Convenient Synthesis of 2,6-di-*tert*-Butyl-4-[5-(3-pyridyl)-4-oxapentyl]phenols and their *thia*-Analogues

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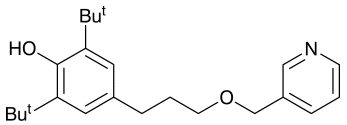
A convenient large scale procedure for the synthesis of Nicanartine {2,6-di-*tert*-butyl-4-[5-(3-pyridyl)-4-oxapentyl]-phenol}, an antiatherosclerotic compound has been developed, the synthetic route towards the thia-analogue as well as various branched-chain oxa- and thia-derivatives of the parent compound has also been investigated.

Searching for a drug which might address therapeutically some of the most important aspects of atherogenesis, Gold *et al.*[1] have synthesized *Nicanartine* {2,6-di-*tert*-butyl-4-[5-(3-pyridyl)-4-oxapentyl]phenol **1**, Mrz 3/124} demonstrating its potential use as antiatherosclerotic drug.

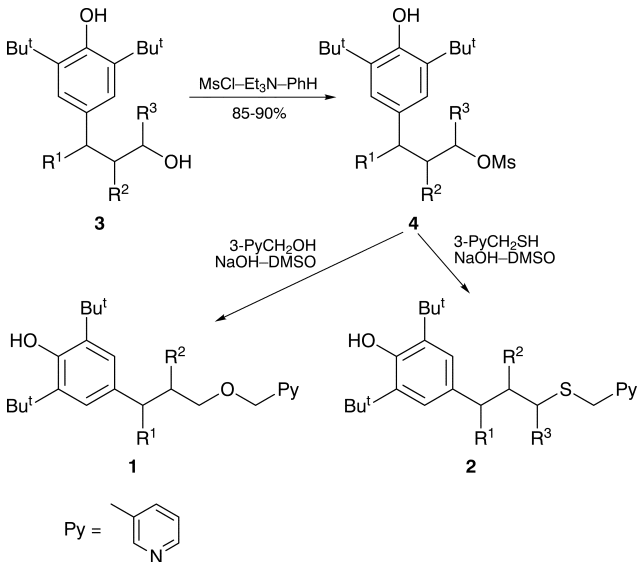


1 Mrz 3/124, Nicanartine

Here we report a convenient and general method for the synthesis of both *Nicanartine* **1** and the corresponding thia-analogue **2** as well as a series of branched chain derivatives of both **1** and **2**.

The key intermediates for preparation of pyridyl ethers **1** and **2** are 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanols **3** (Scheme 1).

Reaction of corresponding **3** with mesyl chloride afforded mesylates **4a**–**j**. Williamson's procedure[2] in DMSO led to the ethers **1a**–**f** and **1i**. Treatment of secondary mesylates **4g**, **h** and **4j** with 3-pyridylmethanol resulted in elimination



Scheme 1 General scheme for the preparation of Mrz 3/124 and analogues

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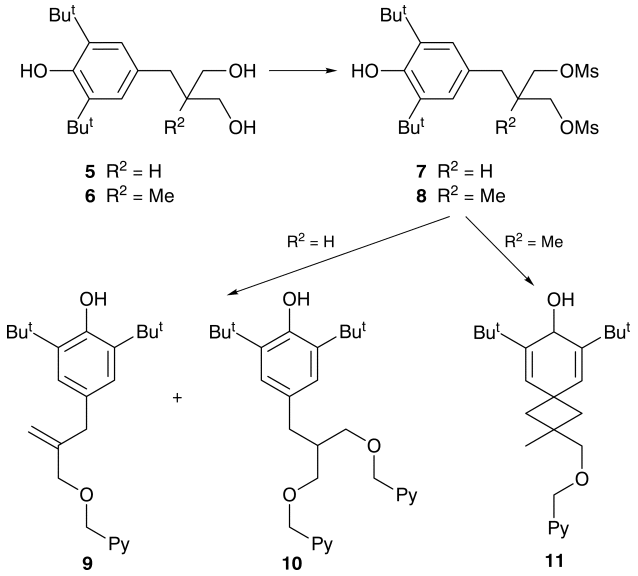

Scheme 2 Reactions of 2-(3,5-di-*tert*-butyl-4-hydroxybenzyl)propane-1,3-diols

products instead of ethers. On the other hand mesylates **4a**–**j** in the reaction with 3-picolylmercaptan generated *in situ* from picolylthiouronium salt[3] and NaOH gave the corresponding thioethers **2a**–**j** (Table 1).

Meanwhile the Williamson's procedure was applied to 2-(3,5-*tert*-butyl-4-hydroxybenzyl)propane-1,3-diols **5** and **6** (Scheme 2).

Treatment of alcohols **5** and **6** with mesyl chloride, gave the corresponding bis-mesylates **7** and **8**. However, condensation with 3-pyridylmethanol gave mixture of bis-ether **9** and unsaturated ether **10** if $R^2 = H$. Introduction of the methyl group ($R^2 = Me$) excluded elimination, and cyclobutane derivative **11** was the only isolated product.

We have to conclude that the Williamson's synthesis from corresponding mesylates and 3-pyridylmethanol is the most appropriate method for the preparation of *Nicanartine* and its analogues. Obviously, the phenolic OH group is sterically hindered by the bulky *o*-substituents, so the regioselectivity is ensured in this reaction and there is no need for protective groups. Secondary mesylates undergo elimination if treated with 3-pyridylmethanol, whereas application of a stronger nucleophile, 3-picolylmercaptan, provides corresponding thioethers.

Techniques used: ^{1}H NMR, HPLC on 4.6 × 250 mm *Silasorb* 600 column and 4.6 ×250 mm *Silasorb* SPH C18 column

Table 1 Syntheses of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propylmethanesulfonates and corresponding ethers and thioethers

				Mesylate			Ether			Thioether		
Entry	R^1	R^2	R^3		Yield (%)	Mp/°C		Yield (%)	Mp/°C		Yield (%)	Mp/°C
1	H	H	H	**4a**	83	116–117	**1a**	76	104–105	**2a**	75	59–60
2	Me	H	H	**4b**	53	72–73	**1b**	53	101–103	**2b**	70	105–106
3	H	Me	H	**4c**	87	59–60	**1c**	47	102–104	**2c**	63	63–64
4	H	Et	H	**4d**	80	oil	**1d**	—	—	**2d**	54	oil
5	H	Pr	H	**4e**	94	oil	**1e**	62	99–101	**2e**	48	82–83
6	H	Bu	H	**4f**	88	oil	**1f**	43	71–72	**2f**	32	80–81
7	H	H	Et	**4g**	86	oil	**1g**	—	—	**2g**	53	73–74
8	H	H	Pr	**4h**	87	oil	**1h**	—	—	**2h**	45	75–76
9	Me	Me	H	**4i**	93	oil	**1i**	39	56–57	**2i**	50	oil
10	Me	H	Pr	**4j**	93	oil	**1j**	—	—	**2j**	63	oil

References: 8

Tables: 3 (yields, mps and ^{1}H NMR spectra of starting mesylates and target products)

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