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A CONVENIENT SYNTHESIS OF 3,3-DIMETHYLBUTYRALDEHYDE

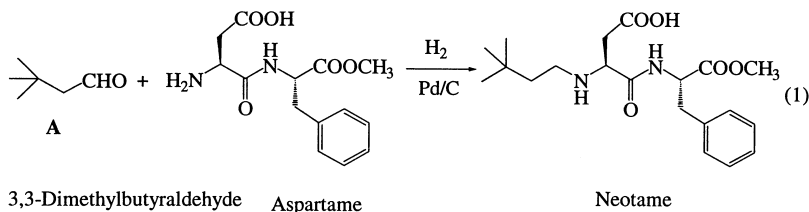
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ABSTRACT

3,3-Dimethylbutyraldehyde is synthesized from the reaction of 1-chloro-3,3-dimethylbutane with DMSO in presence of a base and substoichiometric amounts of MX (M = Na, K; X = Br, I).

Neotame (N-[N-(3,3-dimethylbutyl)-L- α -aspartyl]-L-phenylalanine 1-methyl ester) is the next generation of non-nutritive sweetener from the NutraSweet Company. Neotame has a sweetness intensity about 8000 times that of sucrose and 30–40 times that of aspartame and is expected to have a wide range of applications in food categories.¹ A petition was submitted in December 1998 to the US FDA for the general use of neotame as a sweetener. Neotame is synthesized by reductive alkylation of aspartame with 3,3-dimethylbutyraldehyde (**A**) (Eq. 1).²



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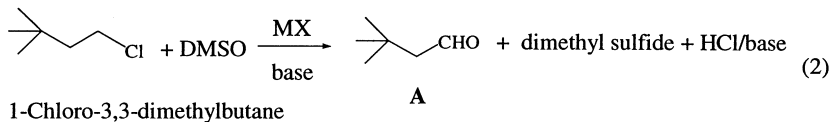
In the process development of neotame, we have required large quantities of high quality **A**. Although **A** can be purchased from various vendors, it is advantageous from a supply standpoint to prepare **A** economically to reduce the overall cost of neotame. Therefore it was decided to explore economic synthetic routes to **A**.

It has been reported in the literature that **A** can be synthesized from the hydrolysis of 1,1-dichloro-3,3-dimethylbutane,³ oxidation of 3,3-dimethylbutanol,⁴ ozonolysis of 4,4-dimethyl-1-pentene,⁵ and reduction of 3,3-dimethylbutyl chloride.⁶ However, none of these methods were able to meet our cost goals.

The oxidation of a primary alkyl chloride or bromide with dimethyl sulfoxide (DMSO) to generate an aldehyde was described by Engel and co-workers.⁷ The reaction was facilitated by addition of 1.5 equivalent of sodium iodide. The reaction proceeds by formation of an alkyl iodide which is oxidized by DMSO.

This methodology seems applicable to the synthesis of **A** from 1-chloro-3,3-dimethylbutane, which can be readily prepared from the condensation of ethylene with *tert*-butyl chloride using AlCl_3 as a catalyst.⁸ However, the usage of 1.5 equivalent of iodide is still undesirable on an industrial scale due to its cost.

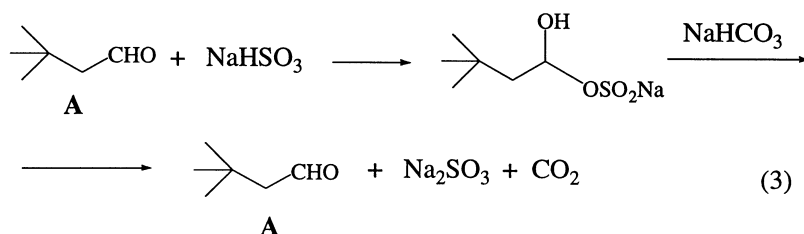
We describe herein a procedure for the synthesis of **A** from 1-chloro-3,3-dimethylbutane in the presence of a base and a substoichiometric amount of alkali bromide or iodide (Eq. 2).



1-Chloro-3,3-dimethylbutane itself does not react with DMSO at an appreciable rate without the addition of bromide or iodide. Alkali bromide or iodide facilitates the reaction by the formation of 1-bromo-3,3-dimethylbutane or 1-iodo-3,3-dimethylbutane, which is subsequently oxidized by DMSO to generate **A**. Since alkali bromide costs much less than alkali iodide, it would be economically advantageous to use bromide in Eq. 2. The reaction also works well with 1-bromo-3,3-dimethylbutane or 1-iodo-3,3-dimethylbutane.

In a typical experiment, a mixture of 1-chloro-3,3-dimethylbutane, DMSO, MX ($\text{M} = \text{Na, K; X} = \text{Br, I}$) and a base was loaded into a reactor and heated to 130–140°C with agitation for up to 14 hours. The usage of

alkali bromide and iodide is about 50% and 10–50% (w/w) respectively. An excess amount of a base, such as bicarbonate, carbonate, or zinc oxide, was used to neutralize HCl. Dimethyl sulfide was formed and distilled from the mixture during the reaction, which was terminated when >95% of the 1-chloro-3,3-dimethylbutane reacted. The reaction mixture was subsequently distilled under house vacuum to yield the crude aldehyde product, which can be purified by further fractional distillation and used for most organic syntheses. The crude aldehyde may also be purified through formation and isolation of the solid **A**/sodium bisulfite adduct, Eq. 3. Regeneration from a base such as sodium bicarbonate in aqueous media generates **A** with a purity >99%.



The final yield of **A** is 58% based on 1-chloro-3,3-dimethylbutane after purification through the aldehyde/bisulfite adduct and regeneration. Compound **A** produced from this process has been used successfully to produce high quality neotame.

In conclusion, we have developed a cost-effective synthetic route to 3,3-dimethylbutyraldehyde (**A**), a precursor to neotame. This process is robust and can be readily practiced on a commercial scale. We have also demonstrated that iodide may not be necessary, at least in our case, for the oxidation of primary alkyl chloride or bromide with DMSO to generate the corresponding aldehyde.

EXPERIMENTS

Preparation of 1-Chloro-3,3-dimethylbutane

This compound was synthesized according to the literature.⁸ The catalyst used in the reaction, AlCl_3 , may react with *tert*-butyl chloride at room temperature to generate an inactive material. It is desirable to add AlCl_3 at low temperature and to introduce ethylene as soon as possible after the catalyst dissolves.

Reaction of 1-Chloro-3,3-dimethylbutane with DMSO/NaI

A 100 ml round bottom flask was loaded with 2.0 g 1-chloro-3,3-dimethylbutane, 2.0 g sodium bicarbonate, 1.0 g NaI and 20 g DMSO- d_6 . The mixture was stirred and heated to 140°C for 2.5 hours. ^1H NMR indicated that 62% 1-chloro-3,3-dimethylbutane was converted to 3,3-dimethylbutyraldehyde.

Reaction of 1-Chloro-3,3-dimethylbutane with DMSO/KBr

A 100 ml round bottom flask was loaded with 3.1 g 1-chloro-3,3-dimethylbutane, 2.1 sodium bicarbonate, 1.5 g KBr and 18 g DMSO- d_6 . The mixture was stirred and heated to 140°C for 4.5 hours. ^1H NMR indicated that the yield of 3,3-dimethylbutyraldehyde was 70%.

Reaction of 1-Chloro-3,3-dimethylbutane with DMSO/NaBr

A 500 ml round bottom flask fitted with a distillation setup was loaded with 46.1 g 1-chloro-3,3-dimethylbutane, 23 g sodium bromide, 20 g zinc oxide and 276 g DMSO. The mixture was stirred and heated with an oil bath to 135–140°C under nitrogen atmosphere for 12–14 hours, during which some low boiling material (mostly dimethyl sulfide) was collected in a receiver.⁹ The reaction mixture was cooled to below 40°C and distilled under house vacuum to collect 31.6 g crude product (80% 3,3-dimethylbutyraldehyde) in a new receiver.

Purification of Crude 3,3-Dimethylbutyraldehyde

To a mixture of 30.6 g of the above described crude product (80% 3,3-dimethylbutyraldehyde) and 240 ml methyl *tert*-butyl ether (MTBE) was added drop wise 30 g sodium bisulfite in 60 ml water over a period of 20 minutes with vigorous agitation at 0–5°C. A white solid precipitated upon addition of the bisulfite solution. The thus formed slurry was stirred for another 80 minutes with ice cooling followed by filtration. The solid was washed with 100 ml MTBE and 2 \times 100 ml 60/40 (vol./vol.) MTBE/methanol and dried in a house vacuum oven (40°C) overnight. The weight of the dry solid is 48.0 g. 40.0 g of this dry solid, 22 g sodium bicarbonate and 200 ml water were loaded into a 250 ml round bottom flask. This mixture was heated to boiling and distilled to yield an azeotropic mixture of

3,3-dimethylbutylraldehyde and water (b.p. 82–85°C). Phase separation gave 18.0 g 3,3-dimethylbutylraldehyde.¹⁰ The overall yield is 58% based on 1-chloro-3,3-dimethyl-butane. The purity of the aldehyde is >99% by GC. b.p. 106°C. ¹H NMR (DMSO-*d*₆): δ 1.01 (s, 9H), 2.24 (d, 2H), 9.75 (t, 1H).

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9. Alternatively 1-chloro-3,3-dimethylbutane was added drop-wise over a period of several hours into a preheated mixture of 1-chloro-3,3-dimethylbutane, sodium bromide, zinc oxide and DMSO at 130–140°C. This mixture continued to be heated at 130–140°C for a total of 12–14 hours and was subsequently subjected to a similar work up procedure to produce 3,3-dimethylbutylraldehyde with similar yields.
10. 3,3-Dimethylbutylraldehyde may be oxidized by air into 3,3-dimethylbutyric acid. Cautions should be taken to limit its contact with air during 3,3-dimethylbutylraldehyde's handling and storage.

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