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Abstract: A thioalkylation of phenols involving reactive phenols, aldehydes, and thiols is described under Mannich-type phenol catalysis to afford thiomethyl phenols in good yields.

Keywords: catalytic reaction, Mannich-type phenol, thioalkylation

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Thioalkylation is an important and widely used procedure for carbon–carbon bond formation and the production of unsymmetrical sulfides.[1] Usually, thioalkylation of phenol proceeds through hydroxymethyl, halomethyl, or Mannich-type phenol as an intermediate.[2] Among them, pyrolysis of Mannich-type phenol provides a powerful procedure for preparation of thioalkylated phenol. Displacement of dialkylamine by a thiol gives the thioalkylated product. However, this powerful procedure involves equimolar amounts of Mannich-type phenol and thiol. In this article, we disclose a more atom-economical reaction for thioalkylation of phenols. We directly prepared thioalkylated phenol from phenol, *para*-formaldehyde thiol, using Mannich-type phenol as a catalyst.

The results in Table 1 reveal that the reaction temperature and the solvent are critical to the thioalkylation. When a solvent was not employed in the model reaction, full conversion was not obtained until 18 h. Raising temperature might improve the reaction rate. However, when the temperature was raised above 120°C, a lot of *para*-formaldehyde was sublimed at the top of the reaction vessel. During the experimentation, we found that the sublimation of *para*-formaldehyde could be avoided by adding alcohol. Although it has been said the protic solvents such as alcohol would accelerate the Mannich reaction,[3] the reactions proceeded more sluggishly with increasing alcohol content (Table 1, entries 5–8).

Under the optimized conditions, the scope of the 2,6-di-tert-butyl-4-dimethylaminomethyl phenol–catalyzed thioalkylation of thiols was extended. Investigation of representative thiols demonstrated that the procedure was feasible for aliphatic and hetero atom-containing thiols (Table 2, entries 1–6). The thiols with electron-donating groups generally gave satisfactory results. It is worthwhile to note that this new approach works well with hetero atom-containing thiols (Table 2, entries 2 and 3).

Table 1. Optimization of thioalkylation of 2,6-dibutylphenol catalyzed by 2,6-dibutyl-4-dimethylaminophenol

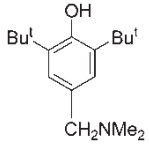
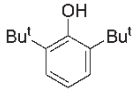
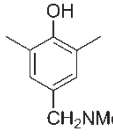
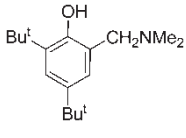
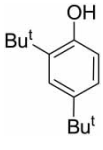
Entry	Temp. (°C)	Solvent	Time[a] (h)	Yield[b] (%)
1	100	none	18	92
2	120	none	14	93
3	140	none	*c*	67
4	160	none	*c*	59
5	120	1:7[d]	9	93
6	120	3:5[d]	8	93
7	120	5:3[d]	7	92
8	120	7:1[d]	5	93
9	120	DMF	4	94

[a]Time for 100% conversion.
[b]Isolated yield.
[c]Stopped the reaction after 15 h.
[d]w (DMF): w(ETOH).

On the other hand, it is worth noting that the reaction gave low reaction rate for thiols with an electron-withdrawing group, such as β-thioglycolic acid or β-mercaptoethanol. In these cases, a considerable amount of unreacted starting materials were recovered after reacting for 15 h. Obviously the low efficiency is due to the low nucleophilicity of the thiols. Among these thiols, the isopropylthiol showed a relatively low conversion because of its volatility.

It was observed that use of the corresponding Mannich-type phenol as a catalyst was effective for the thioalkylation of phenols such as 2,6-dimethyl phenol and 2,4-di-tert-butyl phenol. The full conversion time of thioalkylation of 2,4-di-tert-butyl phenol was much longer than that of 2,6-disubstitued phenols (Table 2, entries 1, 7, and 8). It is well known that deamination of Mannich-type phenols leads to intermediate quinone methides.[4] It is probably due to *para*-quinone methides (*p*-QMs) that are less polarized and more stable than their corresponding *o*-QMs. Accordingly, *p*-QMs are formed more readily than *o*-QMs.[5]

Table 2. Thioalkylation of phenols catalyzed by Mannich-type phenols

Entry	Cat.	Phenols	Thiols	Time[a] (h)	Yield[b] (%)
1			$HSC_{12}H^{n}_{25}$	4	94
2			$HS(CH_2)_3Si(OEt)_3$	4	93
3			$HSCH_2COOC_8H^{i}_{17}$	4	92
4			$HSCH_2COOH$	15[c]	47
5			$HSCH_2CH_2OH$	15[c]	53
6			$HSC_3H^{i}_{7}$	15[c]	
7			$HSC_{12}H^{n}_{25}$	4	91
8			$HSC_{12}H^{n}_{25}$	20	84

[a]Time for 100% conversion.
[b]Isolated yield.
[c]Stopped the reaction after 15 h.

In conclusion, we have developed a new simple approach to thioalkylation of phenols using appropriate readily available Mannich-type phenol as a catalyst. The reaction is more atom-economical and easier to prepare.

EXPERIMENTAL

All ^{1}H spectra were recorded at 400 MHz with $CDCl_3$ as solvent. All reagents were used directly as obtained commercially.

Typical Procedure

Reactions were carried out in a test tube (20 mL) under an N_2 atmosphere with gentle magnetic stirring. Phenol (18 mmol), catalyst (2 mmol), paraformaldehyde (0.9 g, 30 mmol), and n-dodecanethiol (4.04 g, 20 mmol) in N,N-dimethylformamide (4.0 g) was heated at 100–160°C. After completion of the reaction, the mixture was cooled to room temperature, washed with water, and dried. Then the yellowish products were analyzed using ^{1}H NMR.

Data

2,6-Di-tert-butyl-4-((dodecylthio)methyl)phenol (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.068 (s, 2H, C_6H_2), 5.103 (s, 1H, Ph-OH), 3.636 (s, 2H, $PhCH_2S$), 2.442–2.405 (t, $J = 7.2$, 2H, $PhCH_2SCH_2$), 1.569–1.530 [(m, 2H, SCH_2CH_2), 1.398 (s, 18H, $C(CH_3)_3$)], 1.280–1.234 [m, 18H, $(CH_2)_9$], 0.878–0.844 (t, $J = 6.8$, 3H, CH_2CH_3).

2,6-Di-methyl-4-((dodecylthio)methyl)phenol (white solid, mp: 54–55°C). ^{1}H NMR ($CDCl_3$): 6.892 (s, 2H, C_6H_2), 3.573 (s, 2H, $PhCH_2S$), 2.227 (t, 2H, $PhCH_2SCH_2$), 1.57–1.519 (m, 2H, SCH_2CH_2), 1.308 (s, 6H, CH_3), 1.232–1.1.170 [m, 18H, $(CH_2)_9$], 0.875–0.841 (t, $J = 6.8$, 3H, CH_2CH_3).

2,6-Di-tert-butyl-4-((isopropylthio)methyl)phenol (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.096 (s, 2H, C_6H_2), 5.102 (s, 1H, Ph-OH), 3.684 (s, 2H, $PhCH_2S$), 2.870-2.820 (m, 1H, $PhCH_2SCH$), 1.444 [s, 18H, $C(CH_3)_3$], 1.276–1.259 [d, $J = 6.8$, 6H, $CH(CH_3)_2$].

2-((3,5-Di-tert-butyl-4-hydroxybenzyl)sulfanyl)acetic acid (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.093 (s, 2H, C_6H_2), 5.116 (s, 2H, SCH_2COOH), 3.605 (s, 2H, $PhCH_2S$), 1.442 [s, 18H, $C(CH_3)_3$].

4-((3-(Triethoxysilyl)propylthio)methyl)-2,6-di-tert-butylphenol (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.068 (s, 2H, C_6H_2), 5.106 (s, 1H, Ph-OH), 3.817–3.728 (q, $J = 7.8$, 6H, OCH_2CH_3), 3.632 (s, 2H, $PhCH_2S$), 2.488–2.451

(t, $J = 7.8$, 1H, $PhCH_2SC\underline{H}_2$), 1.713–1.673 (m, 2H, $SCH_2C\underline{H}_2$) 1.391 [s, 18H, $C(C\underline{H}_3)_3$], 1.218–1.173 (t, $J = 7.8$, 6H, $OCH_2C\underline{H}_3$), 0.726–0.684 (t, $J = 8.4$, 2H, $C\underline{H}_2Si$).

4-((2-Hydroxyethylthio)methyl)-2,6-di-tert-butylphenol (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.078 (s, 2H, $C_6\underline{H}_2$), 5.147 (s, 1H, Ph-O$\underline{H}$), 3.691–3.662 (m, 4H, $PhC\underline{H}_2SCH_2C\underline{H}_2$), 2.209–1.929 (t, $J = 6$, 2H, $PhCH_2SC\underline{H}_2$), 1.418 [s, 18H, $C(C\underline{H}_3)_3$].

2,4-Di-tert-butyl-6-((dodecylthio)methyl)phenol (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.235–7.229 (d, $J = 2.4$, 1H, $C_6\underline{H}_2$), 6.898–6.892 (d, $J = 2.4$, 1H, $C_6\underline{H}_2$), 6.796 (s, 1H, Ph-O$\underline{H}$), 3.783 (s, 2H, $PhC\underline{H}_2S$), 2.377–2.339 (t, $J = 7.6$, 2H, $PhCH_2SC\underline{H}_2$), 1.523–1.486 (m, 2H, $SCH_2C\underline{H}_2$), 1.401 [s, 9H $C(C\underline{H}_3)_3$], 1.248 [s, 9H $C(C\underline{H}_3)_3$], 1.230–1.212 [s, 18H, (m, 18H, $(C\underline{H}_2)_9$], 0.877–0.843 (t, $J = 6.8$, 3H, $CH_2C\underline{H}_3$).

2-Ethylhexyl 2-(3,5-di-tert-butyl-4-hydroxybenzylthio)acetate (yellowish oil). ^{1}H NMR ($CDCl_3$): 7.091 (s, 2H, $C_6\underline{H}_2$), 5.147 (s, 1H, $C_6H_2O\underline{H}$), 4.189 (s, 1H, $PhCH_2SC\underline{H}_2$), 4.049 (d, 2H, $OC\underline{H}_2CH$), 3.754 (s, 2H, $PhC\underline{H}_2S$), 1.159 (m, 1H, $OCH_2C\underline{H}$), 1.424–1.279 (m, 8H, $CH(C\underline{H}_2CH_3)$ $C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_3$), 0.905–0.897 (m, 6H, $C\underline{H}_3$).

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