An effective total synthesis of 2E-nonene-1,9-dioic acid

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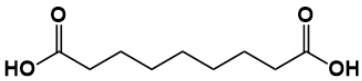
Abstract

An effective total synthesis of 2E-nonene-1,9-dioic acid, these are hormones naturally available in plants. Synthesis of this compound has been studied in detail to attain much purer and stable material in most effective possible route of synthesis.

Keywords: *Azelaic acid, 2E-nonene-1,9-dioic acid*

1. Introduction

2E-nonene-1,9-dioic acid also known as 2-Nonenedioic Acid, apart from its natural occurrence as hormone in plants it's also an impurity in Azelaic acid which is an anti-acne agent.



Azelaic acid

Fig:1 Azelaic acid structure

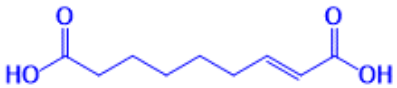


Fig:2 structure of 2E-nonene-1,9-dioic acid

Synthesis has been performed of subject compound Fig:2. To attain much higher yield with maximum purity. However, very few methods are reported for the synthesis of 2E-nonene-1,9-dioic acid, these methods currently have very limited synthetic scope due to the use of expensive and complex to handle reagents, missing selectivity in reaction and the formation of a mixture of products.

Thus, there is a need to develop a simple and high yielding method for the preparation of 2-Nonenedioic Acid under mild reaction conditions.

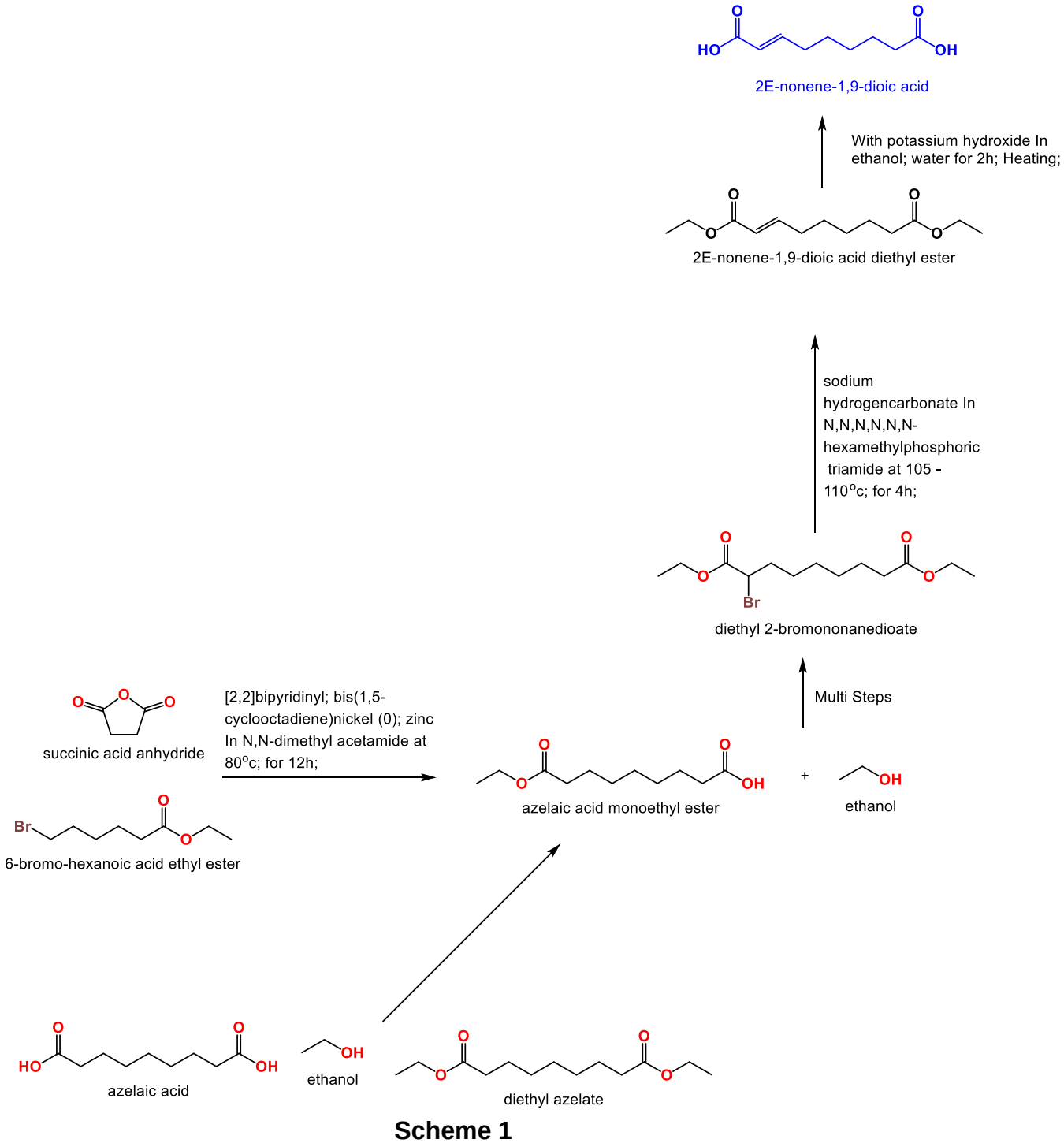
In this communication, research performed highlight our results on the preparation of 2-Nonenedioic Acid via multi stage synthesis with different catalyst and to give the corresponding 2-Nonenedioic Acid in good to excellent yields.

2. Experimental

All of the experiments were carried out in a highly efficient fume hoods. All yields refer to the isolated pure products. Chemicals were purchased from Aldrich, Fluka, and Merck

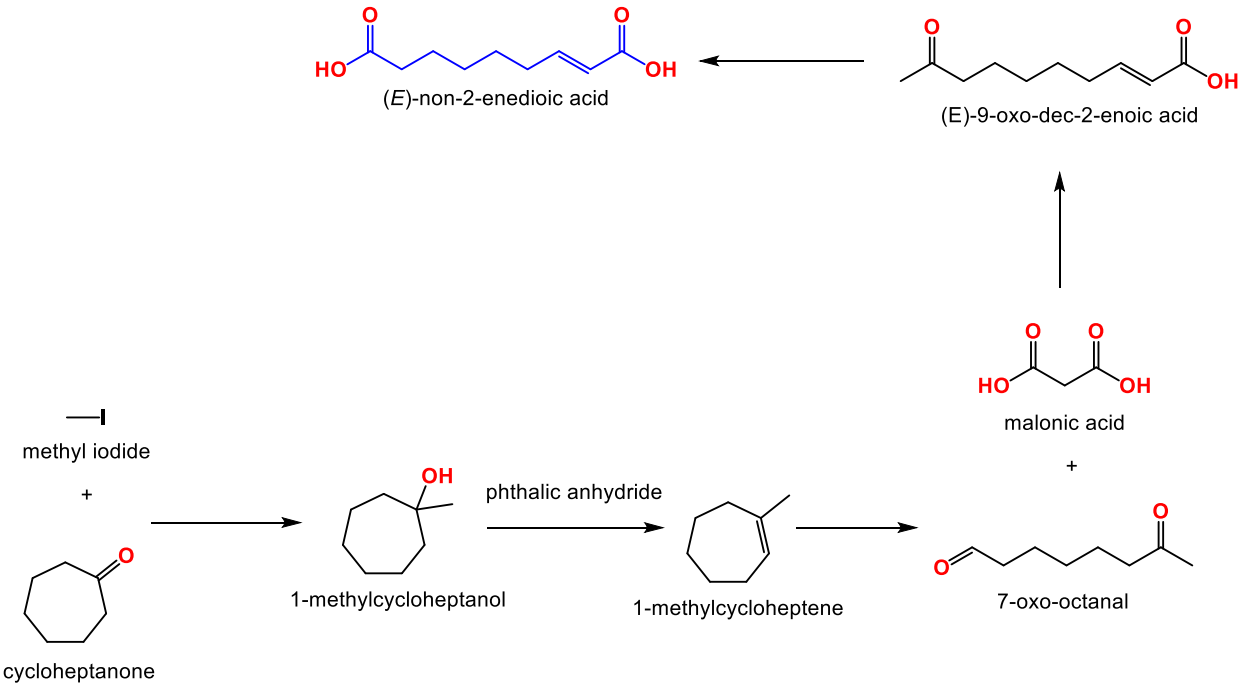
chemical companies and applied without further purification. In all the experiments silica gel 60 (mesh 63-200), Merck was used as solid support. Products were purified by column chromatography or recrystallization and were identified by 1H NMR spectra, and melting point.

Scheme1: Method A, represents the synthetic route scheme, which have been implemented



Scheme 1

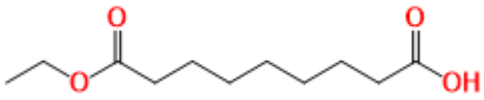
Scheme2: Method B represents alternative synthetic route scheme.



Scheme 2

3.Experimental Procedures

Synthesis of I: Azelaic acid monoethyl ester



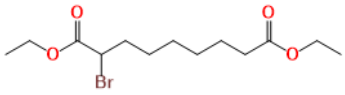
Method-A

In an microwave tube add bis(1,5-cyclooctadiene)nickel (0) (16.6mg, 0.06mmol) and 2,2'-bipyridine(14.0mg, 0.09mmol) and 0.45mL N,N-dimethylacetamide for coordination for 1hour, followed by addition of zinc powder (78.4mg, 1.2mmol, 2.0 equivalent) into the microwave tube, followed by addition of succinic anhydride (0.9mmol, 1.5eq) and 1-bromooctane (0.6mmol, 1.0eq), close the tube and remove out from the glove box, reflux of the reaction mass at 80o for 12-14 hours, Cool to room temperature, uncap microwave tube and add six to ten drops of water to quench the reaction, removing of the solvent under reduced pressure, yielded crude product which is further purified by column chromatography (petroleum ether: ethyl acetate = 5:1) to obtain **1 azelaic acid monoethyl ester** (94.0mg, 85% yield).

Method-B

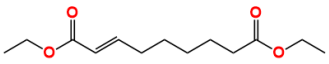
A stirred mixture of 0.2 mole of azelaic acid 0.2 mole of the diethyl azelate, 0.4 mole of EtOH, and 0.01 mole of H2SO4 was refluxed for 4-6 h. The excess EtOH was removed in vacuo, and the residue was poured into cold water and extracted with ether. The ether extract was washed with a small amount of NaHCO3 solution, then with water, and dried over Na2SO4. Vacuum-distillation gave 0.14 mole (72%) of **1 azelaic acid monoethyl ester**

Synthesis of II: diethyl 2-bromononanedioate



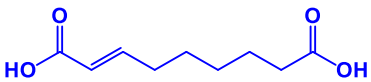
A mixture of 0.1 mole of compound I in 50 ml of SOCl2 was refluxed for 3-4 hours. Then, under mild reflux conditions, 0.105 mole of bromine was very slowly added at that the amount of Bromine vapours in condenser was negligible. After the addition of bromine, the reaction was refluxed mildly for 4-5 hours, until all the bromine vapours are not released. Followed by SOCl2 was distilled under vaccum. 20ml of Ethanol was added to the crude very slowly and refluxed for 1 hour. Reaction mixture was poured in to cold water and extracted with ether, washed with water and with NaHCO3 solution, dried and solven was removed under vaccum to get **II diethyl 2-bromononanedioate** 76%

Synthesis of III: 2E-nonene-1,9-dioic acid diethyl ester



To A stirred mixture of 10 g of II diethyl 2-bromononanedioate, 40 ml of dry HMPA, and 3g of NaHCO3 was heated for 5h at 100-110oC reaction was monitored by GC. The reaction was stopped when most of the starting material was consumed. Then most of the HMPA was vacuum distilled from the reaction mass, the residue was treated with hexane, and the mixture was poured into water. The hexane solution was washed twice with water and dried over Na2SO4. Vacuum-distillation afforded 12.5 g (87%) of **III 2E-nonene-1,9-dioic acid diethyl ester**

Synthesis of IV: 2E-nonene-1,9-dioic acid



A solution of III 6.5g in a mixture of 3.5 g of potassium hydroxide, 25 ml of ethanol, and 14 ml of water was refluxed for 2-3h. after the reaction completed, Most of the alcohol

was vacuum-distilled and then water was added to the residue. The obtained water solution was filtered and the filtrate was acidified with concentrated HCI, the obtained acid was filtered, washed with water, and dried, to obtain 4.75g of **IV 2E-nonene-1,9-dioic acid** 91%

4.Conclusion

With the above experimental proceedings, to prepare the 2E-nonene-1,9-dioic acid, it is the best possible option to implement the discussed conditions for efficient synthesis 2E-nonene-1,9-dioic acid

Acknowledgments

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References

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