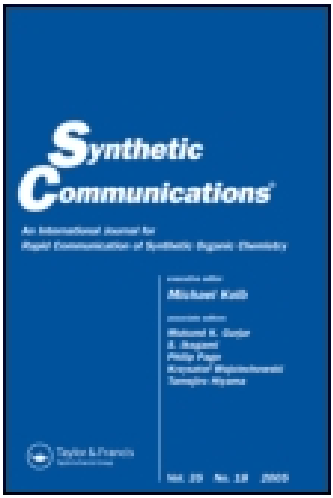

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The Synthesis of (3,5-DI-tert-butyl-4-hydroxyphenyl)methyl-(3-pyridylalkyl)-ethers via 1-(3,5-Di-tert-butyl-4-hydroxyphenyl)methyl Pyridinium Salts.

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THE SYNTHESIS OF (3,5-DI-*TERT*-BUTYL-4-HYDROXYPHENYL)METHYL-(3-PYRIDYLALKYL)-ETHERS *VIA* 1-(3,5-DI-*TERT*-BUTYL-4-HYDROXYPHENYL)METHYL PYRIDINIUM SALTS.

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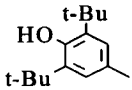
Abstract. The rearrangement of 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl pyridinium salts under basic conditions is described. A method for the synthesis of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl-(3-pyridylalkyl)-ethers is elaborated.

Since 1954 the 2,6-di-*tert*-butyl-4-methylphenol (1) (BHT, butylated hydroxy-toluene) has been one of the most widely used preservatives added to food, cosmetics and drugs. Combination of the BHT residue with a nicotinic acid precursor - pyridyl-3-carbinol[1] gave (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl-(3-pyridyl)-methyl ether (2) with high hypolipidemic and antiatherosclerotic activity.



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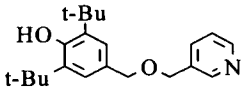

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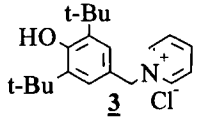
* to whom correspondence should be addressed.

However, the known synthesis of **2** and its analogues[1,2] is a complicated 7 stage procedure including protection and deprotection steps with the total yield of 25%. Introduction of unprotected (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl moiety into a molecule may cause problems due to rapid oxidation and formation of complex quinoid systems. Only a few methods allow direct benzylation with (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl halides[3]. The usage of tertiary amines[4] or quaternary acylammonium salts[5] afford better results. Recently we offered the 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl pyridinium chloride (**3**) as a synthetic tool for the synthesis of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methylmalonic esters[6].



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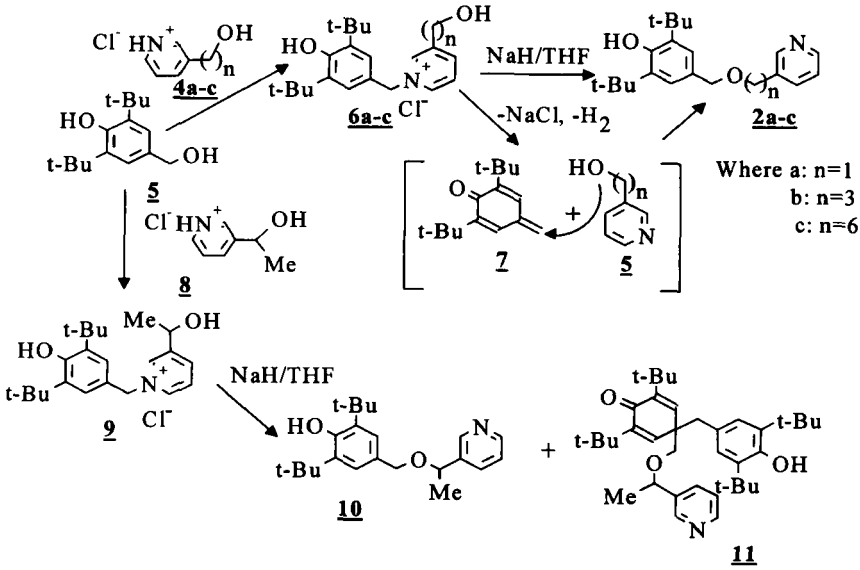
Here we wish to report a convenient synthetic procedure for the preparation of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl-(3-pyridylalkyl)-ethers *via* 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl pyridinium salts.

Interaction of pyridylalcohol hydrochlorides **4a-c** with benzylalcohol **5** results in corresponding pyridinium salts **6a-c**. Further rearrangement of **6a-c** under basic conditions gives ethers **2a-c** (scheme 1). As a first step we suggest initial formation of quinone methide **7** followed by the nucleophilic attack of the pyridylalcohol. Yields depend on the base, temperature and solvent applied (table 1). Sodium hydride in THF at -15°C appears to be the optimum conditions for this rearrangement. More drastic reaction conditions cause (see table 1) dimerization of quinone methide **7** resulting in formation of large amount of colored products[7].

Scheme1. Synthesis of di-*tert*-butyl-benzylethers.



Chain length of pyridylalcohols **4a-c** has no significant effect on the reaction yields (see table 2). Lower yields referred for **2b** and **2c** could be explained by certain loss of substance after crystallization from hexane. In the contrary secondary alcohol **8** gives a mixture of two main products: desired ether **10** and cyclohexadienone derivative **11** (see table 3). Appearance of adduct **11** could be explained as the dimerization of intermediate quinone methide **7** followed by addition of an alcohol **8** molecule. Obviously more sterically hindered alcohol **8** reacts slower with the quinone methide **7** and dimerization of the latter becomes favorable.

Usage of solid sodium hydride in THF is a serious drawback of the method described. The reaction needs certain activation by temperature increase and then,

Table 1. Preparation of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl-(3-pyridyl)methyl ether (**2a**).

No. of run	Base / Solvent	Time / t, (°C)	Yield (%)
1.	NaH / THF	3h / -15	94
2.	NaH / THF	2h / r.t.	45
3.	BaO / MeCN	3h / reflux	41
4.	K_2CO_3 / MeCN	5h / reflux	40
5.	K_2CO_3 / DMF	1h / reflux	traces[a)]
6.	Et_3SiH / THF	24h / r.t	no rxn.
7.	DABCO / THF	24h / r.t.	0[b)]
8.	NaOMe /MeCN	2h / reflux	traces[a)]

[a)]- a lot of colored reaction products were obtained, trace amount of **2** was obtained after flash chromatography.
[b)]- pyridyl carbinol as a free base and alkylated DABCO were detected in reaction mixture.

Table 2. ^{1}H NMR spectra, melting points and yields of (3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl-(3-pyridylalkyl)-ethers ($CDCl_3$, TMS).

No. of cmpd.	δ, (ppm)						Yield, (%)	M.P., (°C)
	t-Bu	CH_2Ar	$Py(CH_2)_nO$	ArOH	C_6H_2	Py		
2a	1.42	4.53	4.44 (2H, s)	5.18	7.11	7.22(1H, m); 7.69(1H, m); 8.48(2H, m).	94	109-10
2b	1.42	4.37	1.75-2.05 (2H, m); 2.72 (2H, t, J=7.5Hz); 3.47 (2H, t, J=6.0Hz)	5.18	7.10	7.15(1H, m); 7.43(1H, m); 8.40(2H, m).	67	72-3
2c	1.41	4.37	1.0-1.8 (8H, m); 2.59 (2H, t, J=7.5Hz); 3.44 (2H, t, J=6.5Hz).	5.15	7.10	7.06(1H, m); 7.44(1H, m); 8.40(2H, m).	72	61-2
10	1.43	4.34	1.53 (3H, d, J=6.2Hz); 4.55 (1H, q, J=6.2Hz).	5.24	7.11	7.22-7.38(1H, m); 7.62-7.82(1H, m); 8.51-8.67(2H, m).	24[a]	93-4

[a] -61% of adduct **11** was isolated.

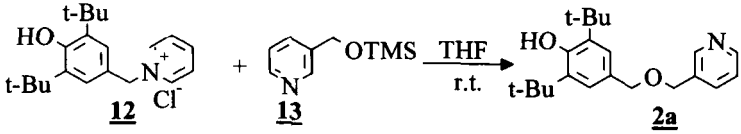
Table 3. ^{1}H NMR spectra, melting points and yields of 1-(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl pyridinium salts ($CDCl_3$, TMS).

No.of cmpd.	R	δ, ppm						Yield, (%)	M.P., (°C)
		t-Bu	R	ArOH	CH_2N^+	C_6H_2	Py		
6a*	CH_2OH	1.36	4.67 (2H, s)	7.20	5.71	7.29	8.07 (1H, m); 8.47(1H, m); 9.09-9.15(2H,m)	82	216-9, dec.
6b	$(CH_2)_3OH$	1.41	2.00 (2H, m); 3.06 (2H, t, J=7.0Hz); 3.64 (2H, t, J=6.0Hz)	5.41	6.00	7.29	7.74 (1H, m); 8.19 (1H, m); 8.64 (1H, m); 9.75 (1H, bs).	73	210-2, dec.
6c	$(CH_2)_6OH$	1.38	0.8-1.75 (8H, m); 2.83 (2H, m); 3.46 (2H, m).	5.44	6.02	7.29	7.98(1H, m); 8.21(1H, m); 9.05-9.55(2H,m);	80	
9	CH_3CHOH	1.41	1.53(3H, d, J=6.0Hz); 5.13(1H, q, J=6.0Hz); 6.3(1H, b.s.)	5.44	5.89	7.29	7.91 (1H, m); 8.92 (1H, m); 8.93 (1H, m); 9.51 (1H, m).	84	200-2, dec
12*	H	1.37	-	7.24	5.74	7.31	8.15 (1H, m); 8.58(2H, m); 9.21 (2H, m).	81	238-42, dec

* - in DMSO-d_6

after the process is started, the temperature in reaction medium should be kept at -15°C to get good yield of product. If the exothermic process is not suppressed, the yields decrease dramatically (see table 1). Attempts to use soluble bases, to avoid activation, failed (table 1, runs 6 and 7). Finally we tried to prepare ether **2a** according to the so called "silyl method"[8]. Treatment of pyridinium salt **12** with O-trimethylsilylpyridylcarbinol **13** in THF at room temperature gives the target ether **2a** in 82% yield (scheme 2):

Scheme 2. Preparation of ether **2a** from O-trimethylsilylpyridylcarbinol.



In conclusion, the procedure presented here is useful for the preparation of the title compounds because of high yields, simple synthetic procedure and low reagent costs.

Experimental. All ^{1}H NMR spectra were recorded on a 90 MHz Bruker WH-90 instrument. Melting points were determined on a Boetius table and are uncorrected. All reactions were carried out in an argon atmosphere. Solvents were prepared before use as described in literature[9].

General procedure for preparation of pyridinium salts 4a-c, 9 and 12.

1-(3-Pyridyl)ethanol hydrochloride (**8**) (4.75g 29.7mmol) was dissolved in 50ml acetonitrile and benzylalcohol (**5**) (20g, 84.6mmol) was added. Reaction mixture was refluxed for 5h, evaporated to dryness, oily residue triturated with ether, filtered and washed with ether to give 8.63g (87%) of **9** as a pale yellow crystalline substance.

General procedure for rearrangement of pyridinium salts 4a-c and 9.

Sodium hydride (412mg, 17.17mmol) was suspended in 120ml THF. The mixture was cooled to -35°C and dry pyridinium salt **6a** (5.0g, 13.76mmol) was added in one portion. Reaction mixture was warmed up to -10°C and kept until the reaction begins (hydrogen evolution). The mixture was stirred at -15°C for 3h, then allowed to warm up to room temperature and poured into 150ml ice cold brine. Organic layer was separated, washed twice with 50ml brine. Aqueous phase was extracted twice with 50ml ether, organic extracts were dried over sodium sulfate and evaporated to give 4.18g of yellow crystals. Recrystallization from hexane gave 3.87g (11.83mmol, 86%) of ether **2a**.

2,6-Di-*tert*-butyl-4-[(3,5-di-*tert*-butyl-4-hydroxyphenyl)methyl]-4-[1-(pyridyl-3)-ethoxy-methyl]-cyclohexa-2,5-dien-1-one (11).

Pyridinium salt **9** (1.026g, 3.10mmol) was treated with 105.0 mg (3.5mmol) 80% NaH in 30ml THF according to the procedure described above. Usual workup gave 1.036g of brown oil. Trituration with hexane afforded 472.2 mg (0.84 mmol) of **11**. Residual oil was chromatographed on 50g *Kieselgel 60* in hexane/EtOAc (5/2) to give 57.5mg (0.10 mmol) of **11** and 260.1mg (0.76mmol,

24%) of ether **10.** Total yield of cyclohexadienone **11**: 529.7mg (0.95mmol, 61%). Melting point: 145-6°C

^{1}H NMR spectra ($CDCl_3$, TMS) δ: 1.16 and 1.19(18H, s, t-Bu); 1.31(3H, d, J=5.8Hz, CCH_3); 1.40(18H, s, t-Bu); 2.72(1H, d, J=12.6Hz, CHAr); 2.95(1H, d, J=12.6Hz, CHAr); 3.12(1H, d, J=8.8Hz, CHO); 3.26(1H, d, J=8.8Hz, CHO); 4.34(1H, q, J=5.8Hz, OCHPy); 5.00(1H, s, OH); 6.45(1H, d, J=2.4Hz, C=CH); 6.60(1H, d, J=2.4Hz, C=CH); 6.86(2H, s, C_6H_2); 7.10-7.30(1H, m, Py-5H); 7.50-7.70(1H, m, Py-4H); 8.49ppm(2H, m, Py-2H and Py-6H).

Reaction of O-trimethylsilylpyridylmethanol with pyridinium salt 12.

O-Trimethylsilylpyridylmethanol (**13**) (2.0ml, 10.6mmol) was dissolved in 5ml THF and added to a suspension of 3.3g (10.0mmol) pyridinium salt **12** in 10ml THF. Reaction mixture was stirred at room temperature for 24h and poured into 30ml of ice-cold brine. Usual workup gave 2.69g (8.22mmol, 82%) of ether **2a**.

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