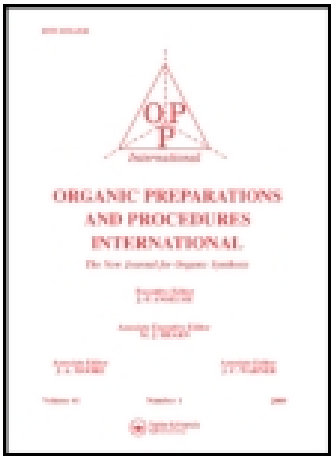

Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

Industrially Viable Preparation of 2,2-Diisopropylpropionitrile, a Key Intermediate of Physiological Coolant WS-23 (2-Isopropyl-N,2,3-trimethylbutyramide)

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Published online: 27 May 2014.

To cite this article: Ramadas Chavakula, Narayana Rao Mutyala & Srinivasa Rao Chennupati (2014) Industrially Viable Preparation of 2,2-Diisopropylpropionitrile, a Key Intermediate of Physiological Coolant WS-23 (2-Isopropyl-N,2,3-trimethylbutyramide), Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 46:3, 277-279, DOI: 10.1080/00304948.2014.903147

To link to this article: http://dx.doi.org/10.1080/00304948.2014.903147

Organic Preparations and Procedures International, 46:277–279, 2014

ISSN: 0030-4948 print / 1945-5453 online
DOI: 10.1080/00304948.2014.903147

OPPI BRIEF

Industrially Viable Preparation of 2,2-Diisopropylpropionitrile, a Key Intermediate of Physiological Coolant WS-23 (2-Isopropyl-*N*,2,3-trimethylbutyramide)

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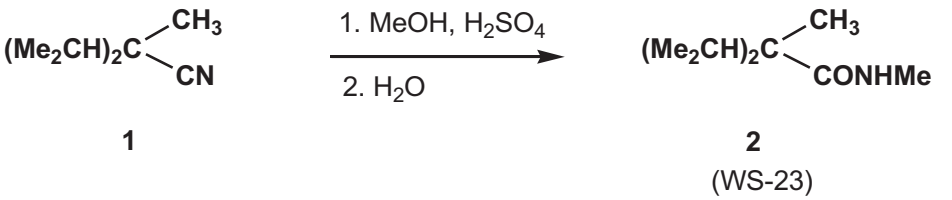
Readily synthesized monosubstituted aliphatic acyclic carboxamides have a physiological cooling effect similar to that obtained with menthol. Among the monosubstituted aliphatic acyclic carboxamides, WS-23[1] (2-isopropyl-N,2,3-trimethylbutyramide, (**2**) is a nearly odorless white powder, characterized by a high cooling capacity with no side effects such as burning, stinging, or tingling sensations. It has been used as a coolant in medicinal preparations, oral care products, foodstuffs, drinks, tobacco products, cosmetics, toiletries, and confectionery products. It has been synthesized[2] by the Ritter reaction of 2,2-diisopropylpropionitrile (**1**) with methanol in the presence of acid (*Scheme 1*). Although 2,2-diisopropylpropionitrile (**1**) is commercially available, it is very expensive, hence, it was our endeavor to develop an eco-friendly methodology for its preparation in good yields.



1 **2** (WS-23)

Scheme 1

Submitted by August16, 2013.
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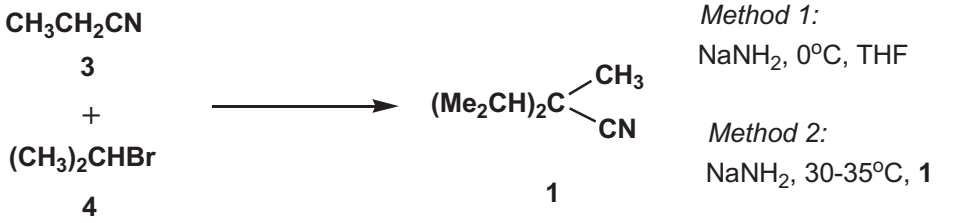
Previous methods[3,4] used to synthesize **1,** by dialkylation of propionitrile with isopropyl bromide, require long reaction times at −60°C to −65°C and involve tedious work-up procedures. In addition, the solvents used in these methods such as liquid ammonia and THF are toxic and not eco-friendly. This communication reports a simple, efficient, economical single-pot synthesis for the large-scale preparation of 2,2-diisopropylpropionitrile (**1**). *Method 1* (*Scheme 2*) is of significance because it does not require any cryogenic conditions, expensive toxic reagents, or harsh reaction conditions and is simpler than other strategies. In our approach, dialkylation of propionitrile with isopropyl bromide in the presence of a sodamide at 0°C–5°C in a minimum amount of tetrahydro-furan afforded **1** in 90% yield. *Method 2* (*Scheme 2*), utilizing the desired product as solvent (either prepared by *Method 1* or purchased) for the diisopropylation of propionitrile is carried out at 30°C–35°C, avoids the use of expensive THF and the product is easier to isolate i (92%).



Scheme 2

Experimental Section

All chemicals were reagent grade and available commercially. 2,2-Diisopropylpropionitrile (**1**) may be purchased from Chem-Impex International, Inc. (935 Dillon Drive, Wood Dale, IL, 60191).^{1}H NMR spectra were recorded on a Bruker AVANCE 400 MHz spectrometer, using $CDCl_3$ as solvent and TMS as internal standard. Infrared spectra were obtained on a Perkin-Elmer Spectrum 100 FT-IR spectrophotometer. Electrospray ionization mass spectroscopy was performed using an ion trap mass spectrometer (Model 6310 Agilent). Gas chromatographic analysis was carried out using a Shimadzu GC-2010 Plus instrument equipped with an Alltech poly(dimethoxysiloxane) 30 m capillary DB-1 column.

Preparation of 2,2-Diisopropylpropionitrile (1) (Method 1)

Sodamide (270.0 g, 6.92 mol) and THF (540 ml) were mixed at 30°C–35°C, and the mixture was cooled to 0°C–5°C (under nitrogen). Then a mixture of propionitrile (**3**) (150.0 g, 2.72 mol) and isopropyl bromide (**4**) (705.0 g, 5.73 mol) was added to the reaction mixture over 3–4 h at 0°C–5°C under mechanical stirring. The reaction mixture was stirred for an additional 6 h at 0°C–5°C, completion of reaction being monitored by gas chromatography (GC). The reaction mixture was cooled to 0°C, and chilled water (600 ml) was added over 60 min. After the addition was complete, the solution was stirred at 30°C–35°C for 30 min. The mixture was concentrated under atmospheric pressure below 95°C to remove most of the tetrahydrofuran. The top organic layer was washed with water (100 ml), 10% aqueous

NaCl and dried over solid sodium sulfate and distilled *in vacuo to* give **1** (341.0 g, 90%) as a colorless oil, bp. 110°C–120°C/600 mmHg, *lit.*[3] 186°C–187°C/760 mmHg.^{1}H NMR: δ 0.96 (6H, d), 1.05 (6H, d), 1.17 (3H, s), 1.95 (2H, m).

Preparation of 2,2-Diisopropylpropionitrile (1) (Method 2)

Sodamide (270.0 g, 6.92 mol) and **1** (240.0 g) were mixed at 30°C–35°C, and the mixture was stirred at 30°C–35°C (under nitrogen) for 30 min. Then a mixture of propionitrile (**3**) (150.0 g, 2.72 mol) and isopropyl bromide (**4**) (705.0 g, 5.73 mol) was added to the reaction mixture over 3–4 h at 30°C–35°C. The temperature of reaction mixture was then maintained at 30°C–35°C for 6 h; completion of reaction was monitored by gas chromatography (GC). The reaction mixture was cooled to 0°C, and chilled water (600 ml) was added over 60 min. After the addition was complete, the solution was stirred at 30°C–35°C for 30 min. The top organic layer was washed with water (100 ml) and with 10% aqueous NaCl. The organic layer was dried over anhydrous sodium sulfate and distilled *in vacuo* to give **1** (588.0 g, 92%) as a colorless oil, bp. 110°C–120°C/600 mmHg.

Acknowledgement

The authors are thankful to Tyche Industries Limited for financial assistance.

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