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NOTE

Environment-Friendly, Mild and One-Step Synthesis of Safrole

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One-step synthesis of safrole, an important flavor compound, was described. Safrole was prepared by Friedel-Crafts reaction of 1,2-methylenedioxybenzene and allyl alcohol with recyclable Catalysts-Nafion-H. Safrole was obtained with a yield of 80 % and little isosafrole was obtained. The catalyst and excess raw material can be recycled and reused.

Keywords: Safrole, Friedel-Crafts reaction, One-step, Nafion-H.

Great efforts of catalysis research have been devoted in recent years on the development and application of effective and safe heterogeneous catalysts. This is an important tendency in industry but also in the laboratory practice. These studies have been especially successful in the development of solid acids to replace aggressive and dangerous homogeneous acid catalyst.

Solid Brønsted acids with super acidic character, such as Nafion-H, are of great interest in the synthesis of fine chemicals. Nafion-H resin is a kind of solid superacid catalyst with the structure of perfluorinated alkyl sulfuric acid. Due to the easy separation after the reaction and highly catalytic activity, it has been widely used in the organic synthesis instead of the triflic acid and concentrated sulfuric acid. It shows highly activity towards Friedel-Crafts alkylation and acylation reactions[1-3]. In order to increase the surface area of the catalyst, the Nafion resin/silica composite catalyst has also been studied and it shows highly catalytic activity[4-6].

Safrole is an abundant Brazilian natural product from sassafraz oil (*Ocotea preliosa* Mer., Lauraceae), which presents interesting functionality and chemical reactivity that suggests its use as an efficient and versatile natural synton[7-12]. The methylenedioxy unit from safrole, has been identified in some clinical antitumor agents like etoposide and teniposide[13]. Safrole has been used as a flavoring agent in drugs and in the manufacturing of heliotropin, perfumes, soaps and piperonyl butoxide (a compound used in a variety of insecticides to enhance the pesticidal properties of other active ingredients). Safrole has also been used as a preservative in mucilage and library paste and as a flotation frother. Oil of sassafras, which contains safrole, was formerly used to flavor some soft drinks, such as root beer. With the increasing scarcity of natural resources and the need for safrole is growing, lots of efforts have been spent on developing simple and practical synthetic route for the preparation of safrole recently[14-16].

Tsukada, *et al.*[14] synthesized safrole from allyl alcohol and 1,2-methylenedioxybenzene catalyzed [Rh(nbd)-$(CH_3CN)_2$] PF_6. Although it used allyl alcohol as the raw material which was obtained easily, allyl alcohol should be converted into the corresponding tosylate and the product was obtained by Friedel-Crafts reaction using a relatively expensive catalyst, only given 45 % of the isolated yields in the key step (Fig. 1).

Lin and Yang[15] synthesized this compound from 1,2-methylenedioxybenzene by bromination with bromine and Grignard reaction with allyl bromide. In this process, poly-brominated product would be produced in the bromination of 1,2-methy-lenedioxybenzene and self-coupling reaction would also occur inevitably in Grignard reaction of 5-bromobenzo-[d][1,3]-dioxole reacting with allyl bromide, thus the final yield of 45.9 % was obtained in this synthetic route. it is feeble that the reaction given the relatively low yield and needed the relatively rigid reaction conditions (Fig. 2).

Protti *et al.*[16] synthesized this compound from 1,2-methylene-dioxybenzene and allyltrimethylsilane irradiated at 310 nm. Though the use of allyltrimethylsilane (ATMS) ensured a straightforward formation of the desired allyl benzenes as the only products and avoided competitive reactions from the 1,2-methylenedioxybenzenium ion, such as nucleophilic addition

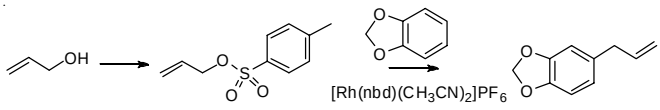

Fig. 1. First synthetic method of safrole

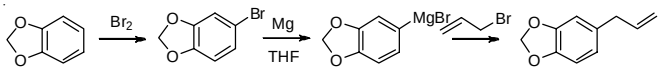

Fig. 2. Second synthetic method of safrole

by the solvent or Wagner-Meerwein hydride and alkyl migration, obtaining the raw material in this process is not easy, the relatively low yield (54-77 %) and no practical applicability of this photochemical reactions is evidently (Fig. 3)[16] .

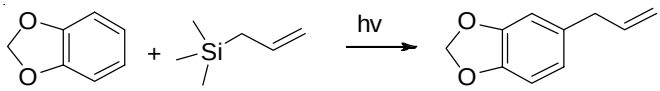

Fig. 3 third synthetic method of safrole

There are still some room for improving synthetic process. Herein we report an environment-friendly, mild and one-step synthetic route for the preparation of safrole.

The synthesis was initiated from 1,2-methylenedioxybenzene and allyl alcohol (Fig. 4) and catalyzed by Nafion-H resin, safrole was obtained in 80 % yield and little isosafrole was obtained.

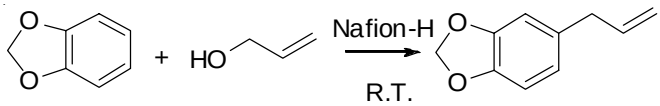

Fig. 4. New synthetic method of safrole

The following reagents and solvents used in this preparation were sourced from some chemical company in China and used without further purification. Structure of the product was characterized by its physical data as well as the IR and NMR spectra. ^{1}H NMR spectras were recorded using Avance 400 MHz spectrometer. IR spectra were determined as KBr pellets on a Bruker Vertex 70 spectrophotometer. ESI-MS were recorded on Dionex MSO Plus Mass Spectrometer.

General procedure: Nafion-H (14.65 g, 10 % wt. % based on the 1,2-methylene-dioxybenzene was used) was added to the mixture of 1,2-methylenedioxybenzene (146.54 g, 1.2 mol) and allyl alcohol (2.33 g, 0.04 mol) and stirred at room temperature until the allyl alcohol is disappeared. The Nafion-H catalyst was filtered off. Excess 1,2-methylenedioxybenzene was removed under reduced pressure. The crude product was vacuum distilled, 5.19 g of safrole, boiling at 120-130 °C (10-15 mm Hg), was obtained. Colourless and typically smelling oil. Total yield (from the allyl alcohol), 80 % of theory. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78 (d, J = 7.8 Hz, 1 H), 6.71 (s, 1 H), 6.69 (d, J = 7.8 Hz, 1 H), 5.99-5.92 (m, 3 H), 5.13-5.08 (m, 2 H), 3.25 (d, J = 6.4 Hz, 2 H). IR (cm^{-1}): 3032, 2990, 1646, 1590. ESI-MS *m/z*: 163.3 $(M + H)^+$.

Regeneration of nafion-H catalyst: The used catalyst was washed several times with acetone and deionized water, followed by drying at 105-110 °C for 10-12 h. The catalystic activity of regenerated catalyst was as good as that of fresh catalyst.

Inspired by the literatures[17,18], we prepared safrole from 1,2-methylenedioxybenzene and allyl alcohol by catalysis of Nafion-H resin. The process of this reaction were optimized. And it was shown that the excess raw material of 1,2-methylenedioxybenzene and 10 % the amount of catalyst (wt. %) based on the 1,2-methylenedioxybenzene was more appropriate than any of the other conditions. The same molar amounts of 1,2-methylene-dioxybenzene and allyl alcohol produced only a little safrole. This is probably due to facile formation of di-allyl ether. Little iso-safrole was detected. This is probably due to stability of the allyl ion which formed by the reaction of allyl alcohol and catalysts of Nafion-H resin. In this process, 1,2-methylenedioxybenzene was successfully used as raw material and reaction solvent avoid using any other solvents. Excess 1,2-methylenedioxybenzene could be recycled and reused. The catalyst Nafion-H could also be recycled. This would not only save costs of raw materials but also to avoid adding other substances, making the process easier.

Conclusion

In conclusion, comparisons of traditional synthesis methods indicated that its ease of work-up, environment-friendly, fairly mild reaction conditions provide an improved access to safrole. The yield of the reaction is 80 % and little isosafrole is obtained. Other applications of this catalyst Nafion-H are under investigation in our laboratory.

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