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Totally hindered phenols. 2,6-Di-*t*-butyl-4-(1,1-dialkyl-1-acetamide)-phenols and their persistent phenoxy radicals

John T. Lai

BFGoodrich Company, 9921 Brecksville Rd, Ohio 44141, USA

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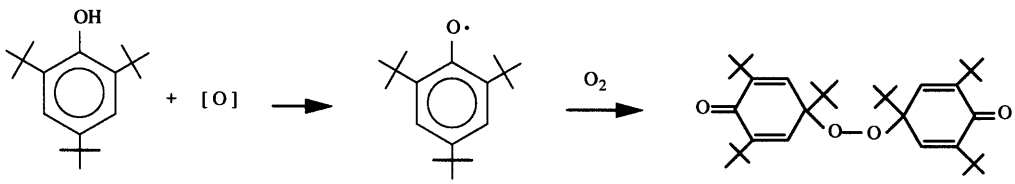
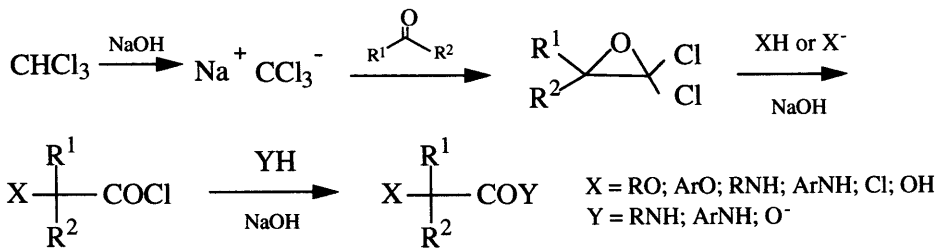
Abstract—2,6-Di-*t*-butyl-4-(1,1-dialkyl-1-acetamide)-phenols were prepared from 2,6-di-*t*-butylphenol, chloroform, ketone and amine with sodium hydroxide. Their phenoxy radicals were found to be more persistent than the well-known 2,4,6-tri-*t*-butylphenoxy blue aroxyl radical. © 2001 Published by Elsevier Science Ltd.

The N-oxy radicals of hindered amines, such as 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO) are very stable.[1] They can be isolated, purified and stored for extended periods of time. Hindered alkoxy radicals, such as *t*-butoxy radical are not stable.[2] One of the favourite degradation pathways is to form acetone and methyl radical, which then combine to form ethane. The hindered phenoxy radicals, although unable to disproportionate, are not stable even when the ring is substituted with bulky groups on the 2- and 6-positions.[3] They can be self-coupled or coupled with an oxygen molecule, in particular through the 4-positions. The well-known blue aroxyl, the 2,4,6-tris-*t*-butylphenoxy radical was isolated and characterized in an inert atmosphere.[4] The persistent radical will, however, couple with oxygen through the ring when exposed to the air (Scheme 1).

I would like to report here a synthesis of 2,6-di-*t*-butyl-4-(1,1-dialkyl-1-acetamide)-phenol. The thought is that the bulky group at the 4-position may stabilize the phenoxy radical by keeping it from coupling with oxygen, or at least make it more persistent than the blue aroxyl radical.



Scheme 1.



Scheme 2.

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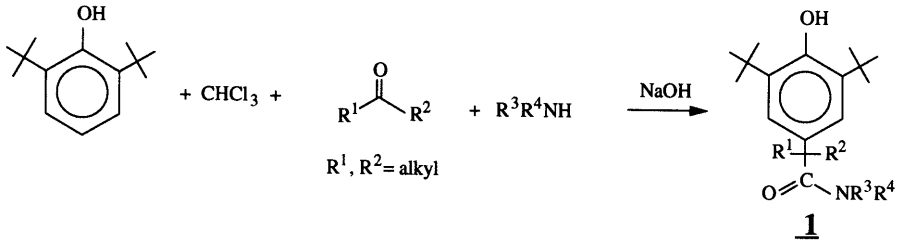
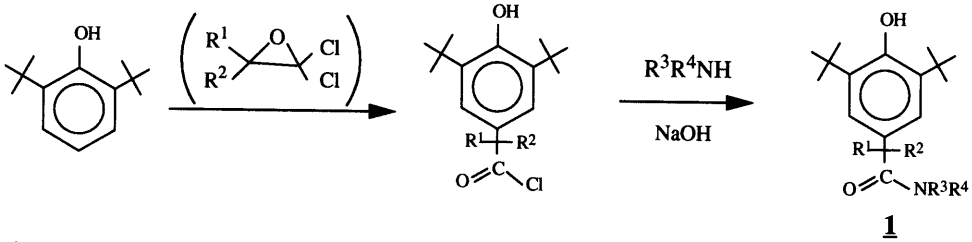


Scheme 3.



Scheme 4.

The ketoform reaction, which I refer to as the reaction among chloroform, a ketone, sodium hydroxide and nucleophiles, was reported earlier in the literature, where the nucleophiles are unhindered phenols,[5] alcohols,[6] aniline,[7] chloride and hydroxide.[8] It was modified and applied in this laboratory to make totally hindered amines such as 3,3,5,5-tetraalkyl-2-piperazinones and 3,3,5,5-tetraalkyl-2-morpholones and other molecules.[9]

The mechanism of the ketoform reaction is depicted in Scheme 2, showing the 1,1-dialkyl-2,2-dichlorooxirane as the reactive intermediate.

When 2,6-di-*t*-butylphenol participates in the ketoform reaction as the nucleophile XH, 2,6-di-*t*-butyl-4-(1,1-dialkyl-1-acetamide) (**1**) is formed in decent yield (Scheme 3), where the 4-carbon on 2,6-di-*t*-butylphenol opens the oxirane intermediate (Scheme 4).

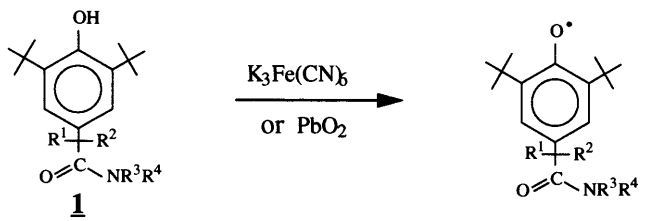
Most dialkyl amines and tertiary alkyl amines work well because they do not compete against the hindered phenol for attacking the dialkyl carbon in the oxirane intermediate. Cyclic amines such as piperidine, morpholine and cyclohexylamine give by-products, so do dimethylamine and less hindered primary amines. Methyl alkyl ketones and cyclic ketones usually give decent conversions. Alkyl aldehydes do not yield the desired product due to possibly the interference of aldol condensation, aldimine formation and less favorable ring closure for making a trisubstituted than a tetrasubstituted oxirane.[10]

The following represents a general procedure: 2,6-Di-*t*-butylphenol (206.3 g, 1.0 mol), chloroform (155.2 g, 1.3 mol), dibutylamine (226.2 mol, 1.75 mol) and cyclohexanone (785.6 g, 8.0 mol) were mixed at 5–10°C under nitrogen. Sodium hydroxide beads (180 g, 4.5 mol) were added at below 15°C during a 4 h period. After stirring at 10°C overnight, the reaction content was filtered. The solid was stirred with 750 ml water, filtered, stirred and filtered again with 500 ml 20% HCl, and finally with 500 ml water and filtered. The initial cyclohexanone solution filtrate was concentrated to strip off the solvent and excess dibutylamine, slurred in 500 ml hexanes and filtered. The two combined solids were recrystallized from heptane to yield 370 g of colorless crystals, melting point 135–138°C.

Table 1 lists some of the hindered phenolic amides made this way, together with their melting points and the reaction yield.

In the absence of the amine, the 2,6-di-*t*-butyl-4-(1,1-dialkyl-1-acetic acid)-phenol **2** can be isolated after the reaction mixture was acidified (Table 2).

The pheoxy radical of **1** can be obtained from the oxidation of **1** with either potassium ferricyanide[4] or lead dioxide.[12]



In a typical experiment for estimating the half-life of the hindered phenoxy radicals, 2.5 mmol $K_3Fe(CN)_6$, 2.3 mmol KOH, 5 ml H_2O and 50 ml toluene were mixed in a 250 ml 3-neck flask under a nitrogen atmosphere. Compound **1** (1 mmol) in 50 ml toluene was added dropwise in 45 minutes. The bluish-colored mixture was stirred for a further 2 hours. A 10 ml aliquot of the toluene solution was diluted with toluene to 100 ml which was quickly dried over $MgSO_4$. A 3 ml aliquot was added to an ESR tube capped under air. The radical shows a singlet in an unresolved hyperfine ESR spectrum. Spectra were taken at different intervals

Table 1.

1[11]	R^1	R^2	R^3	R^4	Mp (°C)	Yield[a] (%)	H NMR[11] (ppm)	IR[11] (cm^{-1})
1a	CH_3	CH_3	C_2H_5	C_2H_5	128–9	74	1.42 (s, 18H), 1.51 (s, 6H), 2.92 (m, 4H), 3.31 (m, 4H), 5.14 (s, 1H), 6.99 (s, 2H)	1600(s), 3510(br)
1b	CH_3	CH_3	H	t-C_4H_9	167–9	61	1.24 (s, 9H), 1.44 (s, 18H), 1.50 (s, 6H), 4.22 (br s, 1H), 5.16 (s, 1H), 7.12 (s, 2H)	1650(s), 3420(s)
1c	CH_3	CH_3	CH_3	CH_2CH_2OH	143–6	63	1.43 (s, 18H), 1.53 (s, 6H), 1.7 (br, 1H), 2.56 (s, 3H), 3.50 (br s, 2H), 3.73 (br s, 2H), 5.12 (s, 1H), 7.00 (s, 2H)	1600(s), 3540(s)
1d	CH_3	CH_3	n-C_4H_9	TMP[b]	192–5	75	0.67 (br s, 6H), 0.8–1.9 (m, 12H), 1.12 (s, 6H), 1.41 (s, 18H), 1.49 (s, 6H), 3.14 (br, 2H), 3.73 (t, 1H), 5.06 (s, 1H), 7.01 (s, 2H)	1580(s), 3440(s)
1e	CH_3	C_2H_5	n-C_4H_9	n-C_4H_9	97–9	82	0.65 (t, 3H), 0.84 (t, 3H), 0.96 (t, 3H), 1.43 (s, 18H), 1.1–2.1 (m, 10H), 2.16 (s, 3H), 2.83 (m, 2H), 3.25 (m, 2H), 5.13 (s, 1H), 6.97 (s, 2H)	1600(s), 3480(br)
1f	CH_3	C_2H_5	CH_3	TMP	188–90	85	0.97 (s, 6H), 1.01 (s, 6H), 1.42 (s, 18H), 0.5–2.2 (m, 13H), 2.79 (s, 3H), 3.78 (m, 1H), 5.04 (s, 1H), 6.97 (s, 2H)	1590(s), 3400(br)
1g	-$(CH_2)_5$-		n-C_4H_9	n-C_4H_9	135–8	88	0.5–3.2 (m, 28H), 1.42 (s, 18H), 5.09 (s, 1H), 7.05 (s, 2H)	1580(s), 3300(br)
1h	-$(CH_2)_5$-		H	DEP[c]	213–6	30	0.99 (t, 6H), 1.2–2.5 (m, 10H), 2.31 (q, 4H), 5.22 (s, 1H), 6.40 (s, 1H), 7.02 (s, 2H), 6.4–7.8 (m, 3H)	1650(s), 3380(s)
1i	-$(CH_2)_5$-		CH_3	TMP	185–7	85	0.89 (s, 12H), 0.8–2.1 (m, 14H), 1.38 (s, 18H), 2.56 (m, 1H), 2.75 (s, 3H), 3.82 (br, 1H), 4.84 (s, 1H), 7.15 (s, 2H)	1610(s), 3400(br)
1j	-$(CH_2)_5$-		n-C_4H_9	TMP	122–5	85	1.40 (s, 18H), 0.5–2.1 (m, 34H), 3.13 (m, 2H), 3.69 (m, 1H), 5.03 (s, 1H), 7.05 (s, 2H)	1630(s), 3520(br)
1k	-$(CH_2)_{11}$-		C_2H_5	C_2H_5	177–80	30	0.58 (t, 3H), 1.11 (t, 3H), 1.2–3.0 (m, 22H), 1.41 (s, 18H), 5.03 (s, 1H), 6.88 (s, 2H)	1600(s), 3450(br)
1l	CH_3	n-C_6H_{13}	H	t-C_8H_{17}	147–50	72	0.74 (s, 9H), 0.86 (t, 3H), 1.2–1.5 (m, 10H), 1.34 (s, 3H), 1.40 (s, 3H), 1.43 (s, 18H), 1.46 (s, 3H), 1.92 (s, 1H), 5.13 (s, 1H), 7.09 (s, 2H)	1650(s), 3430(s), 3550(br)

[a] Isolated yield.
[b] TMP

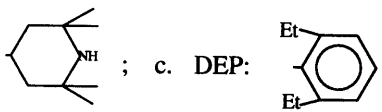
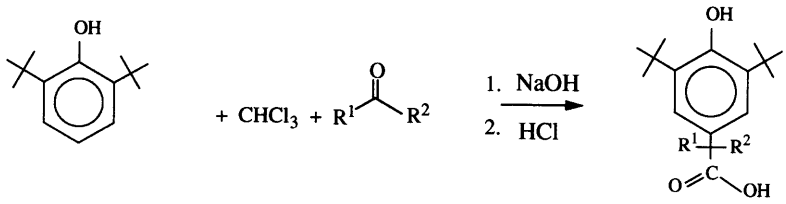


Table 2.



2

2[11]	R^1	R^2	Mp (°C)	Yield (%)	H NMR[11] (ppm)	IR[11] (cm^{-1})
2a	CH_3	CH_3	210–3	71	1.43 (s, 18H), 1.57 (s, 3H), 5.14 (s, 1H), 7.22 (s, 2H), 11.50 (br, 1H)	1700(s), 3610(s)
2b	CH_3	C_2H_5	141–4	38	0.88 (t, 3H), 1.43 (s, 18H), 1.51 (s, 3H), 2.0 (m, 2H), 5.12 (br, 1H), 7.00 (s, 2H), 11.50 (br, 1H)	1680(s), 3640(br)
2c	$-(CH_2)_5-$		187–90	36	1.42 (s, 18H), 1.0–2.6 (m, 10H), 5.139s, 1H), 7.26 (s, 2H), 11.30 (br, 1H)	1680(s), 3600(s)

Table 3.

Phenoxy radical	$t_{1/2}$ (h)	Radical	$t_{1/2}$
2,4,6-tris-*t*-butyl	1.3	**1e**	28.5
1a	10.3	**1f**	42
1b	2.2	**1h**	3.2
1c	6.0	**1i**	50.6
1d	29.5	**1j**	78.2

until the height of the peak dropped below 50% of its original strength. A decay curve was drawn with peak height versus time. Half-life was determined as the time when the radical lost 50% of its original strength.

Table 3 shows the comparison of the half-lives of the phenoxy radicals from **1** to the half-life of 2,4,6-tris-*t*-butylphenoxy radical.

Although the added bulk on the 4-position will extend the life of the hindered phenoxy radicals in air, they all gradually couple with oxygen. The coupled products can usually be isolated as a yellow crystalline solid with structures similar to that obtained from 2,4,6-tris-*t*-butylphenol. It remains to be discovered if any phenoxy radical can be hindered enough to be stable in air.

Acknowledgements

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