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NOVEL ALKYL- AND PHENYLTHIOMETHYLATION OF AROMATIC COMPOUNDS

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It has been found that the Mannich bases, of which methylene is linked to amine nitrogen and alkyl- or phenylmercapto-sulfur affect smoothly, in the presence of acid catalyst, alkyl- or phenylthiomethylation of a number of aromatic compounds, i.e. 2-naphthol, aniline, indole and their derivatives.

The development of procedures practically suitable for the direct introduction of alkyl(or aryl)thiomethyl grouping into an aromatic nucleus has been an important problem in the synthetic field of organo-sulfur chemistry. Although several methods for this object have been available for the special cases in the literature, i.e. the alkylthiomethylation of indole, antipyrine and 2-naphthol with alkanethiol and formaldehyde,[1] that of phenol and indole by sulfoxide-carbodiimide reaction[2] and that of N,N-dimethylaniline and anisole by dimethylsulfoxide-phosphoryl chloride reaction,[3] virtually all of these procedures are unsatisfactory because of very prolonged reaction time or poor yields of the thiomethylated products.

We have found that the Mannich bases, of which methylene is linked to amine nitrogen and alkyl- or phenylmercapto-sulfur, affect smoothly alkyl- and phenylthiomethylation of a number of aromatic compounds by catalytic action of acid. Three types of the Mannich bases, R(or Ar)SCH_2NMe_2 (I),[4,5] [R(or Ar)SCH_2]$_2$NMe (II)[4] or [R(or Ar)SCH_2]$_3$N (III),[4,6] including newly prepared I(R = $C_6H_5CH_2$)[7] and II(R = $C_6H_5CH_2$),[8] were easily prepared on reference to the previously reported methods by the reaction among alkane- or arenethiols, formaldehyde and amines or ammonia, and either of them could be used for the alkyl- and phenylthiomethylation.

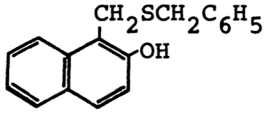
Using 2-naphthol (1) as a substrate, initial experiments were conducted by allowing to react with the Mannich bases, I, II and III, where R is benzyl, in the presence of sulfuric acid in EtOH under reflux. In every run, the smooth 1-benzylthiomethylation proceeded and gave the product 2 in over 95% yield (see Table 1) based on the following stoichiometric relationships.

$$1 + C_6H_5CH_2SCH_2NMe_2 \longrightarrow 2 + Me_2NH$$

$$1 + 1/2(C_6H_5CH_2SCH_2)_2NMe \longrightarrow 2 + 1/2MeNH_2$$

$$1 + 1/3(C_6H_5CH_2)_3N \longrightarrow 2 + 1/3NH_3$$

2 :



From these results the reaction was extensively investigated with a number of other aromatic compounds. In a practical point of view selection of the Mannich bases may be guided by easiness of their preparation and handling. We used I or II at our convenience, because of particularly low yield of III in its preparation (about 30%, where R = $C_6H_5CH_2$). Table 1 shows successful results of the experiments in which, other than 2-naphthol, aromatic amines such as aniline, indole and their N-methyl derivatives were found to be reactive. With these substrates hydrogen chloride was much more effective as a catalyst than sulfuric acid, as indicated in contrast between the runs vii and viii with N,N-dimethylaniline in Table 1, in the latter unreacted starting materials being almost recovered.

General procedures are as follows. A solution of 0.03 mol of substrate and alkyl- or phenylthiomethylamine [0.03 mol for $RSCH_2NMe_2$, 0.015 mol for $(RSCH_2)_2NMe$] in 15 ml of EtOH containing sulfuric acid or dry HCl was refluxed until the starting substrate vanished on TLC. After the solution was rotary evaporated, the resulting oily residue was washed with saturated aq. $KHCO_3$. The oily layer was combined with a benzene extract of the aqueous layer. After drying over K_2CO_3 evaporation of the benzene followed by distillation of the resulting residue gave the product. In the runs of 2-naphthol and that of indole with benzylthiomethylamine, a solid residue obtained by evaporation was washed or triturated with petroleum ether, and then recrystallized from ligroin or MeOH.

By the above general procedures the corresponding alkyl- and phenylthiomethylated products, 2-12, shown in Table 1, were obtained and they gave consistent IR

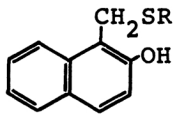
Table 1 Alkyl- and Phenylthiomethylation of Aromatic Compounds

Run No.	Substrate	Reagent	Catalyst (molar equiv.[a])	Reaction Time(hr)	Product No.	Yield(%)[b]
i	2-Naphthol	I(R=$C_6H_5CH_2$)	H_2SO_4(0.2)	1.0	2	99
ii	"	I(R=$C_6H_5CH_2$)	HCl (1.0)	2.0	2	99
iii	"	II(R=$C_6H_5CH_2$)	H_2SO_4(0.2)	0.5	2	95
iv	"	III(R=$C_6H_5CH_2$)	H_2SO_4(0.2)	3.0	2	99
v	"	I(R=C_6H_5)	H_2SO_4(0.2)	1.0	3	99
vi	"	II(R=CH_3)	H_2SO_4(0.2)	1.0	4	85
vii	N,N-Dimethyl-aniline	II(R=$C_6H_5CH_2$)	HCl (1.0)	10.0	5	81
viii	"	II(R=$C_6H_5CH_2$)	H_2SO_4(0.5)	50.0	5	16
ix	"	I(R=C_6H_5)	HCl (1.0)	30.0	6	30
x	"	II(R=CH_3)	HCl (1.0)	15.0	7	60
xi	N-Methylaniline	II(R=$C_6H_5CH_2$)	HCl (1.0)	25.0	8	55
xii	Aniline	II(R=$C_6H_5CH_2$)	HCl (1.0)	40.0	9	49
xiii	Indole	I(R=$C_6H_5CH_2$)	HCl (1.0)	8.0	10	83
xiv	"	II(R=CH_3)	HCl (1.0)	1.0	11	28
xv	1-Methylindole	II(R=CH_3)	HCl (1.0)	3.0	12	29

a) Molar equiv. to the reagent used.

b) Based on the product actually isolated.

and NMR spectra and satisfactory microanalyses.



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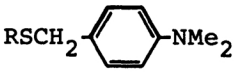

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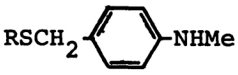

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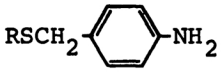

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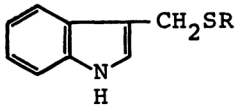

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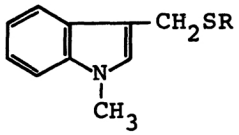


12

1-Substituted products from 2-naphthol —— 2(R = $C_6H_5CH_2$): mp 89°C (lit.[1] mp 89°C). 3(R = C_6H_5): mp 124.5-125°C (lit.[1] mp 126-127°C). 4(R = CH_3): bp 150°C (0.1 Torr)[9] [lit.[2a] bp 100°C(0.001 Torr)].

4-Substituted products from N,N-dimethylaniline —— 5(R = $C_6H_5CH_2$): bp 150-151°C(0.06 Torr), NMR δ(ppm in $CDCl_3$); 2.78 (6H, s, $-NMe_2$), 3.48 (2H, s, $C_6H_5C\underline{H}_2S$-), 3.51 (2H, s, p-$Me_2NC_6H_4C\underline{H}_2S$-), 6.82 (4H, ABq, δ_{AB} = 0.51 ppm, J_{AB} = 8.4 Hz, p-substituted aniline ring protons), 7.20 (5H, s, $C_6\underline{H}_5CH_2S$-). 6(R = C_6H_5): mp 103.5-104°C (lit.[10] mp 106-7°C). 7(R = CH_3): bp 133-135°C(2 Torr)[lit.[10] bp 123°C(5 Torr)].

4-Substituted product from N-methylaniline —— 8(R = $C_6H_5CH_2$): bp 189-191°C (1 Torr), mp 34-35°C (lit.[11] mp 36-38°C).

4-Substituted product from aniline —— 9(R = $C_6H_5CH_2$): bp 150-152°C(0.04 Torr), NMR δ(ppm in $CDCl_3$); 3.37 (2H, s, $-NH_2$), 3.42 (2H, s, $C_6H_5C\underline{H}_2S$-), 3.47 (2H, s, p-$NH_2C_6H_4C\underline{H}_2S$-), 6.66 (4H, ABq, δ_{AB} = 0.51 ppm, J_{AB} = 8.4 Hz, p-substituted aniline ring protons), 7.15 (5H, s, $C_6\underline{H}_5CH_2S$-).

3-Substituted products from indole —— 10(R = $C_6H_5CH_2$): mp 70-71°C (lit.[1] mp 74°C). 11(R = CH_3): mp 85-88°C (lit.[12] mp 87-88°C).

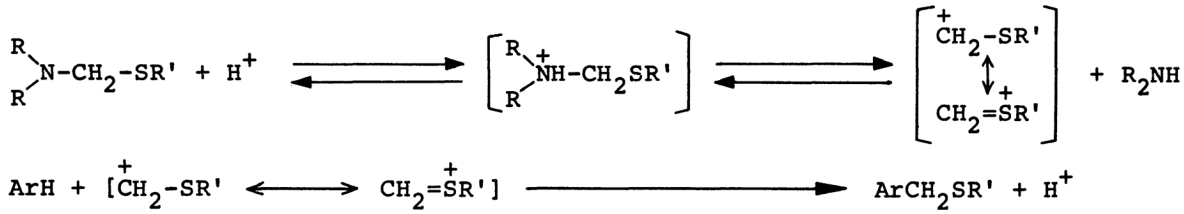
3-Substituted product from 1-methylindole —— 12(R = CH_3): bp 108-109°C(0.01 Torr), NMR δ(ppm in $CDCl_3$); 2.00 (3H, s, $-SCH_3$), 3.68 (3H, s, >NMe), 3.87 (2H, s, $-C\underline{H}_2SCH_3$), 6.90 (1H, s, C_2-H), 7.00-7.90 (4H, m, aromatic protons).

Although, as shown in Table 1, phenylthiomethylation of 2-naphthol and N,N-dimethylaniline with I (R = C_6H_5) was successfully processed in the given yields, attempts to carry out the reaction of indole with I (R = C_6H_5) in the presence of hydrogen chloride resulted in no phenylthiomethylation but in N,N-dimethylaminomethylation. Thus, by the foregoing procedure using 1.0 and 2.0 molar equiv. of hydrogen chloride 3-[(N,N-dimethylamino)methyl]indole was obtained in 23% and 17% yields, respectively.

Anisole, phenol, 4-cresol, 1-naphthylamine and bromobenzene were inert to the alkyl- and phenylthiomethylation under the given conditions.

When we speculate on mechanism for the alkyl- and phenylthiomethylation, the

following scheme may be most plausible at present. Further mechanistic investigation is now under way.



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7) B.p. 136-140°C(20 Torr); NMR($CDCl_3$)δ: 2.20(s, 6H, $-NMe_2$), 3.62(s, 2H, $-SCH_2C_6H_5$), 3.65(s, 2H, $>N-CH_2-S-$), 6.90-7.30(m, 5H, C_6H_5).
8) B.p. 182-5°C(0.05 Torr); NMR($CDCl_3$)δ: 2.35(s, 3H, >NMe), 3.70(s, 4H, $-SCH_2C_6H_5$), 3.80(s, 4H, $>N-CH_2-S-$), 7.15(s, 10H, C_6H_5).
9) Boiling point refers to the bath temperature in a "Kugelrohr" short path apparatus.
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