A Novel Method for the α-Phenylthiomethylation of Carbonyl Compounds

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α-Phenyl- and α-alkylthiomethylations of carbonyl compounds are important synthetic reactions, since the thiomethylated products can also serve as precursors of α-methyl derivatives by reductive desulfurization with Raney nickel and as those of α-methylene derivatives by oxidative sulfur removal with sodium periodate. Recently, several groups[1-4] reported on the α-thiomethylation process; in general, using halomethyl sulfides, but the methods described are restricted and give poor yields of the products. The best method, the reaction of silyl enol ethers derived from ketones with phenyl chloromethyl sulfide in the presence of titanium(IV) chloride, was reported very recently[5].

Acid-promoted phenyl- and alkylthiomethylation of aromatic compounds by the corresponding thiomethylamines has been reported[6]. We have investigated the possibility that the thiomethylation of enamines might offer a more convenient route to α-thiomethylated carbonyl compounds. We now report an effective method for α-thiomethylation of ketones and aldehydes, involving a thiomethylation of enamines, easily prepared from carbonyl compounds, by phenyl- and alkylthiomethylamines in the presence of hydrogen chloride, followed by hydrolysis of the mixture with hydrochloric acid.

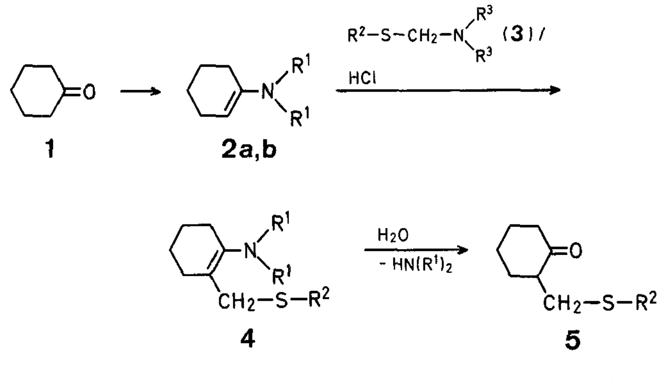
Using *N*-cyclohexen-1-yl-dimethylamine (**2a**; $R^1 = CH_3$) and 4-cyclohexen-1-yl-morpholine [**2b**; $R^1—R^1 = —(CH_2)_2—O—(CH_2)_2—$], initial experiments were conducted by allowing them to react with the phenyl- or alkylthiomethylamine **3a-c** ($R^2 = C_6H_5$, $C_6H_5CH_2$, or CH_3) in the presence of hydrogen chloride in ethanol under reflux. Treatment of the concentrated residue with 20% hydrochloric acid gave the α-phenyl- and α-alkylthiomethylcyclohexanones (**5a-c**). Among these three thiomethylating reagents, the highest yield was obtained with the phenylthiomethylamine derivative **3a**.

Table 1. α-Phenylthiomethylation[a] of Cyclohexanone **1** to **5a** ($R^2 = C_6H_5$)

R^1 or $R^1 \text{---} R^1$ in **2**	R^3 or $R^3 \text{---} R^3$ in **3**	Reaction time [h]	Yield [%][b] of **5a**
$2CH_3$	$2CH_3$	2.0	63
$—(CH_2)_4—$	$2CH_3$	2.0	0
$—(CH_2)_5—$	$2CH_3$	1.5	73
$—(CH_2)_2—O—(CH_2)_2—$	$2CH_3$	1.0	80
$—(CH_2)_2—O—(CH_2)_2—$	$—(CH_2)_5—$	1.0	81
$—(CH_2)_2—O—(CH_2)_2—$	$—(CH_2)_2—O—(CH_2)_2—$	1.0	80

[a] Molar ratio of enamine **2**:**3**:HCl = 1:1:1.

[b] Yield of isolated product.



Control experiments included an examination of the efficiencies of the amine residues of the enamines prepared from cyclohexanone and those of the phenylthiomethylamines. As can be seen in Table 1, the yield of **5a** is greatly influenced by a change of the amine residue (R^1) of the enamines **2**; in the case of a pyrrolidine grouping [$R^1—R^1 = —(CH_2)_4—$], the reaction did not occur and the morpholine grouping [$R^1—R^1 = —(CH_2)_2—O—(CH_2)_2—$] is established as the most effective one. On the other hand, no appreciable difference in the yields was observed by a change of the amine residue (R^3) of the phenylthiomethylamines **3**.

Using **3a** ($R^2 = C_6H_5$, $R^3 = CH_3$) as a reagent, the phenylthiomethylation reaction was extensively examined with morpholine enamines, which were derived from cyclic and acyclic ketones and aldehydes. Results are summarized in Table 2. From the data in Table 2, it can be said that yield of the α-phenylthiomethylated product is lowered when the γ-carbon of enamine is branched (entries 1, 5, 9). Therefore, a higher yield is obtained in the case of an enamine possessing a β-methylene group (entries 7, 10). It is demonstrated by the use of 4-(2-methylpropene-1-yl)-morpholine that no reaction proceeds with enamines not possessing β-hydrogen atoms.

From the above facts, we suggest that the mechanism of this phenylthiomethylation reaction is as shown below. The reaction involves an electrophilic substitution of a phenylthiomethylcarbenium ion, derived

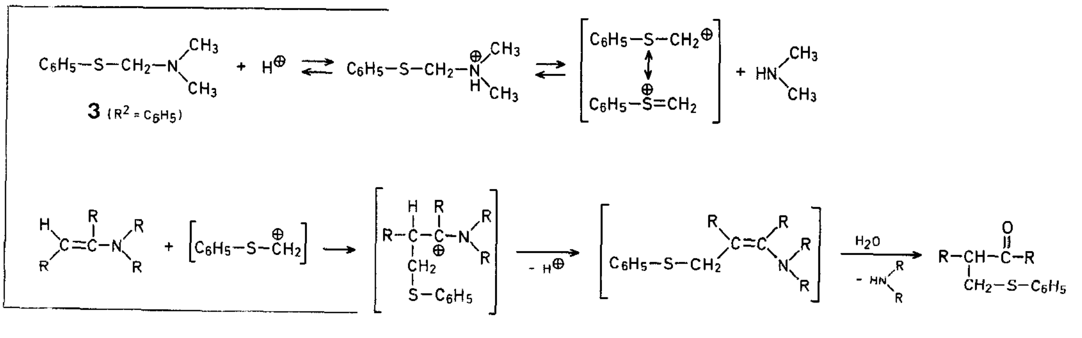


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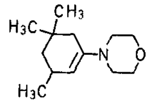
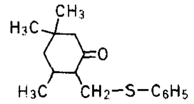
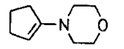
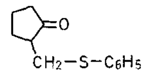
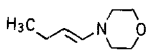
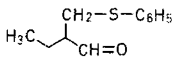
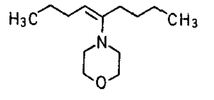
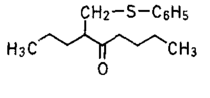
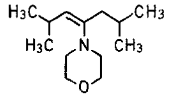
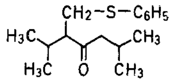
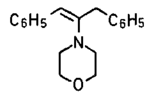
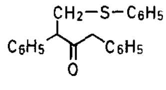
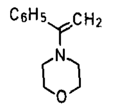
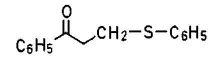
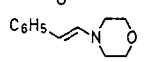
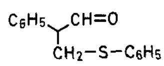
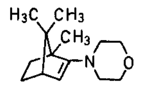
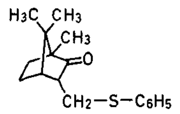
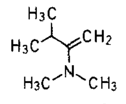
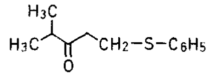
Table 2. α-Phenylthiomethylation and α-Alkylthiomethylation of Carbonyl Compounds

Entry	Enamine	Product	Reaction time [h]	Yield[a] [%]	m.p. [°C] or b.p. [°C]/torr	Molecular formula[b]	I.R. (Nujol or KBr) $\nu_{C=O}$ [cm^{-1}]	¹H-N.M.R. (CDCl₃) $\delta_{-S-CH_3-C-C=O}$ [ppm]
1			1.5	23	186–187°/0.4	$C_{16}H_{22}OS$ (262.42)	1706	3.14 (d, 2H, *J* = 6 Hz)
2			3.5	36	140–145°/0.3 19–20°	$C_{12}H_{14}OS$ (206.30)	1744	3.43 (AB q, 2H, *J* = 10 Hz, 4 Hz)
3			1.0	47	138–140°/4	$C_{11}H_{14}OS$ (194.29)	1725	3.01 (d, 1H, *J* = 6 Hz); 2.98 (d, 1H, *J* = 4 Hz)
4			2.0	43	149–150°/0.5	$C_{16}H_{24}OS$ (246.43)	1709	2.97 (d, 1H, *J* = 5 Hz); 2.92 (d, 1H, *J* = 4 Hz)
5			4.0	14	155–158°/0.6	$C_{16}H_{24}OS$ (264.43)	1711	2.95 (d, 2H, *J* = 6 Hz)
6			3.0	46	65–66°	$C_{22}H_{20}OS$ (332.47)	1710	3.05 (AB q, 2H, *J* = 12 Hz, 6 Hz)
7			1.0	71	61–62°	$C_{15}H_{14}OS$ (242.34)	1698	3.25 (s, 4H)[c]
8			1.5	23	—[d]	$C_{15}H_{14}OS$ (242.34)	1726	2.9–4.0 (m, 2H)
9[e]			3.0	15	145–148°/0.1	$C_{17}H_{22}OS$ (274.43)	1735	3.35 (d, 2H, *J* = 4 Hz); 3.57 (d, 2H, *J* = 4 Hz) *(exo + endo)*
10[f]			2.0	58	110–115°/0.2	$C_{12}H_{16}OS$ (208.32)	1709	3.10 (t, 2H, *J* = 6 Hz)[g]
11	**2a** + **3a** ($R^3 = CH_3$)	**5** ($R^2 = C_6H_5$)	2.0	63	155–158°/5	$C_{13}H_{16}OS$ (220.33)	1706	3.38 (d, 2H, *J* = 9 Hz)
12	**2b** + **3a** ($R^3 = CH_3$)	**5** ($R^2 = C_6H_5$)	1.0	80				
13	**2a** + **3b** ($R^3 = CH_3$)	**5** ($R^2 = C_6H_5CH_2$)	2.0	40	188–191°/0.5	$C_{14}H_{18}OS$ (234.36)	1708	2.86 (d, 2H, *J* = 9 Hz)
14	**2b** + **3b** ($R^3 = CH_3$)	**5** ($R^2 = C_6H_5CH_2$)	3.0	66				
15	**2a** + **3c** ($R^3 = CH_3$)	**5** ($R^2 = CH_3$)	2.0	37	113–114°/6	$C_8H_{14}OS$ (158.26)	1716	2.97 (d, 2H, *J* = 9 Hz)
16	**2b** + **3c** ($R^3 = CH_3$)	**5** ($R^2 = CH_3$)	1.0	42				

[a] Yield of isolated product.

[b] Satisfactory microanalyses obtained: C ±0.34, H ±0.22.

[c] Both CH_2 groups ($C_6H_5-S-\underline{CH_2}\underline{CH_2}-CO-C_6H_5$) show the higher order A_2B_2 pattern on measurement in C_6D_6.

[d] A liquid purified by silica gel column chromatography.

[e] This enamine is a new compound, prepared by the $TiCl_4$-catalyzed reaction reported by White and Weigarten[7]; yield: 33%; b.p. 140°/0.3 torr[6] (b.p. is bath temperature of Kugelrohr apparatus).

$C_{14}H_{23}NO$	calc.	C 75.97	H 10.47	N 6.33
(221.3)	found	76.03	10.28	6.07

I.R. (nujol): $\nu = 1603\ cm^{-1}$ (C=O).

¹H-N.M.R. ($CDCl_3$): $\delta = 4.80$ ppm (d, 1 H_{vinyl}, $J = 4$ Hz).

[f] The corresponding morpholine enamine has been reported to be an isomeric mixture[7].

[g] This is an example of a borderline case between A_2B_2 and A_2X_2 patterns. Although both CH_2 groups ($C_6H_5-S-\underline{CH_2}\underline{CH_2}-CO-$) are essentially triplets, higher order effects are observed and the center and outer peaks of each triplet show additional splitting.

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through protonation of **3a**, at the β-carbon atom of the enamine. The attack of the carbenium ion may be sterically hindered by branched γ-carbon atoms.

α-Phenyl- or α-Alkylthiomethylketones and -aldehydes 5; General Procedure:

A solution of enamine **2** (0.05 mol) and thiomethylamine **3** (0.05 mol) in ethanol (50 ml) containing hydrogen chloride (0.05 mol) is heated under reflux until the starting thiomethylamine cannot be detected by G.L.C. After the solution has been rotary-evaporated, 20% hydrochloric acid (35 ml) is added to the resulting residue and the aqueous mixture is heated for 0.5 h on a steam bath with stirring. The oil which separates is extracted with benzene (50 ml), the benzene solution is washed with 10% aqueous sodium hydroxide solution (50 ml), and then dried with magnesium sulfate. Removal of the benzene followed by distillation under reduced pressure or recrystallization of the resulting residue gives the α-phenylthiomethylated product **5**. If necessary, further purification by chromatography on silica gel is conducted.

Received: November 3, 1980

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