

Unsaturated Nitriles: Optimized Coupling of the Chloroprene Grignard Reagent¹ with ω -Bromonitriles

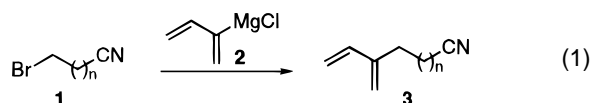
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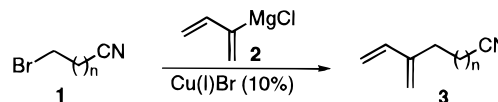
The Diels–Alder reaction is one of the most powerful reactions in organic synthesis.² Efficient access to Diels–Alder precursors has stimulated several expedient diene syntheses for both type I and type II Diels–Alder reactions.³ A particularly efficient synthesis of dienes for type II⁴ intramolecular Diels–Alder (IMDA) reactions⁵ relies on coupling electrophiles with 1-methylene-2-propenylmagnesium chloride (**2**)⁶—the so-called chloroprene Grignard reagent.¹

In connection with our interest in unsaturated nitriles,⁷ we envisaged an efficient entry into type II IMDA precursors by coupling **2** with ω -bromonitriles **1** (eq 1). This coupling reaction is known to tolerate electrophiles containing ester and nitrile groups but has only once been used to assemble dienes containing these functionalities.⁸



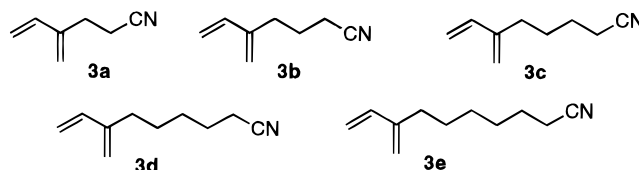
Our initial attempts to couple **1e** ($n = 5$) and **2** with Li_2CuCl_4 were not encouraging. The coupling product **3e** was obtained in low yield along with a significant amount of the elimination product, 6-heptenenitrile. We examined several copper catalysts and found that $\text{Cu}^{\text{I}}\text{Br}$ gave the highest yield of **3e**, although a considerable amount of 6-heptenenitrile was also obtained. Formation of 6-heptenenitrile requires a base that can conceptually arise by a reaction between the bromonitrile and the fine dispersion of magnesium metal that is present in the chloroprene Grignard solution. These magnesium particulates are easily removed from the chloroprene Grignard solution by centrifuging⁹ which provides a clear solution of **2** that cleanly couples with **1e** in the presence

Table 1. Coupling of Chloroprene Grignard **2** with ω -Bromonitriles **1**

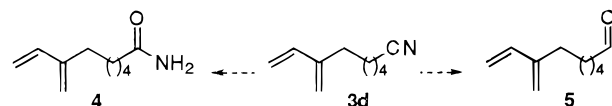


entry	bromonitrile	series (n)	unsaturated nitrile	yield (%)
1	1a	1	3a	98
2	1b	2	3b	76
3	1c	3	3c	74
4	1d	4	3d	73
5	1e	5	3e	71

of $\text{Cu}^{\text{I}}\text{Br}$ (71%, Table I). This optimized procedure is quite general, providing a range of unsaturated nitriles in good yield. The synthesis of **3a** is particularly striking since the proximal nitrile group increases the likelihood of elimination,¹⁰ and yet the yield of the unsaturated nitrile **3a** is excellent (98%) on a 2-g scale!



The reaction is noteworthy in affording good yields without competitive addition to the nitrile group and conceptually shortens routes to precursors for type II IMDA reactions. For example, hydrolysis¹¹ or reduction¹² of **3d** would afford **4**¹³ and **5**,^{4a} respectively, in two steps rather than the previously required six-step sequence.



In conclusion, the coupling of **2** with ω -bromonitriles affords good yields of unsaturated nitriles that are not directly available by other chloroprene-based coupling procedures.¹⁴

Experimental Section

General experimental details can be found in ref 7b. ¹H NMR spectra were recorded at 300 MHz, while ¹³C NMR spectra were recorded at 75 MHz. Solutions of **2** in THF were prepared using ZnI_2 as the initiator rather than ZnCl_2 as described.⁶

General Procedure. A THF solution of **2** (0.3–0.4 M, 1.1 equiv) was slowly added to a cold (0 °C) THF solution containing $\text{Cu}^{\text{I}}\text{Br}$ (10 mol %) and the bromonitrile (1.0 equiv). After the addition the solution was allowed to warm to room temperature and then stirred for a further 16 h. The resultant mixture was opened to the atmosphere, and saturated, aqueous NH_4Cl was added. Once the resultant solution became blue, the mixture was extracted with EtOAc and the combined extracts were dried and then concentrated.

4-Methylene-5-hexenenitrile (3a). The general procedure was employed with 54 mL of a THF solution of **2** (0.45 M, 24.3 mmol), $\text{Cu}^{\text{I}}\text{Br}$ (344 mg, 1.67 mmol), and 3-bromopropanenitrile

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 (8) The reported yield for coupling **2** with **1b** ($n = 2$) is 45%; see: Nunomoto, S.; Kawakami, Y.; Yamashita, Y. *J. Org. Chem.* **1983**, *48*, 1912.
 (9) Large volumes of **2** (≥ 1 L) suitable for coupling are conveniently prepared by allowing the magnesium to settle out from a tall, thin container over a period of 3–4 days. The Grignard reagent is stable at room temperature for several weeks.¹

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(3.0 g, 22.4 mmol). The crude product was purified by vacuum distillation to afford 2.34 g (98%) of **3a** as an oil: IR (film) 3090, 2927, 2246, 1598 cm^{-1} ; ^1H NMR δ 2.50–2.61 (m, 4H), 5.11–5.22 (m, 4H), 6.37 (dd, $J = 17.7, 10.8$ Hz, 1H); ^{13}C NMR δ 16.3, 27.3, 113.9, 117.7, 119.2, 137.4, 142.4; MS m/e 108 (M + H).

5-Methylene-6-heptenenitrile (3b). The general procedure was employed with 3.7 mL of a THF solution of **2** (0.40 M, 1.48 mmol), Cu^1Br (20.7 mg, 0.1 mmol), and 3-bromopropanenitrile (200 mg, 1.35 mmol). The crude product was purified by radial chromatography (1 mm plate, 1:9 EtOAc:hexanes) to afford 124.0 mg (76%) of **3b** as an oil: IR (film) 3088, 2939, 2246, 1595 cm^{-1} ; ^1H NMR δ 1.84 (quintet, $J = 7.3$ Hz, 2H), 2.34 (t, $J = 7.1$ Hz, 2H), 2.37 (br t, $J = 7$ Hz, 2H), 5.02–5.11 (m, 3H), 5.21 (d, $J = 17.7$ Hz, 1H), 6.34 (dd, $J = 17.7, 10.8$ Hz, 1H); ^{13}C NMR δ 16.5, 23.7, 30.1, 113.8, 117.0, 119.5, 138.0, 143.9; MS m/e 122 (M + H).

6-Methylene-7-heptenenitrile (3c). The general procedure was employed with 3.3 mL of a THF solution of **2** (0.40 M, 1.32 mmol), Cu^1Br (19.0 mg, 0.12 mmol), and 4-bromopentanenitrile (200 mg, 1.23 mmol). The crude product was purified by radial chromatography (1 mm plate, 1:9 EtOAc:hexanes) to afford 124.0 mg (74%) of **3c** as an oil: IR (film) 3084, 2931, 2238, 1596 cm^{-1} ; ^1H NMR δ 1.61–1.72 (m, 4H), 2.25 (br t, $J = 6$ Hz, 2H), 2.35 (br t, $J = 7$ Hz, 2H), 4.98–5.09 (m, 3H), 5.20 (d, $J = 17.6$ Hz, 1H), 6.35 (dd, $J = 17.6, 10.8$ Hz, 1H); ^{13}C NMR δ 16.9, 25.0, 26.9, 30.4, 113.3, 116.0, 119.5, 138.4, 145.1; MS m/e 134 (M – H).

7-Methylene-8-octenenitrile (3d). The general procedure was employed with 5.7 mL of a THF solution of **2** (0.40 M, 2.28 mmol), Cu^1Br (31.0 mg, 0.15 mmol), and 4-bromohexanenitrile (356 mg, 2.02 mmol). The crude product was purified by radial chromatography (2 mm plate, 1:9 EtOAc:hexanes) to afford 220.0

mg (73%) of **3d** as an oil: IR (film) 3089, 2937, 2245, 1595 cm^{-1} ; ^1H NMR δ 1.45–1.55 (m, 4H), 1.68 (br quintet, $J = 7$ Hz, 2H), 2.23 (br t, $J = 7$ Hz, 2H), 2.34 (t, $J = 7.1$ Hz, 2H), 4.97 (s, 1H), 5.01 (s, 1H), 5.05 (br d, $J = 11$ Hz, 1H), 5.20 (br d, $J = 18$ Hz, 1H), 6.36 (dd, $J = 17.7, 10.8$ Hz, 1H); ^{13}C NMR δ 17.1, 25.3, 27.2, 28.5, 31.0, 113.2, 115.8, 119.7, 138.7, 145.8; MS m/e 148 (M – H).

8-Methylene-9-decenenitrile (3e). The general procedure was employed with 3.5 mL of a THF solution of **2** (0.50 M, 3.5 mmol), Cu^1Br (21.0 mg, 0.10 mmol), and 4-bromoheptanenitrile (279 mg, 1.47 mmol). The crude product was purified by radial chromatography (2 mm plate, 1:9 EtOAc:hexanes) to afford 170.0 mg (71%) of **3e** as an oil: IR (film) 3089, 2936, 2860, 2244, 1595 cm^{-1} ; ^1H NMR δ 1.33–1.57 (m, 6H), 1.67 (br quintet, $J = 7$ Hz, 2H), 2.21 (br t, $J = 7$ Hz, 2H), 2.34 (t, $J = 7.1$ Hz, 2H), 4.97 (s, 2H), 5.01 (s, 1H), 5.05 (br d, $J = 11$ Hz, 1H), 5.21 (d, $J = 17.6$ Hz, 1H), 6.36 (dd, $J = 17.6, 10.8$ Hz, 1H); ^{13}C NMR δ 17.1, 25.3, 27.8, 28.5, 28.6, 31.2, 113.2, 115.7, 119.8, 138.9, 146.2; MS m/e 164 (M + H).

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Supporting Information Available: ^1H and ^{13}C NMR spectra of all new compounds (10 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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