 118.0, 124.9, 128.6, 128.7, 129.0, 129.7, 139.0 ppm.

***o*-Methylphenylacetonitrile (2f)**: (commercially available): Yield: 198.9 mg (76%); colorless oil; IR (neat): $\tilde{\nu}$ = 2250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.67 (s, 2H), 7.20-7.28 (m, 3H), 7.36 (d, *J* = 7.7 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.1, 21.7, 117.5, 126.6, 128.2, 128.3, 128.4, 130.5, 135.9 ppm.

***o*-Ethylphenylacetonitrile (2g)**: Yield: 199.5 mg (69%); colorless oil; IR (neat): $\tilde{\nu}$ = 2249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.5 Hz, 3H), 2.67 (q, *J* = 7.5Hz, 2H), 3.71 (s, 2H), 7.21-7.26 (m, 2H), 7.29-7.33 (m, 1H), 7.38 (d, *J* = 7.7 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.3, 21.3, 25.6, 117.9, 126.6, 127.7, 128.6, 128.7, 128.8, 141.7 ppm; HRMS (APCI): calcd. for $C_{10}H_{12}N$ $[M+H]^+$ 146.0964, found 146.0963.

3,5-Dimethylphenylacetonitrile (2h): Yield: 174.4 mg (60%); colorless oil; IR (neat): $\tilde{\nu}$ = 2249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 6H), 3.67 (s, 2H), 6.94 (s, 2H), 6.96 (s, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.1, 23.3, 118.1, 125.6, 129.5, 129.6, 138.7 ppm; HRMS (APCI): calcd. for $C_{10}H_{12}N$ $[M+H]^+$ 146.0964, found 146.0968.

Mesitylacetonitrile (2i): (commercially available): Yield: 212.0 mg (67%); white solid: Mp 79 °C; IR (neat): $\tilde{\nu}$ = 2243 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.27 (s, 3H), 2.36 (s, 6H), 3.61 (s, 2H), 6.90 (s, 2H) ppm; ^{13}C-NMR (100 MHz, CDCl3): δ = 17.3, 19.9, 20.8, 117.4, 124.3, 129.3, 136.4, 137.8 ppm.

4-Biphenylacetonitrile (2j): (commercially available): Yield: 220.7 mg (57%); yellow solid: Mp 93 °C; IR (neat): $\tilde{\nu}$ = 2252 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 2H), 7.35-7.47 (m, 5H), 7.57-7.62 (m, 4H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.3, 117.8, 127.0, 127.6, 127.8, 128.3, 128.8, 128.9, 140.1, 141.1 ppm.

***p*-Chlorophenylacetonitrile (2k)**: (commercially available): Yield: 133.7 mg (44 %); colorless oil; IR (neat): $\tilde{\nu}$ = 2251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.74 (s, 2H), 7.27 (d, *J* = 9.1 Hz, 2H), 7.37 (d, *J* = 9.1 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.9, 117.4, 128.3, 129.2, 133.9 ppm.

***p*-Bromophenylacetonitrile (2l)**: (commercially available): Yield: 216.8 mg (55%); white solid: Mp 49 °C; IR (neat): $\tilde{\nu}$ = 2249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.71 (s, 2H), 7.22 (d, *J* = 8.5 Hz, 2H), 7.52 (d, *J* = 8.4 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.2, 117.3, 122.1, 128.8, 129.6, 132.3 ppm.

2-Naphthylacetonitrile (2m): (commercially available): Yield: 177.2 mg (53%); yellow solid: Mp 84 °C; IR (neat): $\tilde{\nu}$ = 2251 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 2H), 7.39 (dd, *J* = 8.6, 1.8 Hz, 1H), 7.49-4.55 (m, 2H), 7.83-7.88 (m, 4H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.8, 117.8, 125.4, 126.5, 126.7, 126.8, 127.2, 127.6, 127.7, 129.0, 132.7, 133.3 ppm.

1-Naphthylacetonitrile (2n): Yield: 247.8 mg (74%); colorless oil; IR (neat): $\tilde{\nu}$ = 2252 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.15 (s, 2H), 7.46-7.50 (m, 1H), 7.55-7.64 (m, 3H), 7.87 (d, *J* = 8.1, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 7.6 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.6, 117.7, 122.3, 125.4, 125.7, 126.3, 126.4, 127.0, 129.0, 129.1, 130.7, 133.6 ppm; HRMS (ESI): calcd. for $C_{12}H_8N$ $[M-H]^+$ 166.0651, found 166.0656.

***p*-Allyloxyphenylacetonitrile (2o)**: Yield: 184.3 mg (53%); colorless oil; IR (neat): $\tilde{\nu}$ = 1244, 1612, 2250 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 2H), 4.54 (dt, *J* = 5.2, 1.6 Hz, 2H), 5.30 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.42 (dq, *J* = 17.2, 1.6 Hz, 1H), 6.00-610 (m, 1H), 6.91 (d, *J* = 8.6 Hz, 2H) 7.23 (d, *J* = 8.8 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 22.7, 68.8, 115.2, 117.8, 118.2, 121.8, 129.0, 132.9, 158.2 ppm; HRMS (APCI): calcd. for $C_{11}H_{11}ON$ $[M]^+$ 173.0835, found 173.0833.

1-Tosylindole-3-acetonitrile (2p): Yield: 254.5 mg (41%); white solid: Mp 160 °C; IR (neat): $\tilde{\nu}$ = 2258 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 3.76 (s, 2H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.39 (t, *J* = 7.4 Hz, 1H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.62 (s, 1H), 7.79 (d, *J* = 8.5 Hz, 2H), 8.02 (d, *J* = 8.3 Hz, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.4, 21.6, 111.3, 113.9, 116.7, 118.8, 123.6, 124.4, 125.5, 126.9, 128.7, 130.0, 134.9, 135.1, 145.3 ppm; HRMS (ESI): calcd. for $C_{17}H_{14}O_2N_2SNa$ $[M+Na]^+$ 333.0668, found 333.0666.

Benzo[b]thiophen-3-acetonitrile (2q): Yield: 184.7 mg (53%); white solid: Mp 65 °C; IR (neat): $\tilde{\nu}$ = 2253 cm^{-1}; 1H-NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 2H), 7.43 (td, *J* = 7.3, 1.6 Hz, 1H), 7.46 (td, *J* = 7.0, 1.4 Hz, 1H), 7.50 (s, 1H), 7.70-7.72 (m, 1H), 7.89-7.91 (m, 1H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.7, 116.9, 120.1, 123.1, 123.8, 124.6, 124.9, 125.0, 136.9, 140.4 ppm; HRMS (APCI): calcd. for $C_{10}H_7NS$ $[M]^+$ 173.0294, found 173.0293.

4-Phenylbutyronitrile (2r): (commercially available): Yield: 193.4 mg (67%); colorless oil; IR (neat): $\tilde{\nu}$ = 2246 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.99 (quin, *J* = 7.2 Hz, 2H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.78 (t, *J* = 7.4 Hz), 7.19 (d, *J* = 7.0 Hz, 2H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.0 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 16.4, 26.9, 34.3, 119.5, 126.5, 128.4, 128.6, 139.7 ppm.

Cyclohexylacetonitrile (2s): Yield: 153.3 mg (64%); colorless oil; IR (neat): $\tilde{\nu}$ = 2245 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.03-1.33 (m, 5H), 1.61-1.71 (m, 2H), 1.74-1.79 (m, 2H), 1.81-1.85 (m, 2H), 2.24 (d, *J* = 6.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 24.7, 25.6, 25.7, 32.4, 34.7, 118.9 ppm; HRMS (APCI): calcd. for $C_8H_{14}N$ $[M+H]^+$ 124.1121, found 124.1122.

Nonanenitrile (2t): (commercially available): Yield: 206.9 mg (74%); colorless oil; IR (neat): $\tilde{\nu}$ = 2246 cm^{-1}; 1H-NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.0 Hz, 3H), 1.21-1.33 (m, 8H), 1.41-1.48 (m, 2H), 1.66 (quin, *J* = 7.2 Hz, 2H), 2.34 (t, *J* = 7.2 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.0, 17.1, 22.6, 25.3, 28.6, 28.7, 28.9, 31.7, 119.9 ppm.

9-Chlorononanenitrile (2u): Yield: 214.7 mg (62%); colorless oil; IR (neat): $\tilde{\nu}$ = 2246 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.32-1.39 (m, 4H), 1.41-1.50 (m, 4H), 1.66 (quin, *J* = 7.2 Hz, 2H), 1.77 (quin, *J* = 6.7 Hz, 2H), 2.35 (t, *J* = 7.2 Hz, 2H), 3.54 (t, *J* = 6.7 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.1, 25.3, 26.7, 28.5, 28.5, 28.6, 32.5, 45.0, 119.8 ppm; HRMS (APCI): calcd. for $C_9H_{17}NCl$ $[M+H]^+$ 174.1044, found 174.1045.

11-Bromoundecanenitrile (2v): Yield: 295.7 mg (60%); colorless oil; IR (neat): $\tilde{\nu}$ = 2246 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.25-1.35 (m, 8H), 1.39-1.46 (m, 4H), 1.66 (quin, *J* = 7.3 Hz, 2H), 1.86 (quin, *J* = 7.3 Hz, 2H), 2.34 (t, *J* = 7.3 Hz, 2H), 3.41 (t, *J* = 7.0 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 17.0, 25.2, 28.0, 28.4, 28.5, 28.6, 29.0, 29.1, 32.6, 33.9, 119.7 ppm; HRMS (APCI): calcd. for $C_{11}H_{21}NBr$ $[M+H]^+$ 246.0852, found 246.0850.

1-Adamantylacetonitrile (2w): Yield: 317.8 mg (91%); white solid: Mp 76 °C; IR (neat): $\tilde{\nu}$ = 2237 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.62-1.75 (m, 12H), 2.01-2.06 (br, 3H), 2.10 (s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.3, 32.1, 32.3, 36.3, 41.7, 117.9 ppm; HRMS (APCI): calcd. for $C_{12}H_{18}N$ $[M+H]^+$ 176.1434, found 176.1435.

β-Phenyl-β,β-tetramethylenepropionitrile (2x): Yield: 223.1 mg (60%); colorless oil; IR (neat): $\tilde{\nu}$ = 2247 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.78-1.81 (m, 4H), 2.01-2.09 (m, 4H), 2.58 (s, 2H), 7.22-7.29 (m, 1H), 7.33-7.38 (m, 4H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 23.0, 30.3, 37.1, 49.1, 118.3, 126.3, 126.7, 128.4, 145.5 ppm; HRMS (APCI): calcd. for $C_{13}H_{16}N$ $[M+H]^+$ 186.1277, found 186.1281.

β,β-Dimethyl-β-phenylpropionitrile (2y): Yield: 207.6 mg (65%); colorless oil; IR (neat): $\tilde{\nu}$ = 2249 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 6H), 2.63 (s, 2H), 7.24-7.30 (m, 1H), 7.34-7.40 (m, 4H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.3, 32.7, 37.0, 118.2, 125.2, 126.9, 128.6, 145.8 ppm; HRMS (APCI): calcd. for $C_{11}H_{14}N$ [M+H]+ 160.1120, found 160.1119.

β,β-Diethyl-β-phenylpropionitrile (2z): Yield: 206.8 mg (55%); colorless oil; IR (neat): $\tilde{\nu}$ = 2246 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.72 (t, *J* = 7.3 Hz, 6H), 1.89 (q, *J* = 7.4 Hz, 4H), 2.74 (s, 2H), 7.21-7.26 (m, 3H), 7.35 (t, *J* = 7.9 Hz, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 8.2, 25.0, 31.4, 43.7, 118.2, 126.1, 126.5, 128.5, 142.8 ppm; HRMS (APCI): calcd. for $C_{13}H_{18}N$ $[M+H]^+$ 188.1434, found 188.1432.

β□Adamantyl-β,β-Dimethylpropionitrile (2za): Yield: 226.7 mg (52%); white solid: Mp 78 °C; IR (neat): $\tilde{\nu}$ = 2235 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 (s, 6H), 1.56-1.71 (m, 12H), 2.01 (br, 3H), 2.23 (s, 2H) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 21.6, 25.8, 28.5, 36.1, 36.6, 36.8, 37.8, 120.0 ppm; HRMS (APCI): calcd. for $C_{15}H_{24}N$ [M+H]+ 218.1903, found 218.1904.

Supporting Information: (see footnote on the first page of this article): Copies of the ^{1}H NMR and ^{13}C NMR spectra of all nitrile products **2a**~**2za**.

Acknowledgments

Financial support in the form of a Grant-in–Aid for Scientific Research (No. 15K05418) from the Ministry of Education, Culture, Sports, Science, and Technology in Japan and Iodine Research Project in Chiba University is gratefully acknowledged.

[1] Books: a) M. North, *Comprehensive Organic Functional Group Transformation* (Eds.: A. R. Katritzky, O. Meth-Cohn, C. W. Rees), Pergamon, Oxford, UK, **1995**; b) S.-I. Murahashi, *Synthesis from Nitriles with Retention of the Cyano Group*, in: *Science of Synthesis* vol. 19, p. 345–402, Thieme, Stuttgart, Germany, **2004**; c) S. J. Collier, P. Langer, *Application of Nitriles as Reagents for Organic Synthesis with Loss of the Nitrile Functionality*, in: *Science of Synthesis* vol. 19, p. 403–425, Thieme, Stuttgart, Germany, **2004**. 556; Reviews: e) P. Anbarasan, T. Schareina, M. Beller, *Chem. Soc. Rev.*, **2011**, *40*, 5049-5067. Typical papers: e) J. B. Medwid, R. Paul, J. S. Baker, J. A. Brockman, M. T. Du, W. A. Hallett, J. W. Hanifin, R. A. Hardy Jr., M. E. Tarrant,L. W. Torley, S. Wrenn, *J. Med. Chem*. **1990**, *33*, 1230-2341; f) D. G. Diana, D. Cutcliffe, D. L. Volkots, J. P. Mallamo, T. R. Bailey, N. Vescio, R. C. Oglesby, T. J. Nitz, J. Wetzel, V. Giranda, D. C. Pevear, F. J. Dutko, *J. Med. Chem*. **1993**, *36*, 3240-3250; g) S. J. Wittenberger, B. G. Donner, *J. Org. Chem*. **1993**, *58*, 4139-4141; h) M. Chihiro, H. Nagamoto, I. Takemura, K. Kitano, H. Komatsu, K. Sekiguchi, F. Tabusa, T. Mori. M. Tominaga, Y. Yabuuchi, *J. Med. Chem*. **1995**, *38*, 353-358; i) I. K. Khanna, R. M. Weier, Y. Yu, X. D. Xu, F. J. Koszyk, P. W. Collins, C. M. Koboldt, A. W. Veenhuizen, W. E. Perkins, J. J. Casler, J. L. Masferrer, Y. Y. Zhang, S. A. Gregory, K. Seibert, P. C. Isakson, *J. Med. Chem*. **1997**, *40*, 1634-1647. (j) P. Wipf, F. Yokokawa, *Tetrahedron Lett*. **1998**, *39*, 2223-2226; i) X. Gu, X. Wan, B. Jiang, *Bioorg. Med. Chem. Lett*. **1999**, *9*, 569-572; k) P. C. Ducept, S. P. Marsden, *Synlett* **2000**, 692-694; l) J. Shie, J. Fang, *J. Org. Chem*. **2003**, *68*, 1158-1160; m) G. Wem, J. Jin, L. Zhang, Y.

Luo. P. Lu. Y. Wang, *Tetrahedron Lett*., **2014**, *55*, 1271-1280.

[2] *Nitriles, Carboxylic Acids, and Derivatives*, in *Comprehensive Organic Transformation*, Ed.; R. C. Larock, 2bd Ed., Wiley-VCH, New York, **1999**, p.1621-1996.

[3] Reviews: a) H. Togo, S. Iida, *Synlett*. **2006**, 2159-2175; b) H. Togo, *J. Synth. Org. Chem*. **2008**, *66*, 652-663; Recent papers: c) S. Ushijima, H. Togo, *Synlett*. **2010**, 1067-1070; d) R. Ohmura, M. Takahata, H. Togo, *Tetrahedron Lett*. **2010**, *51*, 4378-4371; e) Y. Suzuki, Y. Ishiwata, K. Moriyama, H. Togo, *Tetrahedron Lett*. **2010**, *51*, 5950-5953; f) S. Takahashi, H. Togo, *Heterocycles* **2010**, *82*, 593-601; g) S. Ushijima, H. Togo, *Synlett* **2010**, 1562-1566; h) S. Ushijima, H. Togo, *Synlett*, **2010**, 1067-1070; i) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 958-964; j) Y. Suzuki, T. Yoshino, K. Moriyama, H. Togo, *Tetrahedron*. **2011**, *67*, 3809-3814; k) H. Baba, K. Moriyama, H. Togo, *Tetrahedron Lett*. **2011**, *52*, 4303-4307; l) Y. Suzuki, K. Moriyama, H. Togo, *Tetrahedron* **2011**, *67*, 7956-7962; m) S. Ushijima, S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 1436-1442; n) H. Baba, K. Moriyama, H. Togo, *Synlett.* **2012**, *23*, 1175-1180; o) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 4701-4709; p) S. Ushijima, K. Moriyama, H. Togo, *Tetrahedron*, **2012**, *68*, 4588-4595; q) S. Dohi, K. Moriyama, H. Togo, *Tetrahedron* **2012**, *68*, 6557-6564; r) H. Kikui, K. Moriyama, H. Togo, *Synthesis*, **2013**, 791-797; s) Y. Nakai, K. Moriyama, H. Togo, *Eur. J. Org. Chem*., **2014**, 6077-6083; t) T. Tamura, K. Moriyama, H. Togo, *Eur. J. Org. Chem*., **2015**, 2023-2029; u) S. Imai, H. Kikui, K. Moriyama, H. Togo, *Tetrahedron*, **2015**, *71*, 5267-5274; v) S. Shimokawa, Y. Kawagoe, K. Moriyama, H. Togo, *Org. Lett.*, **2016**, *18*, 784-787.

[4] S. Guo, G. Wan, S. Sun, Y. Jiang, J. Yu, J. Cheng, *Chem. Commun*., **2015**, *51*, 5085-5088.

…

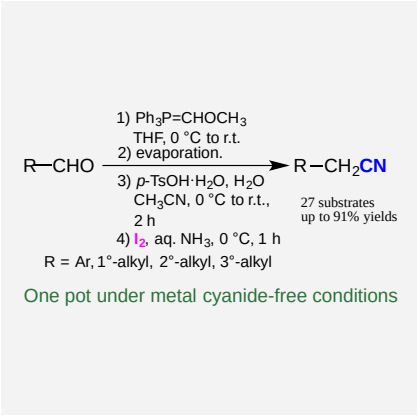
Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

10.1002/ejoc.201700277

Layout 1:

((Key Topic))

C_1-Homologated nitriles were smoothly obtained through the successive treatment of aldehydes with the Wittig reaction, hydrolysis of the methyl vinyl ethers formed, and the reaction of the formed aldehydes with molecular iodine in aq. ammonia. By using this method, various aliphatic aldehydes including neopentyl-type nitriles could be obtained, smoothly.



Masatoshi Ezawa, Hideo Togo*

Page No. – Page No.

One-pot Preparation of C_1-Homologated Aliphatic Nitriles from Aldehydes via Wittig Reaction under Metal Cyanide-free Conditions

Keywords: (Aldehyde / Molecular Iodine / Wittig reaction/ Nitrile / C_1-Homologation)

10.1002/ejoc.201700277

Supporting Information

((Please insert the Supporting Information here))