A new and efficient synthesis of rosefuran. A general synthesis of furans by palladium-catalysed cycloisomerization of (*Z*)-2-en-4-yn-1-ols

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(*Z*)-3,7-Dimethylocta-2,6-dien-4-yn-1-ol, readily available from (*Z*)-3-methylpent-2-en-4-yn-1-ol, undergoes cycloisomerization in the presence of catalytic amounts of K_2PdI_4 to give rosefuran in high yield.

We report a new, efficient and selective synthesis of rosefuran **3**, a natural product present in the highly prized oil of rose[1] and many other natural sources.[2] The synthesis is realized in two steps with a 60% overall isolated yield, according to Scheme 1.

The key step consists of a Pd-catalysed cycloisomerization of (*Z*)-3,7-dimethylocta-2,6-dien-4-yn-1-ol **2**, readily obtainable in 78% yield from the commercially available (*Z*)-3-methylpent-2-en-4-yn-1-ol **1** *via* Pd/Cu-catalysed coupling with 1-bromo-2-methylpropene.[3] Thus, by reacting **2** (1.88 g, 12.5 mmol) under nitrogen in 5 ml of dry *N,N*-dimethylacetamide (DMA) at 100 °C for 24 h in the presence of PdI_2 (45 mg, 0.125 mmol) and KI (41.5 mg, 0.25 mmol), rosefuran **3** was obtained in 85% GLC yield. After the usual work-up, **3** was isolated by transfer distillation (1.44 g, 77%).

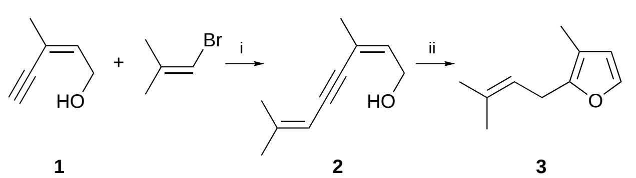
The Pd-based catalytic system here reported also works very well with substrates bearing a terminal triple bond, thus providing a general method for the synthesis of furans by cycloisomerization of (*Z*)-2-en-4-yn-1-ols (Scheme 2).

Terminal enynols are indeed much more reactive than internal ones, and were easily converted to the corresponding furans in excellent yields and with high catalytic efficiencies at 20–45 °C. For example, **1** (3.0 g, 31.2 mmol) was allowed to react under nitrogen at 20 °C† for 18 h without solvent in the presence of PdI_2 (22.5 mg, 0.062 mmol) and KI (20.7 mg, 0.125 mmol) to give, after transfer distillation, 2.6 g of 2,3-dimethylfuran (87%). GLC yield was higher than 92%.

The cycloisomerization process may involve an *anti-exo-dig* intramolecular nucleophilic attack of the hydroxy group to the triple bond coordinated to palladium(II)[4] with formation of a vinylpalladium intermediate **I** and HI (Scheme 3; anionic iodide ligands are omitted for simplicity). Protonolysis of **I** followed by acid-catalysed aromatization leads to the final product with regeneration of the catalytically active species (path *a*). Aromatization of **I** followed by protonolysis is another possibility, however (path *b*).

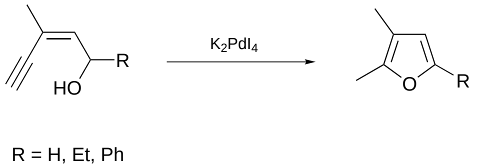
There are few other methods for synthesis of rosefuran starting from nonfuranoid substrates.[5,6] Very recently, **3** was obtained in 11% overall yield by a four-step synthesis involving a [3 + 2] nitrile oxide cycloaddition as the key step.[6g] Another approach utilized the acid-catalysed cyclization into furans of aliphatic β,γ-dihydroxy ketones, obtained by Ru-catalysed addition of allyl alcohols and alkynes followed by dihydroxylation with OsO_4, and afforded **3** in 23% overall yield; isorosefuran (which contains a terminal double bond) was also formed (rosefuran : isorosefuran ratio = 4).[6f] It is noteworthy that a previously reported synthesis of rosefuran starting from enynol **1** required a sequence of five steps and afforded a *ca.* 3 : 1 mixture of **3** and a β-lactone derivative; the latter had to be separated and recycled.[6e]

The Ru-catalysed cycloisomerization of (*Z*)-2-en-4-yn-1-ols has been reported, but it could only be applied to terminal enynols.[7] On the other hand, a recently proposed Pd-based catalytic system suitable for internal enynols did not work with substrates bearing a triple bond conjugated with a double bond such as **2**.[7b] The catalytic system here described, in spite of its simplicity, allows the conversion of (*Z*)-2-en-4-yn-1-ols with either internal and terminal triple bonds into the corresponding furans in high yields and with high catalytic efficiencies, and can also be applied to the synthesis of fragile biologically active furan derivatives, such as rosefuran.

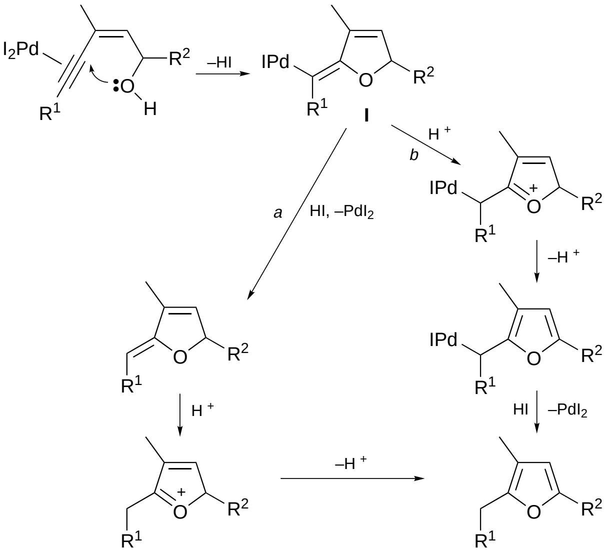


1 2 3

Scheme 1 *Reagents and conditions*: i, $Pd(PPh_3)_2Cl_2$, CuI, Et_2NH, 78%; ii, K_2PdI_4, DMA, 77%



Scheme 2



Scheme 3

Footnotes

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† The reaction temperature must be controlled with the aid of a water bath owing to the exothermicity of the reaction.

References

1 K. Bauer, D. Garbe and H. Surburg, *Common Fragrance and Flavour Materials*, VCH, Weinheim, 1990.

2 For recent examples, see: A. O. Tucker and M. J. Maciarello, *J. Essent. Oil Res.*, 1995, **7**, 653; O. Nishimura, *J. Agric. Food Chem.*, 1995, **43**, 2941; D. Karasawa, S. Shatar, A. Erdenechimeg, Y. Okamoto, H. Tateba and S. Shimizu, *J. Essent. Oil Res.*, 1995, **7**, 255.

3 K. Sonogashira, Y. Tohda and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467.

4 C. Lambert, K. Utimoto and H. Nozaki, *Tetrahedron Lett.*, 1984, **25**, 5323.

5 Reported syntheses of rosefuran from furan derivatives: G. Buchi, E. Sz. Kovats, P. Enggist and G. Uhde, *J. Org. Chem.*, 1968, **33**, 1227; O. P. Vig, A. K. Vig, V. K. Handa and S. D. Sharma, *J. Indian Chem. Soc.*, 1974, **51**, 900; A. J. Birch, J. Slobbe, *Tetrahedron Lett.*, 1976, 2079; A. Takeda, K. Shinhama and S. Tsuboi, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 1903; N. D. Ly and M. Schlosser, *Helv. Chim. Acta*, 1977, **60**, 2085; D. R. Gedge and G. Pattenden, *Tetrahedron Lett.*, 1977, 4443; Z. M. Ismail and H. M. R. Hoffmann, *Angew. Chem.*, 1983, **95**, 737; S. Araki and Y. Butsugan, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1446; L. Meier and H. D. Scharf, *Liebigs Ann. Chem.*, 1986, 731; W. S. Leal, Y. Kuwahara, T. Suzuki and H. Nakao, *Agric. Biol. Chem.*, 1989, **53**, 3279; S. Araki, S.-J. Jin and Y. Butsugan, *J. Chem. Soc., Perkin Trans. 1*, 1995, 549; P. Weyerstahl, A. Schenk and H. Marschall, *Liebigs Ann. Chem.*, 1995, 1849.

6 Reported syntheses of rosefuran from nonfuranoid substrates: (*a*) R. Okazaki, Y. Negishi and N. Inamoto, *J. Org. Chem.*, 1984, **49**, 3819; (*b*) S. Takano, M. Morimoto, S. Satoh and K. Ogasawara, *Chem. Lett.*, 1984, 1261; (*c*) H. Tsukasa, *Agric. Biol. Chem.*, 1989, **53**, 3091; (*d*) R. Iriye, T. Uno, I. Ohwa and A. Konishi, *Agric. Biol. Chem.*, 1990, **54**, 1841; (*e*) J. A. Marshall and W. J. DuBay, *J. Org. Chem.*, 1993, **58**, 3602; (*f*) B. M. Trost and J. A. Flygare, *J. Org. Chem.*, 1994, **59**, 1078; (*g*) A. Barco, S. Benetti, C. De Risi, G. P. Pollini and V. Zanirato, *Tetrahedron*, 1995, **51**, 7721.

7 (*a*) B. Seiller, C. Bruneau and P. H. Dixneuf, *J. Chem. Soc., Chem. Commun.*, 1994, 493; (*b*) B. Seiller, C. Bruneau and P. H. Dixneuf, *Tetrahedron*, 1995, **51**, 13 089; (*c*) H. Kucukbay, B. Cetinkaya, S. Guesmi and P. H. Dixneuf, *Organometallics*, 1996, **15**, 2434.

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